トリフルオロプロペニルリチウム調製法の開発と
それを用いる含フッ素化合物の合成

Generation of Trifluoropropenyllithium and its Application
to the Synthesis of Fluorine-Containing Compounds

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Generation of Trifluoropropenyllithium and its Application to the Synthesis of Fluorine-Containing Compounds

東京大学大学院理学系研究科化学専攻

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略語一覧

Ac	acetyl
Alloc	allyloxycarbonyl
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
Cat.	catalytic
Cbz	benzyloxycarbonyl
cod	cyclooctadiene
cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DFT	Density Functional Theory
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMI	1,3-dimethylimidazolidin-2-one
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
Et	ethyl
gem	geminal
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
KHMDS	pottasium hexamethyldisilazide
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
NMO	trimethylamine oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	NOE correlated spectroscopy
Np	naphthyl

Nu	nucleophile
PCC	pyridinium chlorochromate
Ph	phenyl
Pin	pinacol
PMB	*p*-methoxybenzyl
Pr	propyl
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

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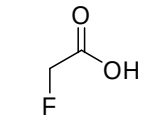
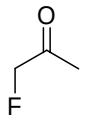
序論

フッ素は、その地殻中の存在量が 0.03%で全元素中 17 位にあり、また、ハロゲンの中では最も豊富な元素である。しかし、天然有機化合物中にフッ素を含有するものは、二次代謝物としてわずか十数種のみ存在するだけであり(図１)、その他のハロゲンを有する天然物が約 3000 種確認されているのと対照的である[1)]。

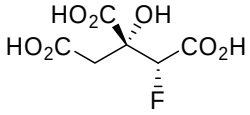
図１　含フッ素天然物



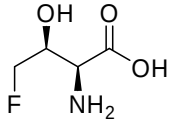
fluoroacetic acid



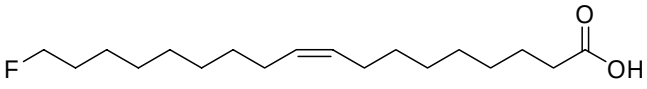
fluoroacetone



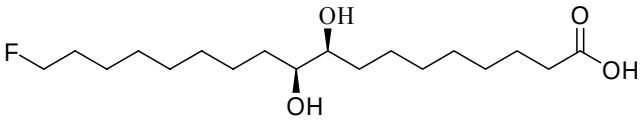
(2*R*, 3*R*)-2-fluorocitrate



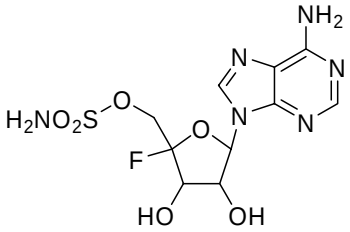
4-fluorothreonine



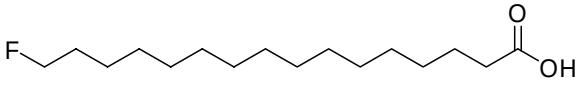
ω-fluorooleic acid



threo-18-fluoro-9,10-dihydroxystearic acid



4´-fluoro-5´-*O*-sulfamoyladenosine



ω-fluoropalmitic acid

そのため、生体にとってフッ素を含有する化合物は「未知物質」としてみなすことができる。さらに、生理活性物質中にフッ素を導入すると、立体的な変化は比較的少ないにも関わらず、電子的性質や脂溶性等の物性が大きく変化し[2)]、薬理学的あるいは薬物動態学的性質に大きな影響を与える[3)]。これらの理由から、現在では医薬、農薬等に関連する生理活性物質の研究において、含フッ素化合物が極めて重要な役割を担うようになっている[4)]。

生理活性物質にフッ素原子およびフッ素を含む原子団を導入すると、一般に次のような効果が期待できる。

① ミミック効果　（擬似効果）

フッ素原子のファンデルワールス半径は水素に次いで小さい。このため生体は、水素原子をフッ素で置き換えた擬似生体分子を、元の分子と区別することなく取込む[1b)]。

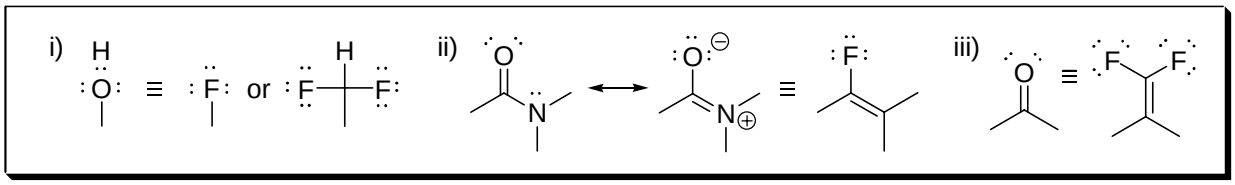
② 疎水性効果

フッ素原子の最外殻電子は、その原子核に強く引き付けられているため、分子間相互作用を受けにくい。そのため、含フッ素化合物の溶解度は水、炭化水素に対して共に低下することが知られている[5)]。生体関連物質にフッ素を導入すると、元の化合物と異なる水相－油相分配挙動を示すようになる[6)]。多くの場合において、相対的に脂溶性が高くなり生体へ吸収され易く、同時に排出が抑制される。このため創薬においては、薬効を物理的に変化させることが可能となる。

③ バイオイソスター

フッ素原子およびフッ素含有原子団は、その立体構造および非共有電子対を含む最外殻の電子構造がヒドロキシ基やアミド基等と類似しており、バイオイソスターとみなせる（図 2）。フッ素の非共有電子対は水素結合能を有しており、また、生体内のレセプターの多くは官能基の水素結合により生理活性物質を受容していることから、これらのバイオイソスターを含む化合物に同様の役割を期待できる。

図 2　バイオイソスター



④　ブロック効果

炭素－フッ素結合は、その結合エネルギーが炭素－炭素結合と比較して大きく、切れにくいことが知られている。また、フッ素の電子求引効果により酸化は抑制される。これらを利用すると、フッ素を導入することにより生体内での代謝を抑えることができる。例えば、生理活性物質に含まれるフェニル基にフッ素原子もしくはトリフルオロメチル基を導入すると、これが生体内でのフェノール等への代謝を阻害するため、排出を抑制することができる[7)]。その例として、抗マラリア活性を有する dihydroartemisinin 誘導体を図３に示す。

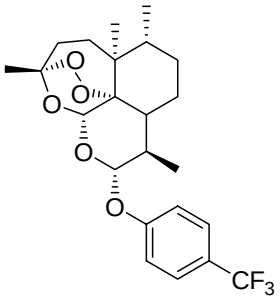


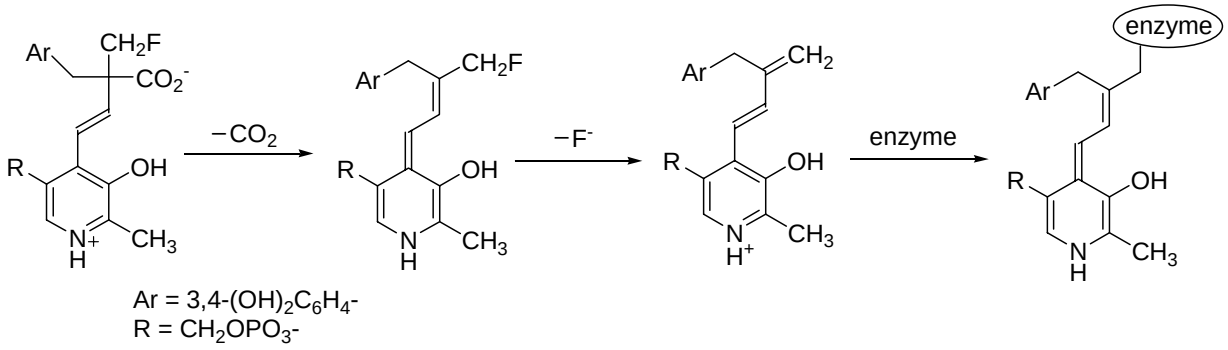
図３

⑤　電子求引性

フッ素は希ガスを除く全元素中で最大の電気陰性度を持ち、フッ素原子およびフッ素含有原子団は強力な電子求引効果を示す。近傍にアミノ基、ヒドロキシ基、カルボキシ基が存在すると塩基性度の減少や酸性度の増加が起こるため、レセプターとの親和性を調節することができる[8]。

⑥　脱離能

フッ素は、フッ化物イオンとしての脱離能を有する。式１に示すフルオロメチル基を有する化合物は、この脱離能を利用した酵素阻害剤である[9]。代謝により脱炭酸が進行するとフッ素原子が脱離基として作用し、求電子性に富んだメチレン中間体を生成する。この中間体が酵素の求核部位を不可逆的に捕捉することで阻害活性を発現する。



(1)

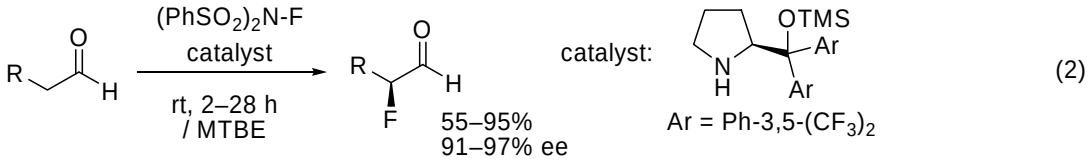
以上、含フッ素化合物と生理活性の関連について紹介してきたが、フッ素置換基により生理活性を発現・増大させるには、分子の特定の位置へフッ素を導入することが重要であり、そうした合成技術が必要不可欠であることが分かる。位置選択的にフッ素化された化合物の合成法として種々の手法が開発されているが、大別すると(ⅰ)フッ素化試薬を使用する手法と(ⅱ)含フッ素炭素置換基を有する小分子を使用する手法（ビルディングブロック法）の二つになる。

フッ素化試薬には、以下に示す求電子的および求核的なものがある[10]。

①　求電子的反応

フッ素ガス(F_2)を用いる反応により、C－H 結合を C－F 結合に置き換えることが可能である。ただし、ラジカル反応であり、F_2 の持つ高エネルギーおよび C－F 結合の安定性のために多量のエネルギ

ーが放出され、位置選択的な反応は困難である[11]。F_2の高い反応性を避けることを目的として、他の元素にF_2を反応させて調製したフッ素化物$FClO_3$[12]、XeF_2[13]、CF_3OF、$CsSO_4F$[14]を使用する方法が開発されている。また、N－F 結合を有する化合物は立体選択的なフッ素化にも有効であり、カルボニル化合物のα位への不斉フッ素化等が報告されている(式２)[15]。これらのフッ素化反応は、一電子移動を伴って進行すると考えられ、F^+種は関与していないとされている[15e]。



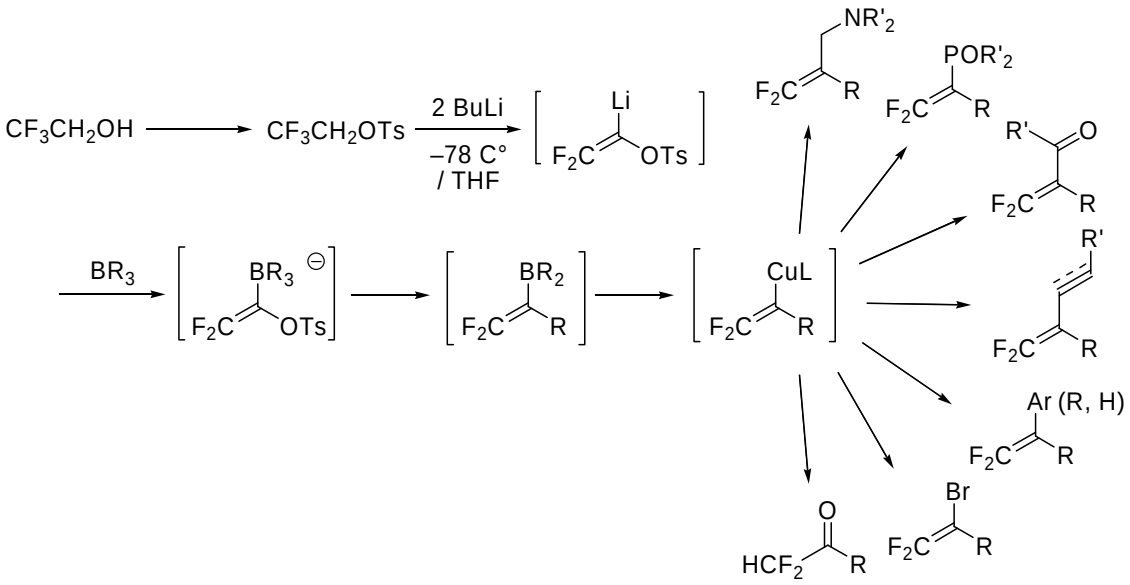
(2)

② 求核置換反応

従来より HF、SF_4、KF、*n*-Bu_4NF (TBAF)等が求核的フッ素化に使用されている。HF、SF_4は、毒性や腐食性が高く、実験室レベルで扱うことは困難であり[10]、実験室的には HF－pyridine、TBAF が使用される[16]。

芳香族化合物にフッ素原子を導入する手法としては、Balz－Schiemann 反応が古くから知られている[17]。また、電子求引性置換基を有する芳香族塩素およびニトロ化合物には、KF、CsF 等でフッ化物イオンを求核的に作用させるとフッ素原子を導入することができ、それぞれ Halex 反応、脱ニトロフッ素化反応として知られている[10]。Balz－Schiemann 反応ではジアゾニウム塩に爆発性があり、また、Halex 反応や脱ニトロフッ素化反応では高温条件が必須となる等の問題点がある。ただし、最近になって、無水の TBAF を用いることにより室温下で Halex 反応、および脱ニトロフッ素化反応を行う手法が報告された[18]。また、*S*-adenosylmethionine と KF から 5'-フルオロアデノシンを生成する酵素も発見され、発酵法による含フッ素化合物合成への道が開ける可能性もある[19]。

上記の求電子的、求核的手法のいずれも、反応の多様性に欠けることから合成手法としての応用例は限定されている。更に、フッ素化試薬による合成は一般に反応器具や反応条件に特殊なものを必要とし、また、官能基を有する基質には適さないことが多い。こうした状況の中で、あらかじめフッ素原子を含んだ小分子を用いるビルディングブロック法が研究され発展してきた[20]。この方法論を用いると、従来の有機合成化学の手法を組み込んで合成経路を設計できる。従って、ビルディングブロック法では一つの基本ユニットから多種の化合物を得ることができる。例えば、当研究室においては入手容易なトリフルオロエタノールからジフルオロビニル金属種を調製し、これを鍵中間体に様々な置換ジフルオロビニル化合物へ合成する手法を開発している(式 3)[21]。



(3)

含フッ素ビルディングブロックは、一次工業製品であるフロンやフッ素系樹脂用モノマー等より誘導されることが多く、多数のものが安価に供給されている。現在用いられている含フッ素ビルディングブロックを、炭素数で分類し表１にまとめる[10,20]。

表１ 含フッ素ビルディングブロック

炭素数	ビルディングブロック
C-1	$CHClF_2$ (HCFC-22) CH_2F_2 (HFC32) CBr_2F_2 (FC-12B2) CF_3SiMe_3
C-2	CF_3CCl_3 (FC-113a) CF_3CHCl_2 (HCFC-123) $CClF_2CCl_3$ (FC-112)
	$CF_3CHBrCl$ (FC-123B1) $CF_3CH_2F_2$ (HFC-134a) CF_2=CClF (FC-1113)
	CF_3CH_2OH CHF_2CHO CF_3CHO
	CF_3CO_2H CHF_2CO_2H CH_2FCO_2H CXF_2CO_2H (X=Cl,Br)
C-3	CF_3CH=CH_2 CF_3CF=CF_2 fluoroacetones
C-4	CH_2=$CH(CF_3)CH_2SiMe_3$ CH_2=$C(CF_3)CO_2H$ CF_3CH=$CHCONH_2$

含フッ素一次工業製品のほとんどは C-1～C-3 の小分子である。C-4 以上の含フッ素化合物は、一次工業製品を増炭して合成することが多く、より高価なものとなる。近年フロンガス規制の影響から、特に C-1 化合物に関しては国内で入手困難なものも増加しており、主要ビルディングブロックは C-1 から C-3 以上の化合物へ移行しつつある。従って現在では、C-3 以上の新規ビルディングブロックの

開発と応用展開が、フッ素化合物合成における重要な課題の一つとなっている。

このような背景のもと、筆者は、フッ素を有するビルディングブロックの反応性、特にフッ素の性質を十分活用することによって、そのビルディングブロックに特徴的な合成反応を開発することに研究の目標を置いた。そこで、含フッ素 C-3 ユニットの一つとして 3,3,3-トリフルオロプロプ-1-エン-2-イル基を有する化合物(以後 1-(トリフルオロメチル)ビニル化合物と呼ぶ)に着目した。このユニットは、その反応性を考える上で次の特徴がある。

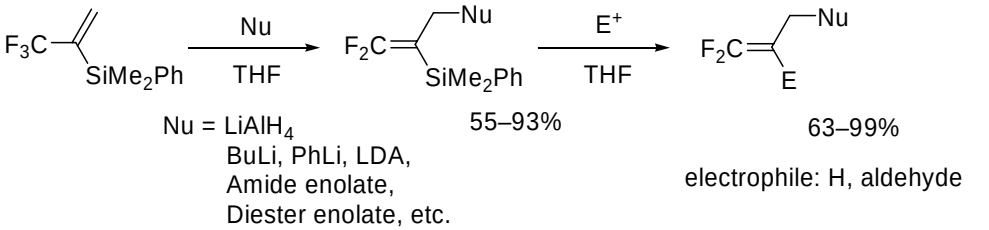
① 求電子性の高い末端アルケンを有する。

② アリル位に脱離基として作用するフッ素原子を有する。

③ α-アニオンを安定化するトリフルオロメチル基を有する。

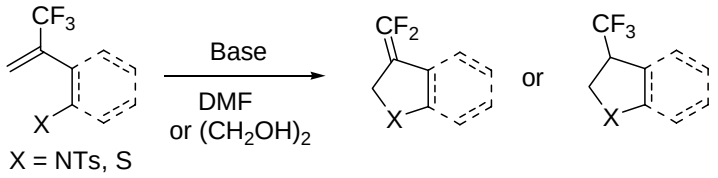
このため、(トリフルオロメチル)ビニル化合物がフッ素の特徴を生かした反応開発に適する基質と考えた。ここで、この(トリフルオロメチル)ビニル化合物に関する既知反応を紹介する。

(トリフルオロメチル)ビニル化合物に対して S_N2'型の求核反応が進行すると、ジフルオロメチレン基を有する化合物を生成する[22]。生成物に組み込まれるジフルオロメチレンユニットはカルボニル基のミミックとなるほか、更に様々な反応へ応用することが可能であり、複雑な含フッ素化合物へ誘導することもできる[23]。しかし、この S_N2'型反応に使用可能な求核種はアルキルリチウム等の反応性の高いものであり、合成反応としての応用が限られていた。当研究室では、1-(トリフルオロメチル)ビニルシリル化合物を開発し、その S_N2'型反応により各種ジフルオロビニル化合物を得ている(式 4)[24]。ここでは、トリフルオロメチル基とシリル基の二つのα-アニオン安定化効果によりビニル末端炭素の求電子性が増し、反応性の低いアミドエノラート等とも反応する。得られた(ジフルオロビニル)シリル化合物は更に求電子剤との反応により、二置換ジフルオロビニル化合物へ導かれる。



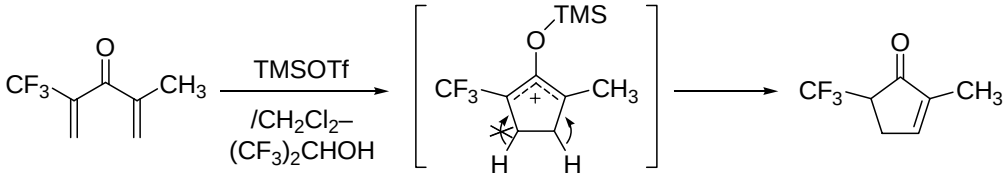
(4)

一方、(トリフルオロメチル)ビニル基への求核付加反応を分子内反応に応用すると、分子間では反応例のないヘテロ求核種によっても S_N2'型反応が進行することを見出している。これを応用することで通常では困難な 5-*endo-trig* 環化[25]に成功し、含フッ素炭素置換基を有する種々のヘテロ環の構築法を開発している(式 5)[26]。プロトン源存在下では付加反応が優先し、また、プロトン源がない場合には、トリフルオロメチル基上のフッ素の脱離を伴って、ジフルオロメチレン基に変換される。これにより、2 種の含フッ素炭素置換基をもつ化合物を作り分けることができる。



(5)

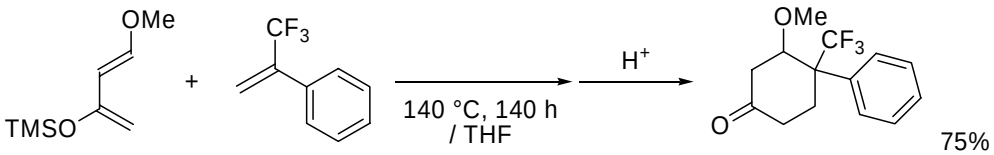
CF_3基は電子求引性基であるため、CF_3基のα位にはカチオンが生成し難い。このことを利用して、(トリフルオロメチル)ビニル基を有する不飽和ケトンの Nazarov 環化反応で、生じる二重結合の位置を制御して生成物を得ている(式 6)[27]。



(6)

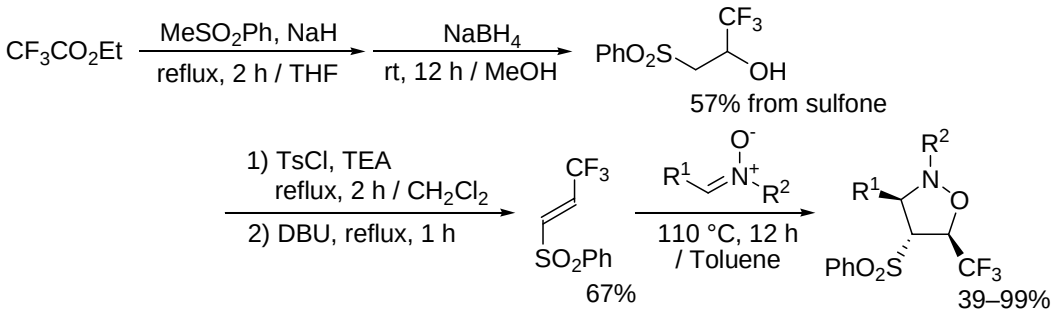
また、トリフルオロメチル基を有するアルケンには、その強力な電子求引性の誘起効果によるπ電子の偏り、LUMO エネルギーレベルの低下が起こる [28,29]。通常、付加環化反応における dienophile や 1,3-dipolarophile 等には、共鳴効果を有する電子求引性の置換基が導入されている。トリフルオロメチル化されたアルケンは、これらの置換基を有するアルケンと同等かそれ以上の反応性を示すことが知られている。以下に反応例を示す。

トリフルオロメチルスチレンは Danishefsky ジエンと反応し、第四級炭素上にトリフルオロメチル基を有する化合物を与える(式 7)[28]。



(7)

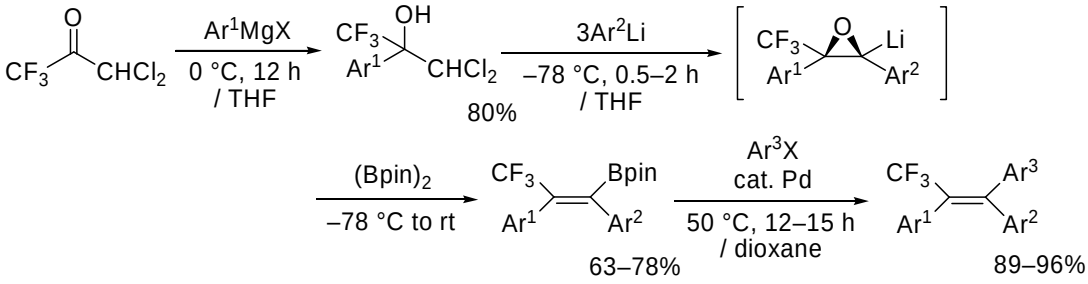
対応するα-メチルスチレンでは同様の反応が進行しないことから、トリフルオロメチル基の強力な電子求引性により LUMO エネルギーレベルが低下し、反応性が向上したものと見ることができる。また、1,3-双極子を用いた(トリフルオロメチル)ビニル化合物の付加環化反応でも、良好な結果が得られている。例えば、トリフルオロ酢酸から誘導されたトリフルオロプロペニル=スルホンはニトロンとの双極子付加反応に使用され、イソオキサゾリンが得られている(式 8)[30]。



(8)

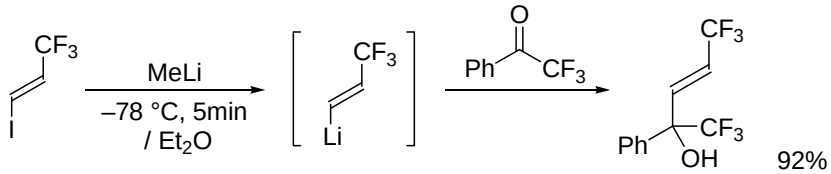
以上述べたように、(トリフルオロメチル)ビニル基を有する化合物は様々な反応性を示し、高度な含フッ素化合物の構築に有望な化合物群である。次に、既存の(トリフルオロメチル)ビニル化合物の合成法に関して、以下に概観する。

Hiyama は C-3 のビルディングブロックから多置換の(トリフルオロメチル)ビニル化合物の合成を報告している[31]。工業原料である 3,3-ジクロロ-1,1,1-トリフルオロアセトンから誘導されるリチオオキシランを経由し、三種の異なるアリール基を特定の位置へ導入した四置換オレフィンが生成する(式 9)。

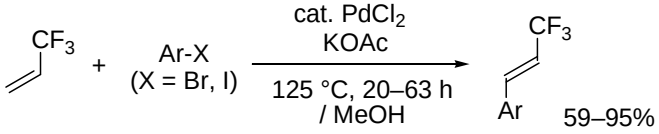


(9)

(トリフルオロメチル)ビニル基の末端における炭素－炭素結合形成は、(3,3,3-トリフルオロプロプ-1-エン-1-イル)リチウムと求電子剤の反応(式 10)[32]、もしくは 3,3,3-トリフルオロプロペンとハロゲン化アリール等との Heck 反応により達成されている(式 11)[33]。

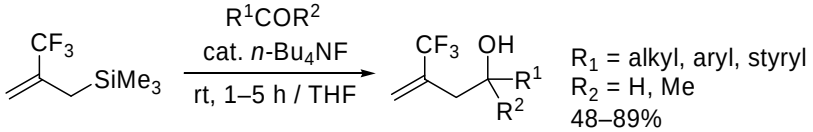


(10)

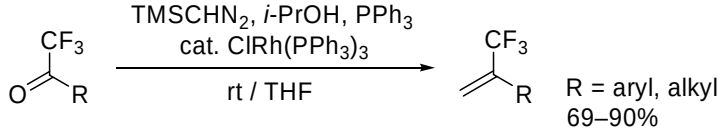


(11)

また、C-3 以外のビルディングブロックである 2-(トリフルオロメチル)アリルシランやトリフルオロ酢酸エステルを使用して、1-(トリフルオロメチル)ビニル化合物の合成が行われている(式 12,13)[23,34,35]。しかし、これらは出発物質の調製や反応に複数の工程を必要とする。

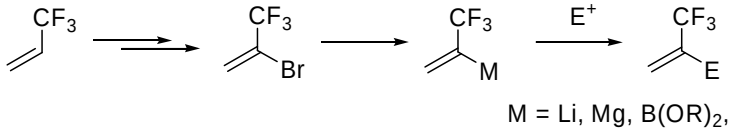


(12)



(13)

一方、1-(トリフルオロメチル)ビニルユニットを導入する手法としては、対応する C-3 の(3,3,3-トリフルオロプロプ-1-エン-2-イル)金属を用いるのが最も簡便な手法(式 14)と考えられる [20,36]。



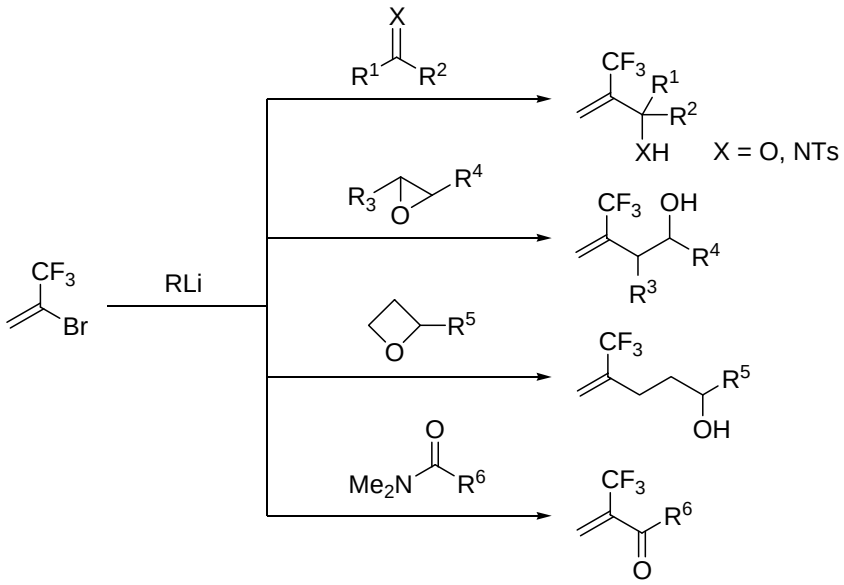
(14)

このビニル金属化合物は、対応する臭化物のハロゲン－金属交換反応等により調製される。2-ブロモ-3,3,3-トリフルオロプロペンは、工業原料である 3,3,3-トリフルオロプロペン [37]の臭素化－脱臭化水素化により得られる [36a]。これらのうち、Sn、B、Zn 化合物等はハロゲン化物とのカップリング反応に使用されるが、反応性の高い Li、Mg 化合物の場合はβ-脱離を起こし易く熱的に不安定であり、取り扱いが困難である。そのため、1-(トリフルオロメチル)ビニルユニットを使用した sp^2C－sp^3C 結合形成の例は極めて数が限られており、また、高い基質依存性や低収率等の問題が残されている [36a]。特にカルボニル化合物、オキシラン等の脂肪族化合物への付加反応が未解決であり、新たな手法の開発が望まれている。

上で述べたように、C-3 ビルディングブロックの 1-(トリフルオロメチル)ビニルリチウム(式 14)は当該置換基を脂肪族化合物に直接導入可能であるが、不安定なため取り扱いは困難であり、応用例は少ない。そこで、このリチウム種を利用した 1-(トリフルオロメチル)ビニル基の導入に関して詳細な検討を行い、合成手法として有効に利用することを試みた。

まず第一章では 1-(トリフルオロメチル)ビニルリチウムを使用した合成反応について述べる。2-ブロモ-3,3,3-トリフルオロプロペンに低温下で *s*-BuLi を作用させ、リチウム－ハロゲン交換により当該リチウム化合物を速やかに調製し、反応性の高いアルデヒドもしくは *N*-トシルイミンとの反応を行っ

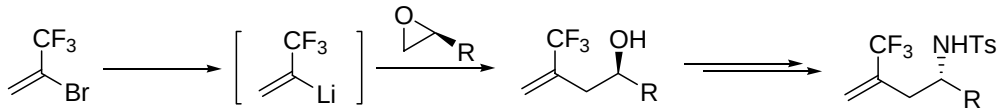
たところ、2-(トリフルオロメチル)アリルアルコールおよびアリルアミドが良好な収率で得られた。このリチウム－ハロゲン交換反応において *n*-BuLi を用いると、低温では反応が遅く、系内はビニルリチウムと *n*-BuLi の混合物となる。しかし、この混合物に適度な反応性を有するオキシラン、オキセタンあるいは *N,N*-ジメチルアミド等の求電子剤を加えると、ビニルリチウムのみが効率良く捕捉され、対応する(トリフルオロメチル)ビニル基を有する種々のアルコールおよびα-トリフルオロメチル-α,β-不飽和ケトンがそれぞれ収率良く得られた(式 15)。



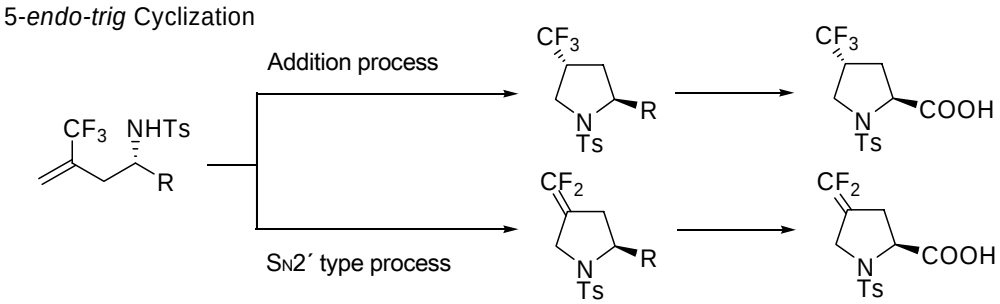
(15)

第二章では、第一章において見出した 1-(トリフルオロメチル)ビニルリチウムと光学活性オキシランの反応で得られる含フッ素光学活性アルコールを用いた、求核的 5-*endo-trig* 環化を鍵反応とする含フッ素光学活性プロリンの合成について述べる(式 16)。環化前駆体となる *N*-(3-トリフルオロメチルホモアリル)スルホンアミドを塩基で処理すると、付加反応あるいはフッ素化物イオンの脱離を伴う S_N2'反応が進行し、収率良く 5 員環ピロリジン骨格を構築できた(式 17)。これにより、CF_2=基、CF_2H 基、CF_3 基の各フルオロ炭素置換基を 4 位へ選択的に導入した光学活性プロリン誘導体を合成することができる。

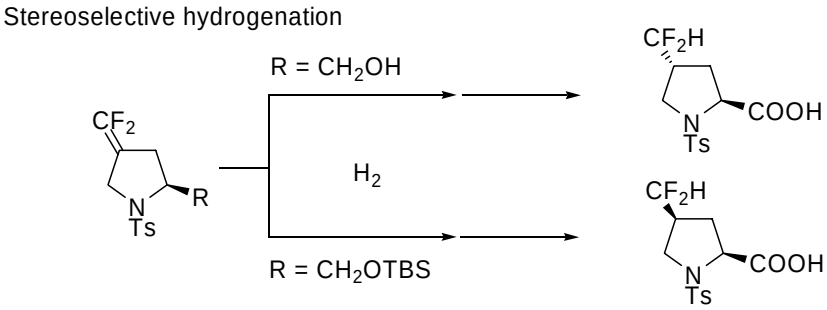
(Trifluoromethyl)vinylation of optically active oxirane



(16)

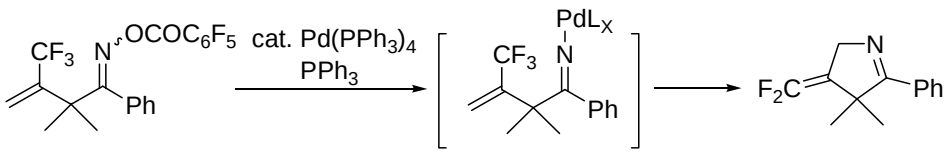


(17)



(18)

また、フッ素含有原子団に特徴的な合成反応の開発として、(トリフルオロメチル)ビニル基を利用した新規反応の探索を行い、(トリフルオロメチル)ビニルリチウムとオキシランとの反応から誘導した *O*-アシルオキシム誘導体の Heck 型環化反応を見出した（第三章)。式 19 における *O*-アシルオキシムに対してパラジウム触媒を作用させると、酸化的付加により N－Pd 種が生成し、続いて分子内アルケン挿入が進行する。環化様式は C－Pd 結合へのアルケン挿入で一般に困難とされる 5-*endo* 型であるが、1-(トリフルオロメチル)ビニル基の効果によりピロリン環の構築が可能になった。さらに、生成した２価のパラジウムをトリフェニルホスフィンで還元することにより、反応を触媒化することもできた。



(19)

以下本論において、それぞれの内容について詳細に述べる。

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MP2 6-31G*	Me	F_3C	O=C(OMe)
E (kcal/mol)	-73704.5	-260129.0	-191725.6
LUMO (eV)	5.1	3.7	2.8
HOMO (eV)	-9.6	-11.2	-10.6

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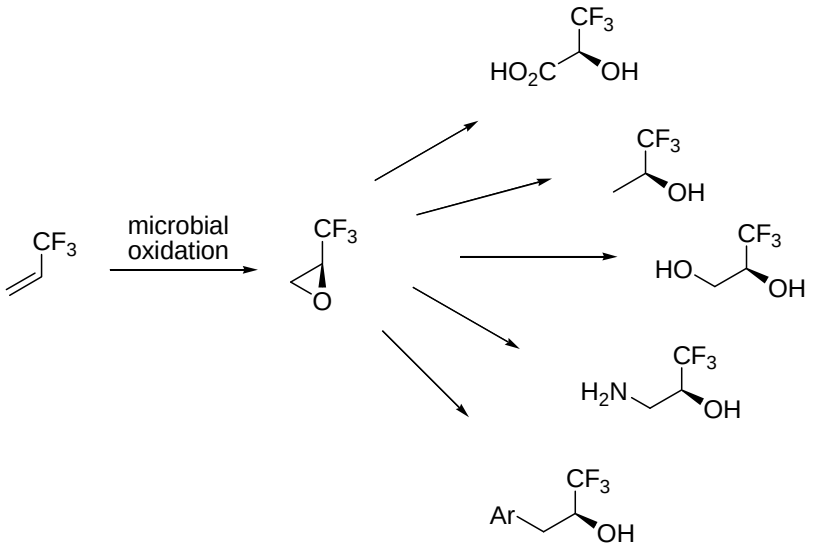
第一章 トリフルオロメチルビニルリチウムを利用するトリフルオロメチルビニル化合物の合成とその応用

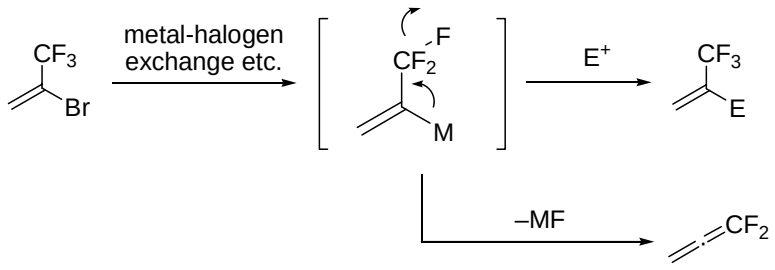
緒言

序論で述べたように、(トリフルオロメチル)ビニル化合物はその多様な反応性に興味が持たれ、合成化学的にも有用性の高い化合物である。例えば、トリフルオロプロペンを不斉エポキシ化して合成される 3,3,3-トリフルオロプロペンオキシドは、式 1 に示すように様々な化合物へと誘導することができ、トリフルオロメチル化合物の有用な合成手法となっている[1)]。



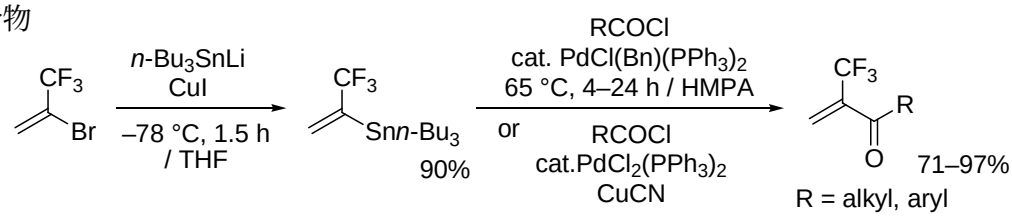
(1)

1-(トリフルオロメチル)ビニル化合物の合成法はいくつか知られているが、C-3 ユニットとして 1-(トリフルオロメチル)ビニル基を一挙に導入する方法が最も簡便と考えられる。各種金属化合物が 2-ブロモ-3,3,3-トリフルオロプロペンから調製され、(トリフルオロメチル)ビニル化合物合成に用いられている。ただし、これら金属化合物は本質的にβ位のフッ素原子の脱離を伴って 1,1-ジフルオロアレンへ分解し易く、特にイオン性の高い金属－炭素結合を有するものは極めて不安定である(式 2)。そのため、使用されるのは比較的安定な 1-(トリフルオロメチル)ビニル金属化合物に限られる。以下にその調製法、及びカップリング反応への応用例を示す。



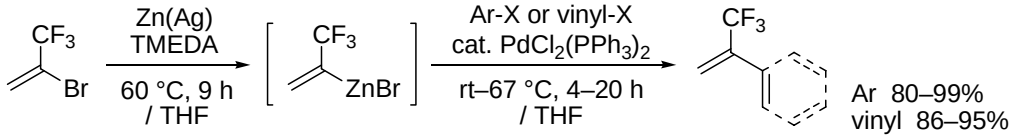
(2)

スズ化合物



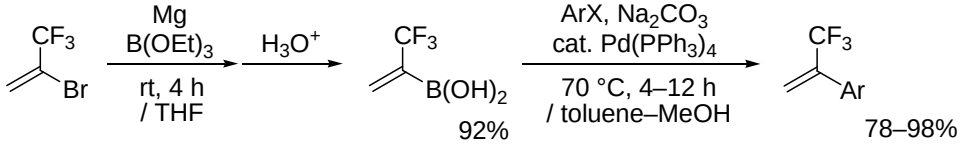
(3)

亜鉛化合物



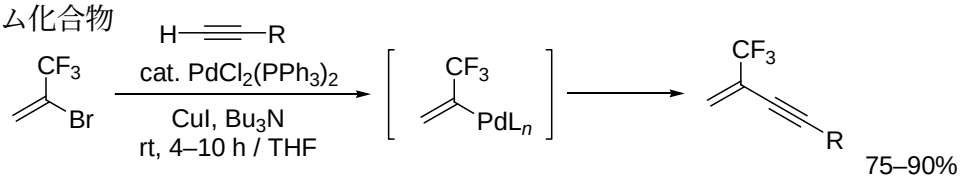
(4)

ホウ素化合物



(5)

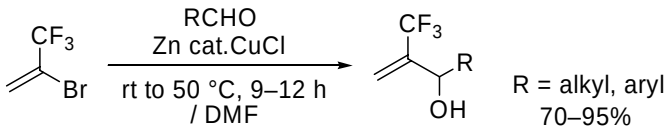
パラジウム化合物



(6)

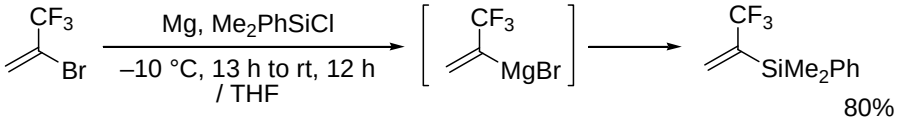
2-ブロモ-3,3,3-トリフルオロプロペンとビス(トリアルキル)銅アート錯体との反応により、1-(トリフルオロメチル)ビニルスズ化合物が合成されている。得られたビニルスズ化合物は、種々のカルボン酸塩化物との Stille カップリング反応により、α-トリフルオロメチル-α,β-不飽和ケトンを生成する(式 3)[2]。また、1-(トリフルオロメチル)ビニル亜鉛化合物は TMEDA 存在下、Zn(Ag)で処理すると調製できる [3]。これは、溶液中室温下でも安定であり、パラジウム触媒を用いるとハロゲン化ビニルおよびハロゲン化アリールとカップリングする(式 4)。対応するホウ素化合物は Grignard 試薬を系内のホウ酸エステルで捕捉することにより合成・単離され、これを使用した Suzuki カップリングが報告されている(式 5)[4]。その他に、パラジウム触媒を用いる Sonogashira 反応等も報告されている(式 6)[5]。

一方、(トリフルオロメチル)ビニル金属化合物のカルボニル化合物への付加反応は、上述したカップリング反応と比較して少ない。亜鉛を用いた Barbier 型の反応が報告されており、アルデヒドへ付加して収率良くアリルアルコールを生成する(式 7)[6]。ただし、アルデヒドの共存下で金属種の発生を行う必要があり、あらかじめ調製した亜鉛化合物はアルデヒドとは反応しない。また、ケトンとの反応に関する報告例はない。



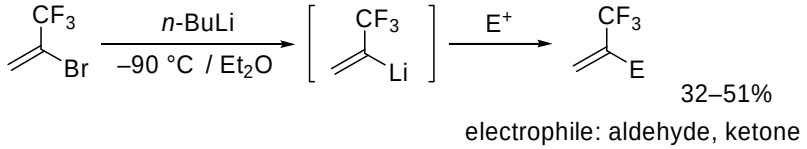
(7)

イオン結合性の高い金属化合物である 1-(トリフルオロメチル)ビニルリチウムやマグネシウム化合物は熱的に極めて不安定であり、反応例は限定されている。Jiang は、2-ブロモ-3,3,3-トリフルオロプロペンの Grignard 試薬がホウ素化合物の合成に使用できることを報告しているが、この Grignard 試薬は不安定で保存することができず、求電子剤の存在下で調製を行う必要がある(式 5)[4]。当研究室では同様の手法で 2-(ジメチルフェニルシリル)-3,3,3-トリフルオロプロペンを合成している(式 8)[7]。また、求電子剤として塩化スズを使用しても同様に反応が進行し、ビニルスズ化合物が簡便に合成できることを確認している [8]。ただし、この手法では求電子剤に制約があり、例えばアルデヒドとの反応を試みたが、付加生成物を得ることはできなかった [9]。



(8)

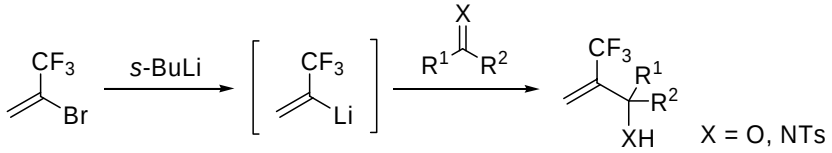
Tarrant は対応するリチウム化合物を、リチウム－ハロゲン交換によって調製している [10]。一般に有機リチウム化合物は反応性が高く、様々な求電子剤と反応する。しかし、1-(トリフルオロメチル)ビニルリチウムは－78 ℃においても不安定であり、さらに低い－90 ℃で調製、使用する必要がある(式 9)。アルデヒド、ケトン等の求電子剤と反応させているが、収率は 30－50%と低く、また、求電子剤と *n*-BuLi を少量ずつ交互に臭化ビニルに加えるという煩雑な操作が必要である。



(9)

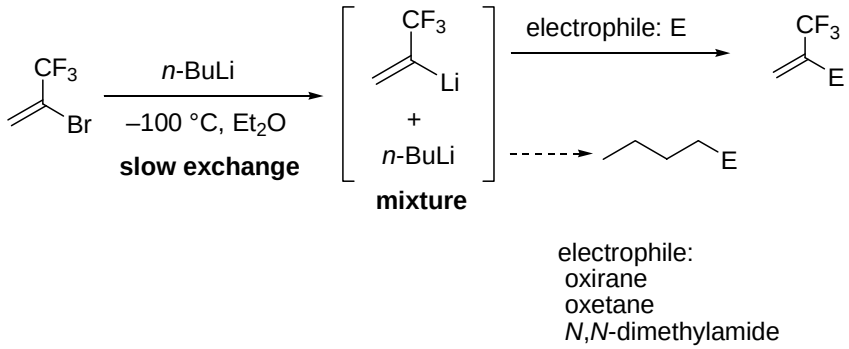
上述したように、C-3 ビルディングブロックである 1-(トリフルオロメチル)ビニル金属種を用いた炭素－炭素結合形成反応のうち、カップリング反応による sp^2C－spC あるいは sp^2C－sp^2C 結合形成はある程度確立されているが、付加反応もしくは置換反応による sp^2C－sp^3C 結合形成反応の例は少なく、高い基質依存性や低収率等の問題も残されている。そのため、1-(トリフルオロメチル)ビニル基を持つ脂肪族化合物を直接合成する手法の開発が望まれる。そこで筆者は、式 9 に示したリチウム化合物を利用する 1-(トリフルオロメチル)ビニル基の導入法を、あらためて詳細に検討することとした。

まず、ビニルリチウム化合物の発生法に関して詳細な検討を行ったところ、*n*-BuLi に換えて *s*-BuLi を使用することで、低温においてもリチウム－ハロゲン交換が速やかに進行することがわかった。式 10 に示すように、得られたビニルリチウムにアルデヒドおよび *N*-スルホニルイミンを反応させると、良好な収率で目的のアリルアルコールおよびアミドを得ることができた(第一節)。



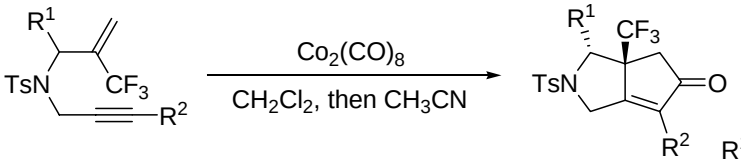
(10)

この手法では、ビニルリチウムの分解と競争的に反応を行う必要があるため、比較的反応性の高い求電子剤を必要とする。そこで、*n*-BuLi を用いるリチウム－ハロゲン交換反応の検討を行ったところ、低温においては交換が遅いため *n*-BuLi と 1-(トリフルオロメチル)ビニルリチウムの混合物となるが、ここに適度な求電子性の化合物を共存させると、ビニルリチウムと *n*-BuLi の会合度に由来する反応性の違いを利用することにより、ビニルリチウムのみが選択的に反応して目的とする(トリフルオロメチル)ビニル化合物を効率良く得ることができた(式 11)。ビニルリチウムの反応に関して、第二節では、オキシランおよびオキセタンを求電子剤として用いた 1-(トリフルオロメチル)ビニル基を有するアルコールの合成について、また、第三節では、カルボン酸ジメチルアミドを用いたα-トリフルオロメチル-α,β-不飽和ケトンの合成に関して述べる。



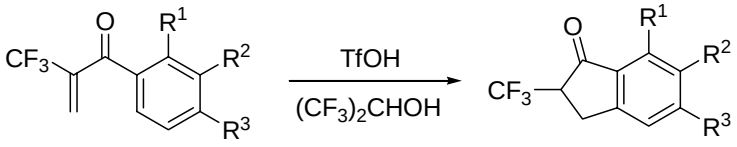
(11)

続いて、これらの反応で得られた(トリフルオロメチル)ビニル化合物を用い、様々な含フッ素化合物合成への応用を試みた。まず、第一節において得られた 2-(トリフルオロメチル)アリルアミドを 1,6-エンインへ誘導し、Pauson－Khand 反応を適用することで、核間にトリフルオロメチル基を持つ縮環化合物を得ることができた(式 12)。また、第三節において得られたα-トリフルオロメチル-α,β-不飽和ケトンを用い、Nazarov 環化によるα-(トリフルオロメチル)インダノン類の合成を行った(式 13)。以上、2 つの合成法を第四節で述べる。



R^1 = Ph, *n*-Pr
R^2 = H, Et

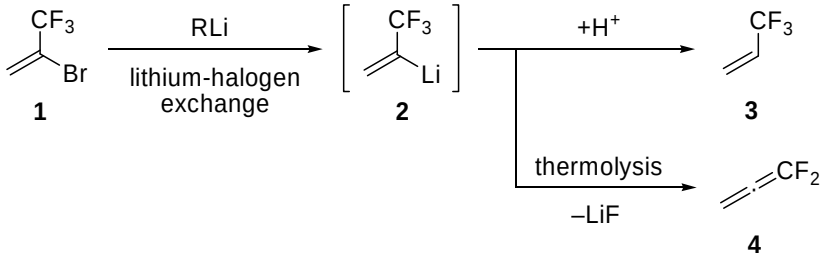
(12)



(13)

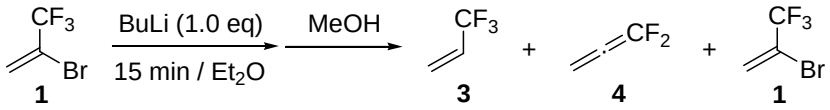
第一節　2-(トリフルオロメチル)アリルアルコール **5** およびアミド **8** の合成

まず、2-ブロモ-3,3,3-トリフルオロプロペン **1** とアルキルリチウムのリチウム－ハロゲン交換反応を詳細に検討し、1-(トリフルオロメチル)ビニルリチウム **2** の調製法の確立を図った。緒言にも述べたようにビニルリチウム **2** は熱的に不安定で、β-フッ素脱離による 1,1-ジフルオロアレン **4** への分解が予想された(式 14)。



(14)

エーテル中、温度を変えて臭化ビニル **1** にアルキルリチウムを作用させ、15 分後に反応を停止して、生成する化合物を ^{19}F NMR 測定により定量した。結果を式 15 および表 1 に示す。*n*-BuLi を用い－78 ℃で処理すると、δ_F = 56 ppm (t)、94 ppm (s)、96 ppm (d)にピークが観察され、文献値および標品との比較からそれぞれ 1,1-ジフルオロアレン **4**、原料の臭化ビニル **1**、3,3,3-トリフルオロプロペン **3** と同定された [11]。ここで、ジフルオロアレン **4** が 54%生成しており、LiF の脱離が進行したことがわかった。また、プロペン **3** が 20%生成したことから、ビニルリチウム **2** は 20%存在していたことになる。－105 ℃まで温度を下げるとビニルリチウム **2** の分解を防ぐことはできたが、同時にハロゲン－リチウム交換も遅く、原料 **1** が 76%回収された。*n*-BuLi を使用したリチウム－ハロゲン交換は、ビニルリチウム **2** が比較的安定に存在する温度では進行が遅く、効率的に **2** を発生させることは困難と考えられる。一方、*s*-BuLi を作用させると、－105 ℃においても 90%の **1** が消費され、ビニルリチウム **2** が 60%生成することがわかった。このとき、26%のアレン **4** が観察されたことから、合計 86%のビニルリチウム **2** が生成し、相当量の *s*-BuLi が消費されたものと考えられる。同様に *t*-BuLi を用いると、ビニルリチウム **2** とアレン **4** の合計は 85%となった。以上のことから、*s*-BuLi あるいは *t*-BuLi を用いることによりリチウム－ハロゲン交換は低温においても十分速く進行し、15 分間でほぼ完了することがわかった。また、*t*-BuLi を用いると *s*-BuLi と比較してビニルリチウム **2** の分解が若干多いことがわかった。

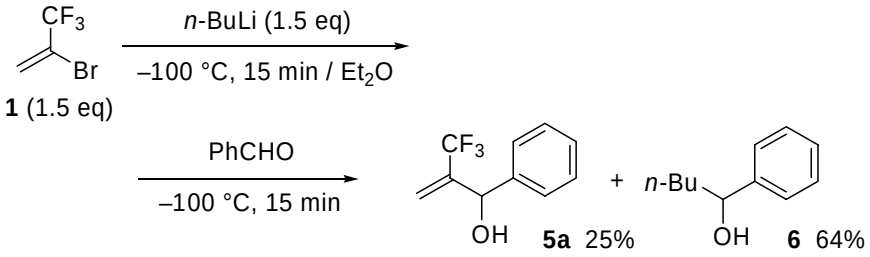


(15)

Table 1. Lithium–halogen exchange reaction of vinyl bromide **1** with RLi

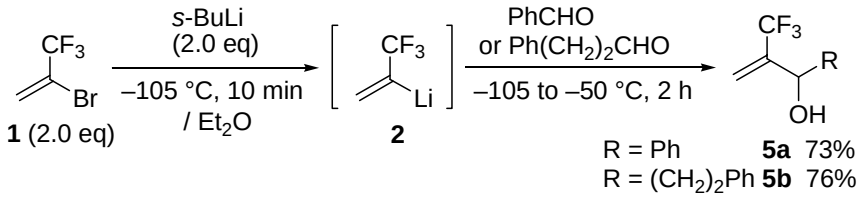
RLi	Temp.	Yield / %		
		3	**4**	**1**
n-BuLi	–78 °C	20%	54%	17%
	–96 °C	31%	11%	58%
	–105 °C	14%	1%	76%
s-BuLi	–105 °C	60%	26%	10%
t-BuLi	–105 °C	50%	35%	5%

続いて、Tarrant によって報告されたアルデヒドとの反応 [10](式９)の詳細な調査、およびリチウムーハロゲン交換反応に用いるアルキルリチウム種の比較を行うために、*n*-BuLi および *s*-BuLi によりそれぞれビニルリチウム **2** の調製を行い、ベンズアルデヒドとの反応を再検討した。Tarrant による－90 ℃よりも低い－100 ℃で反応を行ったところ、文献記載の 2-(トリフルオロメチル)アリルアルコール **5a** が 25%生成すると共に、ブチルリチウム由来の付加物 **6** が収率 64%で得られた(式 16)。ビニルリチウム **2** の分解を防ぐためにより低温で反応を行うと、リチウムーハロゲン交換反応が不十分となり、残存した *n*-BuLi が求電子剤と反応し、収率が低下したものと考えられる。



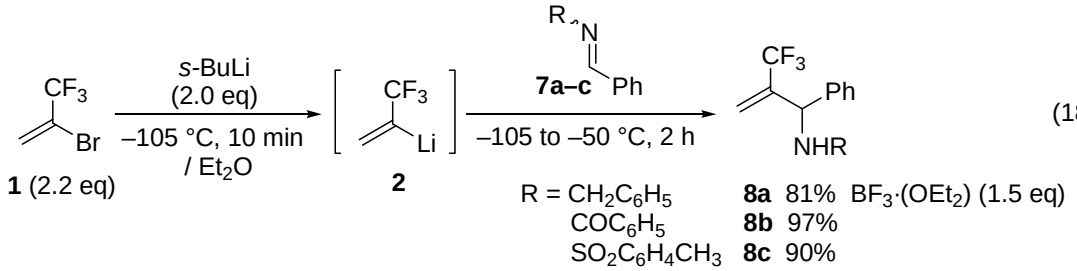
(16)

一方、*s*-BuLi を用いると、リチウムーハロゲン交換反応は－105 ℃においても、速やかに進行する。この手法でビニルリチウム **2** を発生させ、ベンズアルデヒドとの反応を試みたところ、目的とするアリルアルコール **5a** の収率を 73%まで向上させることができた(式 17)。また、アルキル基を有するアルデヒドとして 3-フェニルプロパナールとの反応を行い、対応するアリルアルコール **5b** を収率 76%で得ることができた。



(17)

ところで、アリルアミンは様々なヘテロ環化合物の合成等に使用される有用な化合物群である[12]。上述のビニルリチウム **2** に、求電子剤としてアルデヒドの換わりにイミンを反応させると、2 位にトリフルオロメチル基を有するアリルアミンが合成できることになる。なお、−105 ℃においても 15 分の調製時間に約 3 割のビニルリチウム **2** が分解してしまうので、求電子剤に対して約 2 倍モル量の臭化ビニル **1** と *s*-BuLi を用いることとした。結果を式 18 に示す。

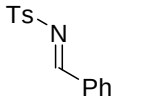
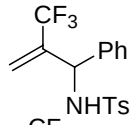
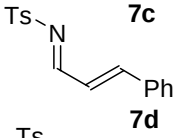
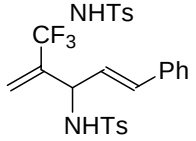
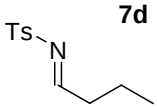
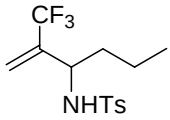
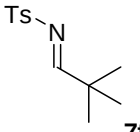
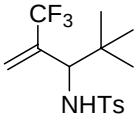
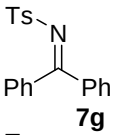
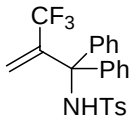
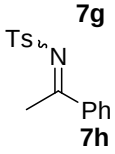


(18)

まず、ベンズアルデヒドの *N*-ベンジルイミン **7a** との反応を試みたが、反応は進行せず、原料が回収された。そこで、イミンを活性化するため、ビニルリチウム **2** の溶液にイミンを加えた後に $BF_3{\cdot}OEt_2$ (1.5 倍モル量)を添加したところ、目的の 2-(トリフルオロメチル)アリルアミン **8a** を収率 81%で得ることができた[13]。さらに、より反応性の高いイミンである *N*-アシルおよびスルホニルイミン **7b**[14],**7c**[15] との反応を検討した。これらの化合物は $BF_3{\cdot}OEt_2$ による活性化を必要とせず、良好な収率で目的物 **8b**,**8c** を得ることができた。

基質の合成の容易さ、安定性、および生成物の変換の容易さを考慮し、*N*-スルホニルイミン **8c** を基質として選択し、その一般性を調べた(表 2)。

Table 2. Synthesis of [2-(trifluoromethyl)allyl]sulfonamide **8**

Entry	*N*-Tosylimine	Product	Yield / %
1	 **7c**		**8c** 90
2	 **7d**		**8d** 89
3	 **7e**		**8e** 77
4	 **7f**		**8f** 96
5	 **7g**		**8g** 76 (91)[a]
6	 **7h**	–	–

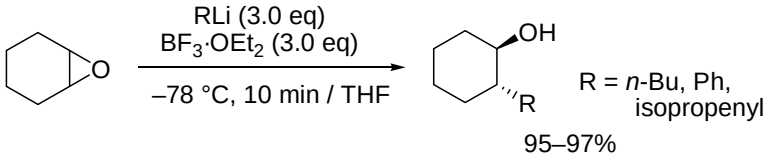
a) 2-Bromo-3,3,3-trifluoropropene (3.5 eq) and *s*-BuLi (3.2 eq) were used.

フェニル、スチリル、プロピル、*t*-ブチルアルドイミン **7c–f** との反応では、良好な収率で 2-(トリフルオロメチル)アリルアミド **8c–f** が生成した(entries 1–4)。また、ケトイミンとしてベンゾフェノンイミン **7g** との反応を試みたところ、若干収率が低下した。そこで、臭化ビニル **1** および *s*-BuLi をそれぞれ 3.5、3.2 倍モル量用い、ビニルリチウム **2** の量を増やしたところ、収率は 91%まで改善された(entry 5)。一方、アセトフェノンイミン **7h** を用いると目的物は生成しなかった(entry 6)。これはイミン **7h** のα位プロトンの酸性度が高く、脱プロトンが優先したと考えている。

以上のように、(トリフルオロメチル)ビニル基を持つ化合物の合成法に関して、これまで使用例がほとんどない 1-(トリフルオロメチル)ビニルリチウム **2** に着目し、アルデヒドや *N*-トシルイミン **7c–g** との反応を行い、良好な結果を得た。ただし、この手法では適用できる求電子剤も反応性の高いものに限定されるので、広範な求電子剤との反応を目指して、さらに検討を行った。

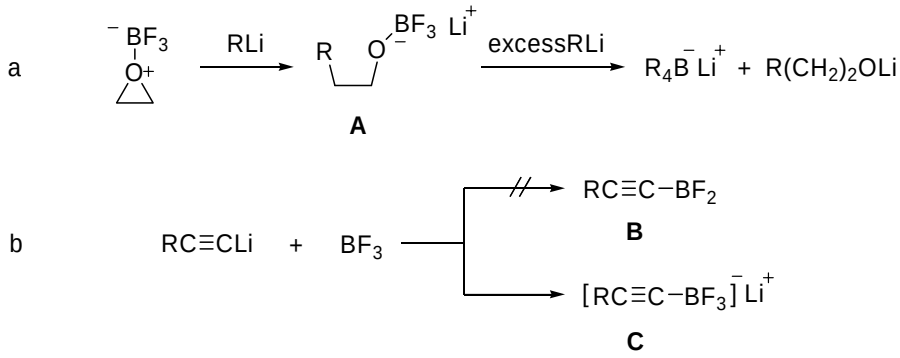
第二節　3-(トリフルオロメチル)ホモアリルアルコール **12** の合成

アルキル、ビニル、フェニルリチウムは、BF_3·OEt_2 存在下、様々なオキシラン及びオキセタンを容易に開環し、対応するアルコールを与えることが知られている(式 19)[16]。



(19)

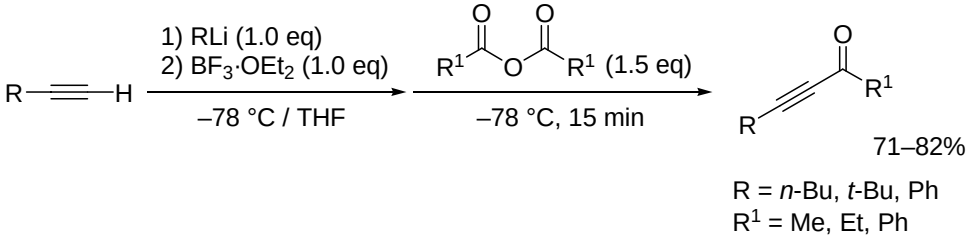
Mechanism



(20)

これらの反応では、有機リチウムと Lewis 酸である BF_3 の相互作用に関心がもたれるが、^{11}B NMR を使用した反応追跡により以下のことが報告されている。Ganem によると、アルキルリチウムと BF_3 は THF 溶媒中、−78 ℃においてそれぞれ反応することなく独立して存在し、オキシランと反応することを明らかにしている。式 20 の機構 a に示すように、エーテル酸素原子が BF_3 に配位し、それからアルキルリチウムの求核攻撃が起こり、トリフルオロボラート **A** を生成する。アルキルリチウムと BF_3 から生成すると考えられる RBF_2 や R_2BF は反応途中で観測されず、また別途調製した RBF_2 を用いても BF_3 存在下でオキシランを開環しないことが確認されている [16a]。

一方、Brown はリチウムアセチリドと酸無水物との反応を THF 中、BF_3 存在下で行い、対応するアルキノンを合成している(式 21)。^{11}B NMR 実験の結果、式 20 における機構 b に示すようにやはりアルキニルホウ素 **B** は生成せず、ホウ素アート錯体 **C** が活性種であると報告している [16b]。



(21)

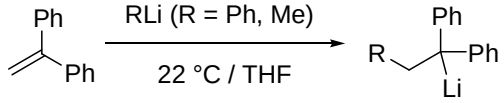
ところで、有機リチウム化合物は溶液中でクラスターを形成している。MeLi や *n*-BuLi は四量体以上に会合し易いが、ArLi は一般に 2 量体や単量体を形成する(表 3)[17]。

Table 3. Typical aggregation state of RLi

Tetrameric	Dimeric	Monomeric
MeLi	*i*-PrLi	$PhCH_2Li$
EtLi	*s*-BuLi	(ArLi)[a]
n-BuLi	*t*-BuLi	(*t*-BuLi)[a]
(*s*-BuLi)[b]	ArLi	

a) <–100°C. In THF or in TMEDA. b) In cyclohexane–TMEDA.

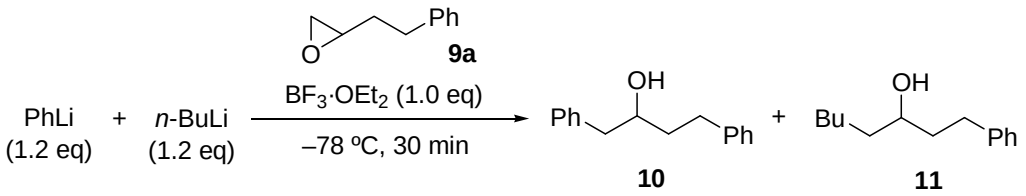
有機リチウム種の会合状態は反応性に影響し、まれにその塩基性度から予想され序列とは逆の反応性を示すことも知られている [18]。つまり、会合状態の差を利用することによって、sp^3 炭素リチウム化合物より sp^2 炭素リチウム化合物が高い反応性を示すこともある。例えば Waack は 1,1-ジフェニルエチレンへの有機リチウム化合物の付加反応速度に関して報告している。MeLi と PhLi では MeLi の方が高い塩基性度を示すが、当付加反応では濃度 0.5 M において PhLi の方がより高い反応性を示す(式 22)。



c	[0.05 M]	[0.5 M]
k^{Ph}/k^{Me}	0.33	1.5

(22)

これを踏まえ、上で述べたオキシランの開環反応において PhLi と *n*-BuLi の競争反応を試みたところ、PhLi による開環の方が優先するという結果が得られた(式 23, 表 4)。これは、*n*-BuLi が高会合状態にあり、会合しにくい PhLi より反応性が低くなったため、PhLi による開環体 **10** が優先的に得られたものと理解できる。また、溶媒を THF から Et_2O に変更すると、**10** の選択性は向上した。これは極性の低い溶媒中では *n*-BuLi の会合状態が高まり、反応性がさらに低下するため、反応性の差がより大きくなったものと考えられる。

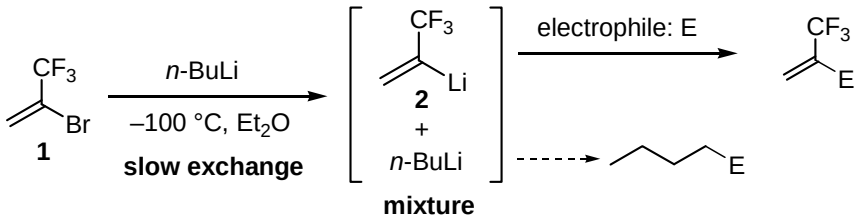


(23)

Table 4. Competitive reaction between PhLi and *n*-BuLi

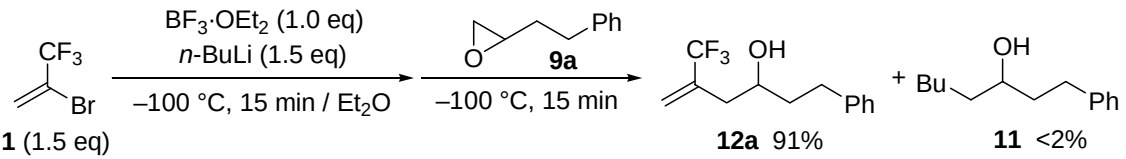
Solvent	Ph-Adduct **10**	Bu-Adduct **11**	Ratio
THF	79%	13%	86 : 14
Toluene	76%	11%	87 : 13
Et_2O	42%	1.5%	97 : 3

第一節で述べた *s*-BuLi と臭化ビニル **1** を用いる(トリフルオロメチル)ビニル基の導入法では、ビニルリチウム種 **2** が熱的に不安定なために生成した **2** をすばやく捕捉する必要があり、適用できる求電子剤は反応性の高いものに限定されることが問題であった。そこで、リチウム化合物の会合状態の差を利用すれば、リチウム－ハロゲン交換反応を行いながら **2** のみを求電子剤と反応させることができるため、より反応性の低い求電子剤を用いることが可能になると考えた。すなわち 1-(トリフルオロメチル)ビニルリチウム **2** では、①リチウム－フッ素間の相互作用[19]により、分子内、分子間においてフッ素原子がリチウムへ配位し易く、また②トリフルオロメチル基が嵩高いため、会合し難いと予想される。会合しにくいことが理由ならば、ビニルリチウム **2** は *n*-BuLi より高い反応性を示すことが期待できる。第一節で述べたように、*s*-BuLi の代わりに *n*-BuLi を 2-ブロモ-3,3,3-トリフルオロプロペン **1** に作用させると、－100 ℃ではリチウム－ハロゲン交換反応が比較的遅く、反応系内では *n*-BuLi とビニルリチウム **2** が共存する状態になる。ここでもし、上述したような *n*-BuLi とビニルリチウム **2** に反応性の相違があれば、ビニルリチウム **2** を選択的にオキシランで捕捉できることになり、生成するビニルリチウム **2** は熱分解する前に求電子剤と反応することができるものと考えられる(式 24)。



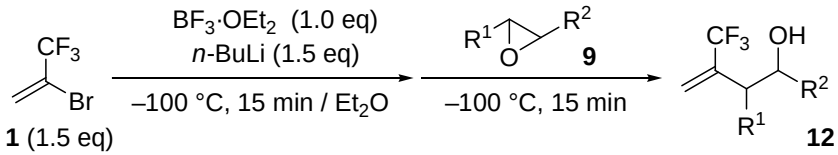
(24)

求電子種として 2-フェネチルオキシラン **9a** を選び、エーテル中、－100 ℃で 1.5 倍モル量の *n*-BuLi と臭化ビニル **1** および 1.0 倍モル量の $BF_3{\cdot}OEt_2$ を作用させた。反応は予期した通り進行し、目的のアルコール **12a** を 91%の収率で得ることができた(式 25)。BuLi 付加物 **11** は 2%以下であり、*n*-BuLi による開環をほぼ抑えることができた。



(25)

続いて、オキシラン **9** に関して基質一般性を調べた。その結果を表 5 に示す。



(26)

Table 5. Synthesis of 3-(trifluoromethyl)homoallyl alcohols **12**

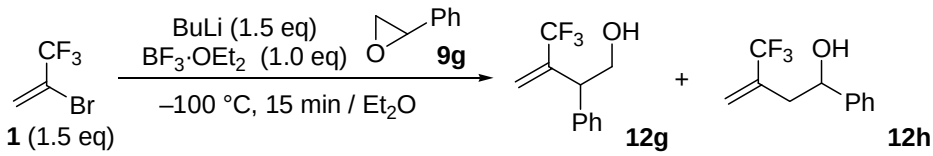
Entry	Oxirane	Product	Yield / %
1	Ph, O **9a**	CF_3 OH, Ph	**12a** 91
2	Ph, O **9b**	CF_3 OH, Ph	**12b** 89
3[a)]	OPMB, O **9c** (99% ee)	CF_3 OH, OPMB	**12c** 81 (99% ee)
4	O **9d**	OH, CF_3	**12d** 40[b)]
5	Ph, O, Ph **9e**	–	–
6	O **9f**	CF_3 OTs	**12f** 34

a) PMB : *p*-methoxybenzyl.
b) ^{19}F NMR yield relative to internal standard ($(CF_3)_2CTol_2$).

モノアルキル置換オキシラン **9a–c**[20,21]を用いると、収率 80～90%で 3-(トリフルオロメチル)ホモアリルアルコール **12a–c** が得られた(entries 1–3)。また、光学活性オキシラン **9c** の光学純度は生成物において変化しないことが確認された(entry 3)。2,3-ジアルキルオキシラン **9d** では中程度の収率で目的物 **12d** を得ることができたが(entry 4)、2,2-ジベンジルオキシラン **9e** を試みたところ反応は進行しなかった(entry 5)。無置換のエチレンオキシド **9f** では低収率であったが、これは **9f** のオリゴマー化が原因と考えられる。なお、生成物の沸点が低いことを考慮し、対応するトシラート **12f** へ変換

した後に単離した(entry 6)。

続いて、2-フェニルオキシラン **9g** の検討を行った(式 27, 表 6)。



(27)

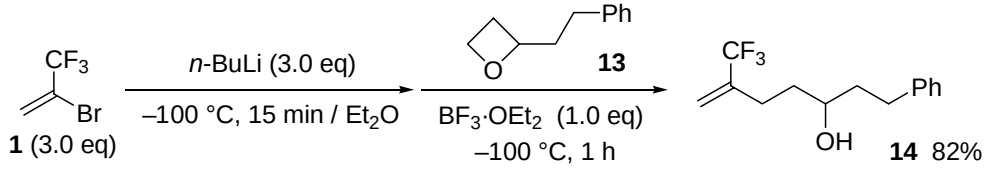
Table 6. Reaction of vinyllithium **2** with 2-phenyloxirane **9g**

Entry	Method	Yield / %[a)]	ratio[a)] **12g** : **12h**
1	A	48	37 : 63
2	B	49	67 : 33
3	C	31	19 : 81

a) Determined by ^{1}H NMR
A: Addition order; **1**, $BF_3{\cdot}OEt_2$, *n*-BuLi, oxirane **9g**
B: Addition order; oxirane **9g**, **1**, $BF_3{\cdot}OEt_2$, *n*-BuLi
C: Addition order; **1**, *t*-BuLi, $BF_3{\cdot}OEt_2$, oxirane **9g**

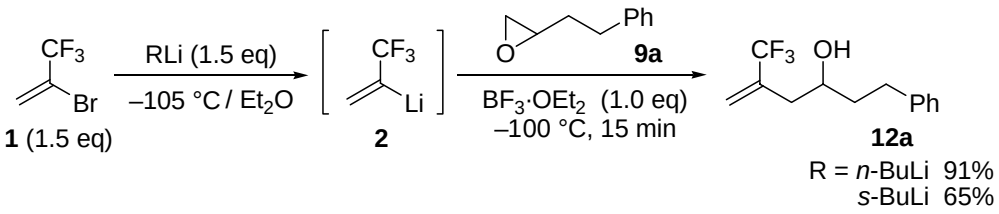
2-フェニルオキシラン **9g** を用いて反応を行うと、フェニル基のα位とβ位への攻撃が競争し、ホモアリルアルコールは 2 種の位置異性体 **12g**,**12h** の混合物として得られた(entry 1)。このときの試薬の添加順序は臭化ビニル **1**、$BF_3{\cdot}OEt_2$、*n*-BuLi、オキシラン **9g** であり、β位へ求核攻撃が起こった生成物 **12h** が優先して得られた(**12g** : **12h** = 37 : 63)。しかし、試薬の添加順序をオキシラン **9g**、臭化ビニル **1**、BF_3、*n*-BuLi とすると、選択性は逆転しα位への付加生成物 **12g** が優先した(**12g** : **12h** = 67 : 33)。これは、あらかじめ $BF_3{\cdot}OEt_2$ とオキシランが複合体を生成することでα位へ攻撃し易くなったものと考えられる。また、entry 3 に示すように、*n*-BuLi の代わりに *t*-BuLi を用いて entry 1 の試薬順で反応を行うと、**12h** の選択性を向上させることができた。

続いて、4 員環環状エーテルであるオキセタン **13**[22)]を使用し、1-(トリフルオロメチル)ビニルリチウム **2** との反応を試みた。オキシランの反応と同様の条件を適用すると、期待した(トリフルオロメチル)ビニル基を有するアルコール **14** が収率 30%で得られた。臭化ビニル **1** および *n*-BuLi をそれぞれ 3 倍モル量用いると、収率は 82%に改善することができた(式 28)。



(28)

最後に、*s*-BuLi をリチウム－ハロゲン交換反応に用いて 1-(トリフルオロメチル)ビニルリチウム **2** を調製し、オキシラン **9a** との反応を試みた。反応条件を *n*-BuLi を使用した式 25 と比較するため、1.5 倍モル量の *s*-BuLi および臭化ビニル **1** を使用したところ、アルコール **12a** の収率は 65%と低かった(式 29)。このことから、オキシランの開環反応においては、リチウム－ハロゲン交換に *n*-BuLi を使用する方が効率良く生成物を与えることを確認できた。



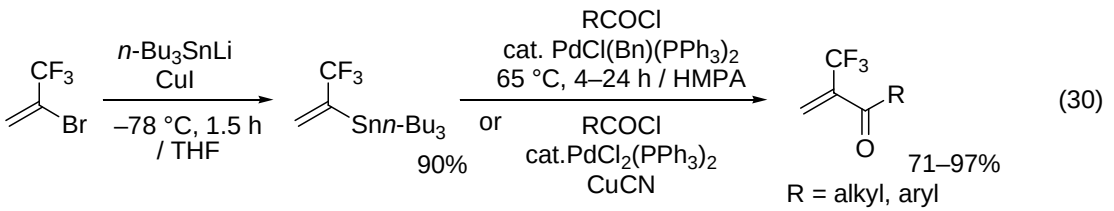
(29)

以上、1-(トリフルオロメチル)ビニルリチウム **2** と *n*-BuLi の会合度の違いを利用すると、リチウム－ハロゲン交換を行わせながらビニルリチウム **2** をオキシランあるいはオキセタンで選択的に捕捉することができ、(トリフルオロメチル)ビニル基を持つアルコールを効率良く合成することができた。この反応では、適切な反応性を有する求電子剤の選択が鍵である。すなわち、求電子剤の反応性が高過ぎると反応系内に残る *n*-BuLi との反応も進行し、また反応性が低過ぎると求電子剤との反応が遅く、ビニルリチウム **2** の熱分解が進行するため収率が低下する。BF_3 で活性化したオキシラン **9** やオキセタン **13** は共に適度な反応性を持つため、良好な収率で置換生成物を与えたものと考えられる。

第三節　α-トリフルオロメチル-α,β-不飽和ケトン **16** の合成

近年、主鎖にトリフルオロメチル基を有するポリマーが様々な用途に用いられており、トリフルオロメチル基を有するα,β-不飽和カルボニル化合物はそのモノマー原料として注目を集めている [23]。しかし、モノマーとしては主にトリフルオロメタクリル酸が用いられており、不飽和ケトンのモノマーはほとんど知られていない。

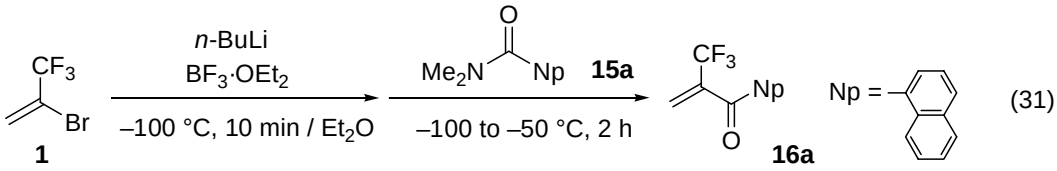
α-トリフルオロメチル-α,β-不飽和ケトンの合成には、式 30 に示すように 1-(トリフルオロメチル)ビニルスズ化合物と酸塩化物との反応が知られている [2]。



(30)

しかし、有機スズ種化合物の毒性を考慮すると実用的な手法ではなく、これに代わる合成法が求められている。α-トリフルオロメチル-α,β-不飽和ケトンは、1-(トリフルオロメチル)ビニルリチウム **2** とカルボン酸 *N,N*-ジアルキルアミド等の反応により合成できると考えられる。そこで第二節で述べた 1-(トリフルオロメチル)ビニルリチウム **2** と *n*-BuLi の会合度の違いを利用して、－100 ℃でリチウム－ハロゲン交換を行いながら、ビニルリチウム **2** をアミドにより選択的に捕捉することを試みることにした。

求電子剤として 1-ナフチルカルボン酸 *N,N*-ジメチルアミド **15a** を選び、まず反応条件の検討を行った(式 31)。



(31)

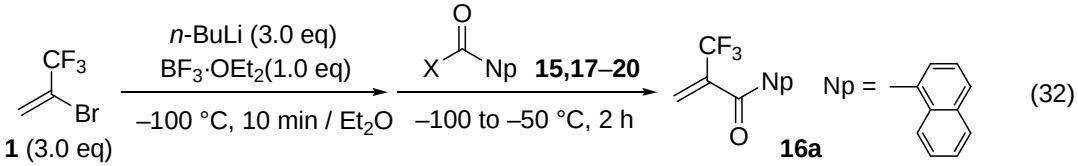
Table 7. Reaction of naphthylamide **15a** with vinyllithium **2**

Entry	**1** (eq)	*n*-BuLi (eq)	BF_3·OEt_2 (eq)	Yield / %
1	1.5	1.5	0	0
2	1.5	1.5	1.0	7
3	3.0	3.0	1.0	44
4	3.0	3.0	2.0	9
5	2.0	2.0	1.0	39
6	5.0	2.0	1.0	55

臭化ビニル **1** および *n*-BuLi をそれぞれ 1.5 倍モル量用いて反応を行ったが原料回収に終わったため、BF_3·OEt_2 を 1 倍モル量添加したところ、目的のα-トリフルオロメチル-α,β-不飽和ケトン **16a** を収率 7%で得ることができた(表 7, entries 1,2)。原料の回収量が多かったため、臭化ビニル **1** および *n*-BuLi を 3 倍モル量まで増やしたところ、収率は 44%まで改善した(entry 3)。しかし、BF_3·OEt_2 を 2 倍モル量に増やすと、収率は著しく低下した(entry 4)。また、臭化ビニルおよび *n*-BuLi を 2 倍モル量に減らした entry 5 では、3 倍モル量使用した entry 3 と比較して収率は若干減少したが、回

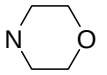
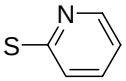
収原料と合わせた物質収支は改善された。これは、*n*-BuLi を過剰に使用すると生成物への求核付加等の副反応を起こすためと考えられた。そこで、*n*-BuLi を完全に消費するために、臭化ビニル **1** を 5 倍モル量に増量したところ、予期した通り 55%まで収率が向上した(entry 6)。

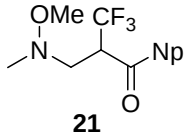
続いて、ジメチルアミノ基以外の脱離基を有する 1-ナフチルカルボン酸アミド **17–20** を使用して反応を試みた(式 32, 表 8)。



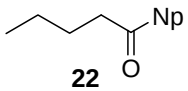
(32)

Table 8. (Trifluoromethyl)vinylation of amides **17–20**

Entry	amide X		Yield / %
1	NMe_2	**15a**	44
2	NMe(OMe)	**17**	23
3		**18**	35
4		**19**	–
5	NMePh	**20**	5



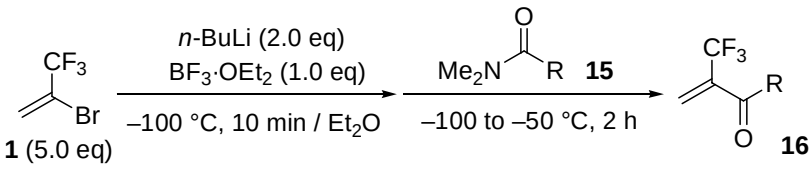
21



22

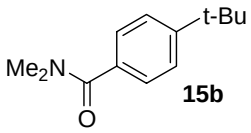
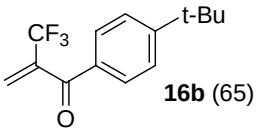
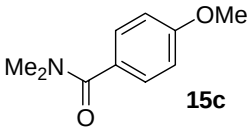
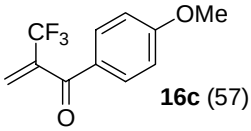
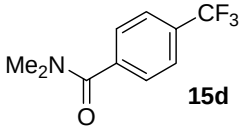
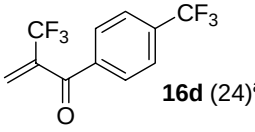
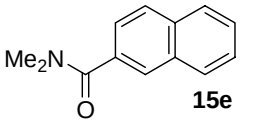
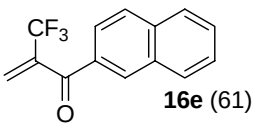
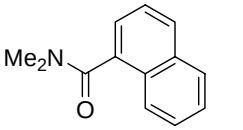
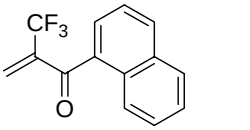
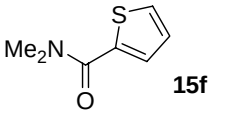
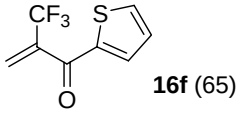
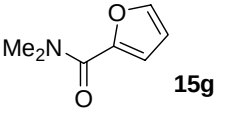
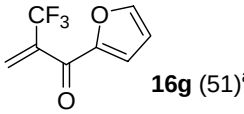
ケトン合成に広く利用されている *N*-メトキシ-*N*-メチルアミド(Weinleb アミド)**17** を用いたところ、目的とするα-トリフルオロメチル-α,β-不飽和ケトン **16a** が 23%で得られ、他にケトン **16a** にアミンが 1,4-付加した **21** が 54%副生した。このことから、生成物も高い求電子性を有しているため、脱離基の求核性まで考慮に入れた適切な反応系を構築する必要があると考えられた。また、モルホリン部位を有するアミド **18** では、望みのケトン **16a** と共にブチル=ケトン **22** も副生した。同じくケトン合成に使用される *S*-ピリジルチオエステル **19** を用いると、多種の混合物が得られ、目的の **16a** は生成しなかった。*N*-メチル-*N*-フェニルアミド **20** は反応性が低く、収率は 5%であった。

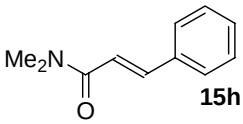
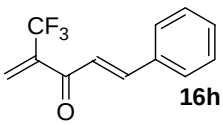
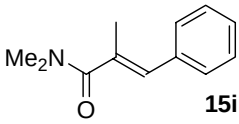
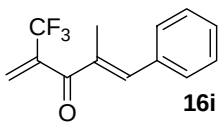
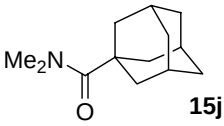
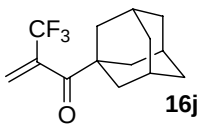
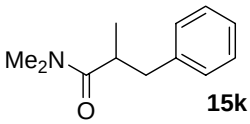
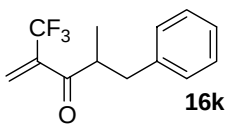
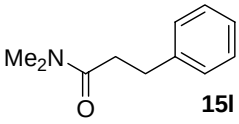
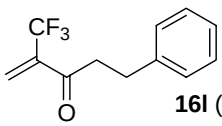
続いて、様々な *N,N*-ジメチルカルボン酸アミド **15** との反応を行い、基質一般性を調べた(式 33)。反応条件は最も良好な結果が得られた表 7 の entry 6 の条件を用いた。



(33)

Table 9. Synthesis of α-trifluoromethyl-α,β-unsaturated ketones **16**

Entry	Dimethylamide	Product (Yield / %)
1	 **15b**	 **16b** (65)
2	 **15c**	 **16c** (57)
3	 **15d**	 **16d** (24)[a]
4	 **15e**	 **16e** (61)
5	 **15a**	 **16a** (55)
6	 **15f**	 **16f** (65)
7	 **15g**	 **16g** (51)[a]

Entry	Dimethylamide	Product (Yield / %)
8	 **15h**	 **16h** (38)
9	 **15i**	 **16i** (66)
10[b]	 **15j**	 **16j** (73)
11[c]	 **15k**	 **16k** (78)
12[c]	 **15l**	 **16l** (42)[a]

a) ^{19}F NMR yield relative to internal standard ($CF_3C_6H_5$).
b) Vinyl bromide **1** (2.0 eq), and $BF_3{\cdot}OEt_2$ (1.3 eq) were used.
c) $BF_3{\cdot}OEt_2$ (1.3 eq) was used.

表 9 に示すように、概ね良好な収率で目的とする不飽和ケトン **16** を得ることができた。アリールおよびヘテロアリールカルボン酸アミド **15b–g** を用いると、4-(トリフルオロメチル)安息香酸アミド **15d**(entry 3)を除き、60%程度の収率でケトンが得られた(entries 1–7) 。**15d** から生成する 4-(トリフルオロメチル)フェニル=ケトン **16d** は求電子性が高いため、ビニルリチウム **2** の求核付加がさらに進行し、収率が低下したと推測される(entry 3)。

スチリル=ケトン **16h** も、38%と低収率でしか得られなかった(entry 8)。これは活性なビニル基が二つ存在するため、副反応が起こり易くなったものと考えられる。実際、スチリル基の 1 位にメチル基を導入したアミド **15i** からは、収率 66%でケトン **16i** が得られた。スチリル基への求核攻撃が抑制されたためと考えている(entry 9)。

最後に、脂肪族カルボン酸アミド **15j–l** との反応を行った。1-アダマンタンおよび第二級アルカンアミド **15j**,**15k** は良好な収率でケトン **16j**,**16k** を与えた(entries 10,11)。これに対し第一級アルカンアミド **15l** を用いると中程度の収率となった。**15l** のα位プロトンが脱プロトンされて、ビニルリチウム **2** や *n*-BuLi が消費されたためと考えている。

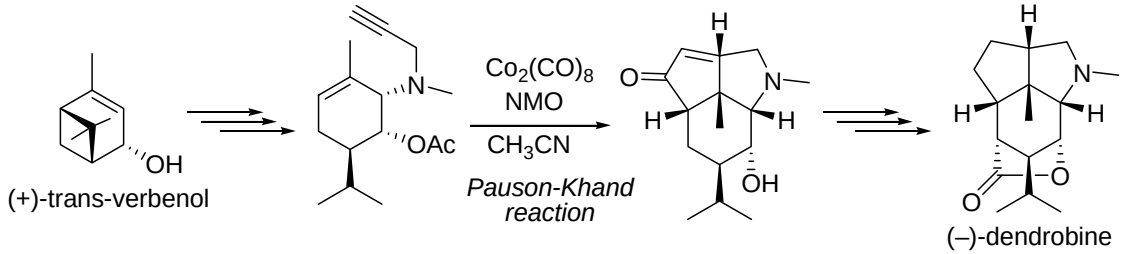
以上、1-(トリフルオロメチル)ビニルリチウム **2** とカルボン酸ジメチルアミド **15** との反応により、様々な置換基を有するα-トリフルオロメチル-α,β-不飽和ケトン **16** を合成することができた。この化合物は、含フッ素モノマーとしてのみでなく、Diels－Alder 反応や Nazarov 環化反応を利用して複雑な骨格を有する含フッ素化合物へ誘導することができる有用な中間体として期待される。

第一節から第三節まで述べたように、筆者は、含フッ素 C-3 ビルディングブロックとして、不安定性のためにこれまでほとんど使用されていなかった 1-(トリフルオロメチル)ビニルリチウム **2** の効率的な調製と反応の手法を探索した。その結果、①*s*-BuLi を用いることによって－105 ℃においても十分速くリチウム－ハロゲン交換が進行し、得られたビニルリチウム **2** とアルデヒドや *N*-トシルイミン等の反応性の高い求電子剤とを反応させることができた。また、②1-(トリフルオロメチル)ビニルリチウム **2** と *n*-BuLi の会合度の違いを利用して、－100 ℃でリチウム－ハロゲン交換を行いながら、オキシランや *N*,*N*-ジメチルカルボン酸アミド等の適度な反応性の求電子剤によりビニルリチウム **2** を選択的に捕捉する方法を確立した。この二種のブチルリチウムを使い分ける方法により、反応性の異なる求電子剤へ(トリフルオロメチル)ビニル基を導入する方法を開発した。特に、α位にトリフルオロメチル基を持つ不飽和ケトン **16** の合成においては、生成物が比較的求電子性の高いアルケン部位を有するにも関わらず、求核性の高いリチウム種 **2** を用いて目的を達成した。

次節では、得られた 2-(トリフルオロメチル)アリルアミド **8** およびα-トリフルオロメチル-α,β-不飽和ケトン **16** を用い、合成化学的応用に関して検討を行った結果について述べる。

第四節　トリフルオロメチルアルケンの合成化学的応用

ステロイドやアルカロイドには核間メチル基を持つ化合物が多く存在し、合成目標として広く取り上げられてきた[24]。例えば、アルカロイドの一つで(−)-Dendrobine 等の核間メチル基を含む骨格構築には、分子内 Pauson−Khand 反応が利用されている(式 34)[25]。

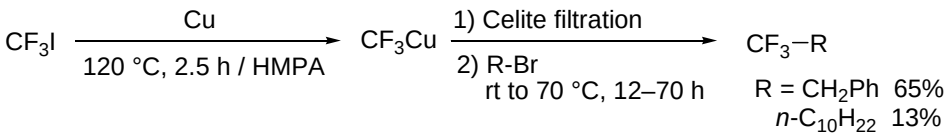


(34)

Pauson−Khand 反応は 1971 年に Pauson により発見された。アルキン、アルケン、一酸化炭素の三成分が一度に連結し環化する反応であり、分子内反応に応用すると縮環構造を含む複雑な骨格を一挙に構築することができる[26]。

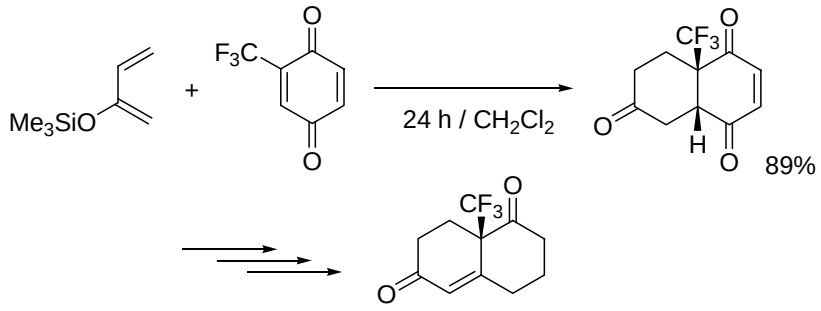
序論でも述べたが、生理活性天然物の一部の置換基をフッ素もしくは含フッ素置換基に置き換えると、代謝の阻害や体内動態、レセプターとの相互作用に変化をもたらすことから、フッ素導入は創薬開発における重要なツールの一つとなっている。上述の核間メチル基をトリフルオロメチル基に置き換えると、次のような効果が期待できる。①メチル体と立体障害の程度に差が少なく、目的のレセプターとの同程度の親和性を示し、②強い電子求引性効果によりトリフルオロメチル基の近傍の官能基の反応性に影響を及ぼし、分子の生理学的活性を変化させる。

しかしながら、縮環部位にトリフルオロメチル基を直接導入する手法は、ほぼ未開拓と言える。例えば、有機銅試薬は一般的に 1,4-付加に有効とされるが、$CuCF_3$ は主にハロゲン化アリール、ハロゲン化ビニルのハロゲン置換反応に使用され、1,4-付加の例は報告されていない(式 35)[27]。従って、求核的なトリフルオロメチル化反応により核間トリフルオロメチル基を効率的に導入することは困難である。また、求電子的トリフルオロメチル化による核間トリフルオロメチル基の導入は、現在のところ報告されていない。



(35)

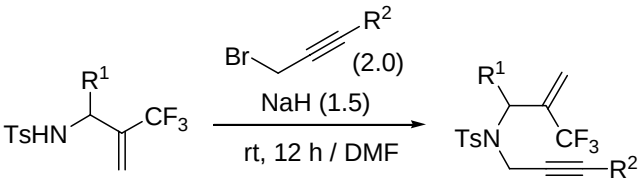
そのため、Kobayashi、Taguchi、Bégué、Blazejewski および Wakselman は、トリフルオロメチル基を含む化合物の分子内、分子間環化を使用して、核間トリフルオロメチル基を含む縮環骨格を構築している(式 36)[28]。



(36)

Wieland–Miescher Ketone analogue

そこで、第一節において合成した 2-(トリフルオロメチル)アリルアミド **8** を 1,6-エンイン化合物 **23** へ誘導し、これを用いて分子内 Pauson－Khand 反応を行えば、核間にトリフルオロメチル基を有する縮合環骨格を構築できると考えた。まず、アリルアミド **8** を臭化プロパルギルおよび塩基で処理し、1,6-エンイン化合物 **23** を調製した(式 37)。

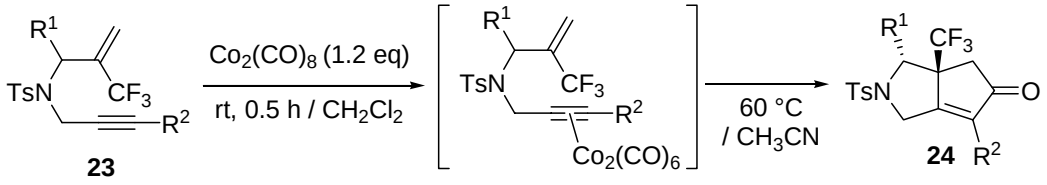


(37)

R^1 = Ph **8c**
R^1 = Pr **8e**

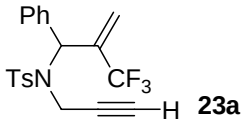
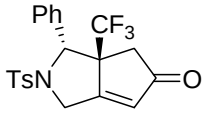
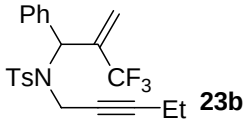
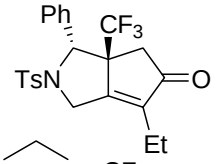
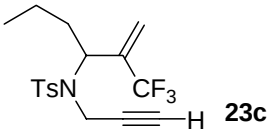
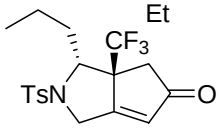
R^1 = Ph, R^2 = H **23a** 92%
R^1 = Ph, R^2 = Et **23b** 90%
R^1 = Pr, R^2 = H **23c** 84%

得られた 1,6-エンイン化合物 **23a** に $Co_2(CO)_8$ を加えてアセトニトリル中で加熱したところ、目的とする Pauson－Khand 反応が進行し、核間トリフルオロメチル基を有する縮環ピロリジン化合物 **24a** を収率 81%で得た(表 10, entry 1)。生成物は 3a 位のトリフルオロメチル基および 3 位のフェニル基における立体異性体の混合物として得られ、その比は *anti*∶*syn* = 94∶6 と高い *anti* 選択性を示した。内部アルキニル基を有する基質 **23b**、および、アリル位にプロピル基を有する基質 **23c** を用いた場合にも、*anti* 選択性が若干低下したものの、良好な収率で目的物 **24b**,**24c** を得ることができた(entries 2,3)。



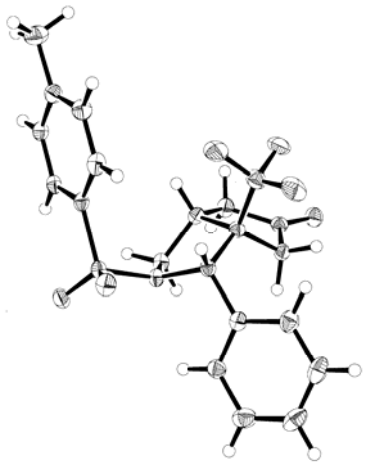
(38)

Table 10. Intramolecular Pauson–Khand reaction of 2-trifluoromethyl-1,6-enynes **23**

Entry	1,6-Enyne	Product	Time	Yield / %	*anti* : *syn*[a]
1	 **23a**		3 h	**24a** 81	94 : 6[b]
2	 **23b**		2 h	**24b** 85	83 : 17[c]
3	 **23c**		3 h	**24c** 71	86 : 14[c]

a) Isomer ratio was determined by ^{19}F NMR.
b) Configuration of the major isomer was determined to be anti by X-ray crystallography of the cyclopentanone, derived via reduction of cyclopentenone **24a**.
c) Configuration was determined in analogy with **24a** by comparing ^{1}H and ^{19}F NMR data of each isomer.

縮環ピロリジン化合物 **24** の立体化学は、エノン **24a** の major 異性体を水素添加することで得られたケトン **25** の X 線結晶構造解析により決定し、*anti* 体であることを確認した(Figure 1)。



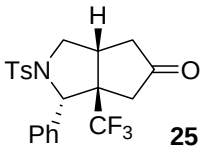
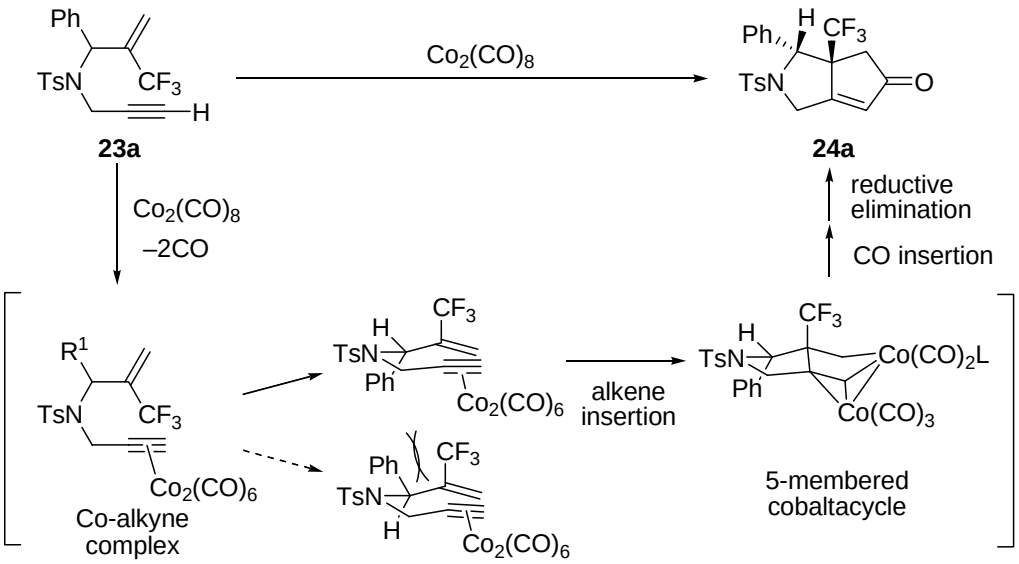


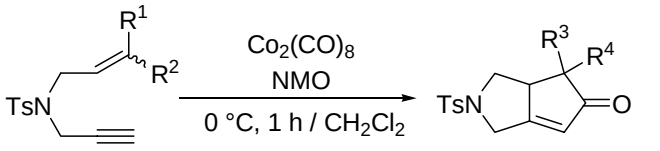
Figure 1. X-ray structure of ketone **25**.

anti 体が優先する理由に関しては次のように説明できる。この立体配置は、コバルト-アルキン錯体 **D** の C－Co 結合に(トリフルオロメチル)ビニル基が挿入し、5 員環コバルタサイクル **E** を形成する段階で決まるが、トリフルオロメチル基とフェニル基の立体障害を避けるため、*anti* 選択的な立体配置を優先的に取るものと考えられる。



(39)

トリフルオロメチル基やフッ素置換基を有する 1,6-エンイン化合物の Pauson－Khand 反応に関しては、これまで良い結果は報告されていない(式 40)[29]。上記の CF_3 基を有するエンインの反応は、核間トリフルオロメチル基を導入する手法の一つとして有用なだけでなく、フッ素化合物の Pauson－Khand 反応としても稀な成功例である。

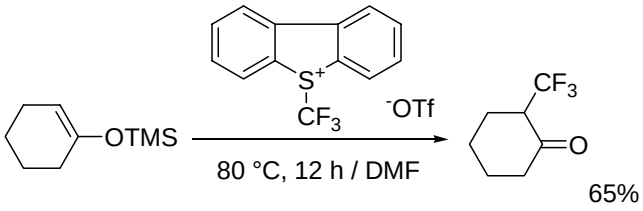


R_1, R_2, R_3, R_4 = F 0%
R_1, R_3, R_4 = H, R_2 = F 37%
R_1 = Cl, R_2, R_4 = CF_3, R_3 = H 14%

(40)

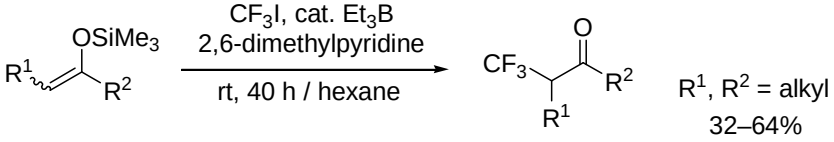
上述した核間トリフルオロメチル基を有する縮環化合物の合成に続いて、第三節で合成したα-トリフルオロメチル-α,β-不飽和ケトンを用いた環状α-トリフルオロメチル-ケトンの合成検討について述べる。

ケトンのα位へトリフルオロメチル基を導入するには、*S*-(トリフルオロメチル)ジベンゾチオフェニウム塩等の求電子的なトリフルオロメチル化剤を用いる手法が報告されている(式 41)[30]。しかし、こうした試薬は高価であり、また、反応にはジベンゾチオフェンの生成を伴う。



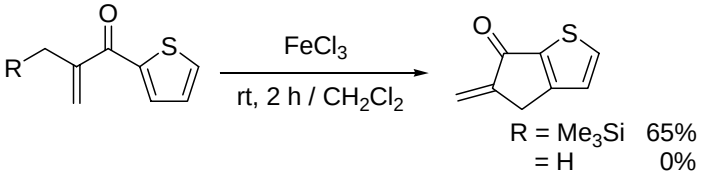
(41)

また、式 42 に示すように CF_3I から Et_3B により CF_3 ラジカルを発生させ、シリルエノールエーテルで捕捉することで、同様にα-トリフルオロメチルケトンが合成できる。しかし、この反応では収率の基質依存性が大きく[31]、新たな CF_3 導入手法が求められる。

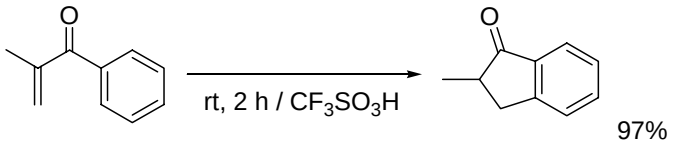


(42)

Nazarov 環化反応はジビニル=ケトンの分子内環化反応であり、シクロペンタノン骨格を容易に構築することができる[32]。しかし、片側のビニル基をアリール基に替えたビニル=アリール=ケトンでは環化反応が進行しにくいことがわかっており、Kang は、トリメチルシリル基のβ-カチオン安定化効果により、この困難な環化反応を達成している(式 43)[33]。また、トリフルオロメタンスルホン酸を溶媒量使用するとビニル=アリール=ケトンの環化も進行することが報告されている(式 44)[34]。



(43)

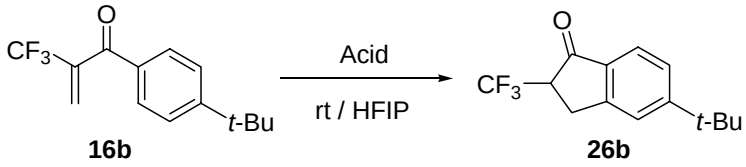


(44)

第三節において得られたアリール基を有するα-トリフルオロメチル-α,β-不飽和ケトン **16** の Nazarov 環化反応が可能であれば、2 位にトリフルオロメチル基をもつインダノンが合成でき、C-3 の含フッ素ビルディングブロックから短工程で含フッ素炭素環が構築できる。そこで、Nazarov 環化の検討を行った。

4-*t*-Bu-フェニル基を有するα-トリフルオロメチル-α,β-不飽和ケトン **16b** に対して 3 倍モル量の酸を添加し、ヘキサフルオロイソプロパノール(HFIP)中で反応を行った(式 45)。Nazarov 環化反応に

通常使用される塩化鉄はほとんど活性を示さず(表 11, entry 1)、また、Me_3SiOTf も本基質には効果を示さないことがわかった(entry 2)。そこで強酸であるトリフルオロメタンスルホン酸を用いたところ、反応の進行は遅いものの、目的物の 2-トリフルオロメチル-1-インダノン **26b** が収率 18%で得られた(entry 3)。トリフルオロメタンスルホン酸を 10 倍モル量まで増やすと 87%まで収率は改善された(entry 4)。

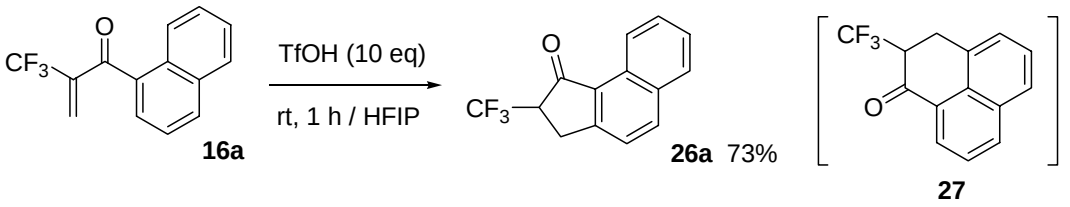


16b **26b** (45)

Table 11. Nazarov cyclization of α-trilfuoromethyl-α,β-unsaturated ketone **16b**

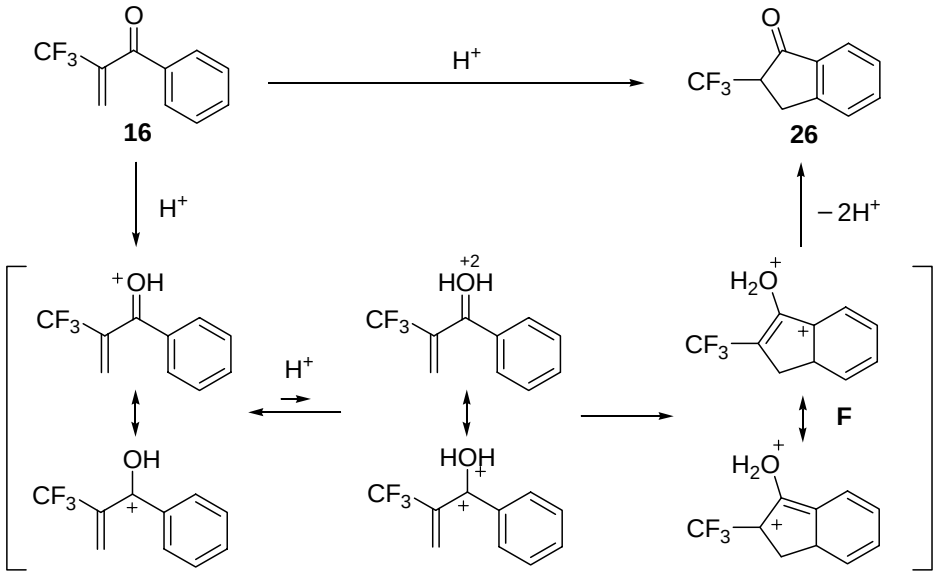
Entry	Acid (eq)	Time	Yield **/ %**
1	$FeCl_3$ (3.0)	20 h	3
2	TMSOTf (3.0)	20 h	trace
3	TfOH (3.0)	20 h	18
4	TfOH (10)	3 d	87

続いて、1-ナフチル基を有するケトン **16a** の環化を試みた。反応は速やかに進行し、室温、一時間でインダノン **26a** が収率 73%で得られた(式 46)。この基質に関してはナフチル基の 8 位で Friedel－Crafts 型の環化が進行する可能性も考えられたが、2 位での結合形成が優先的に進行し、Nazarov 環化体のみが得られた。



16a **26a** 73% **27** (46)

強酸を使用する Nazarov 環化反応ではジカチオン中間体が提唱されており[34]、式 47 にその推定反応機構を示す。ナフチル基を有するケトン **16a** において速やかに反応が進行したのは、中間体 **F** のカチオンがベンジル位となるため、共鳴効果により **F** が安定化され、反応が促進されたものと考えられる。



(47)

以上、1-(トリフルオロメチル)ビニルリチウム **2** より得られた 2-(トリフルオロメチル)アリルアミド **8** および α-トリフルオロメチル-α,β-不飽和ケトン **16** を使用し、含フッ素 C-3 ビルディングブロックを基盤として複雑な骨格を有するフッ素化合物を構築することができた。次章では、第二節によって調製した(トリフルオロメチル)ホモアリルアルコール **12** を出発原料とする含フッ素光学活性プロリンの合成について詳細を述べる。

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9 Attempted Barbier-type reaction of benzaldehyde with 2-(trifluoromethylvinyl)Grignard reagent: To a suspension of Mg (48 mg, 2.0 mmol) in THF (10 mL) was added PhCHO (102 μL, 1 mmol) and 2-bromo-3,3,3-trifluoropropene (0.21 mL, 2.0 mmol) at 0 °C. The suspension was stirred for 6 h at that temperature, the reaction was quenched by saturated aqueous NH_4Cl. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. ^{19}F NMR spectra of crude products showed that the desired fluorinated allyl alcohol was not obtained.

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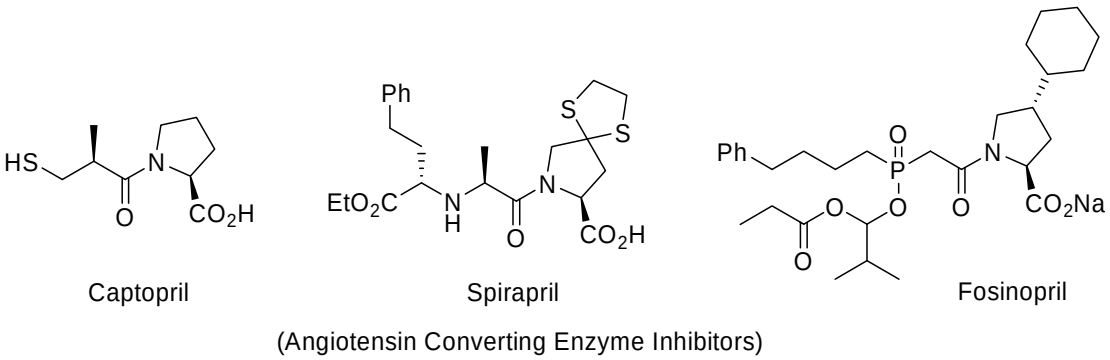
第二章　含フッ素光学活性プロリン類の合成

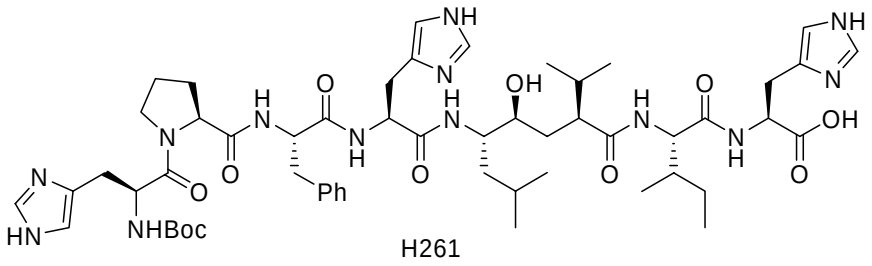
緒言

プロリンは、タンパク質を構成する約 20 種のアミノ酸の中で唯一、窒素原子とα炭素原子がアルキル鎖で橋架けされた５員環構造を有している。こうした構造は、生体内においてペプチド鎖の「折れ曲がり構造」を形成する役目を果たしており、タンパク質の高次構造まで深く関連している [1]。また応用分野においては、生理活性物質 [2]、不斉配位子 [3]、有機触媒 [4]等の幅広い用途にプロリン誘導体が使用されている。

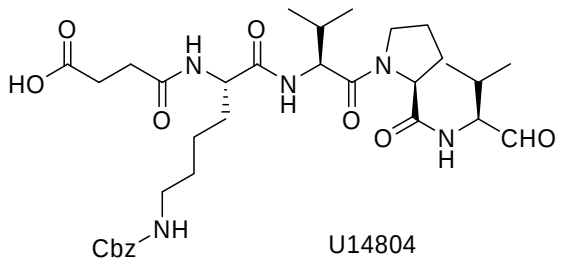
図１　含プロリン生理活性化合物



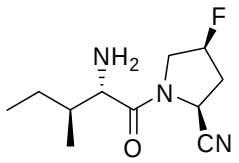
(Angiotensin Converting Enzyme Inhibitors)



(Renin Inhibitor)



(Human Elastase Inhibitor)

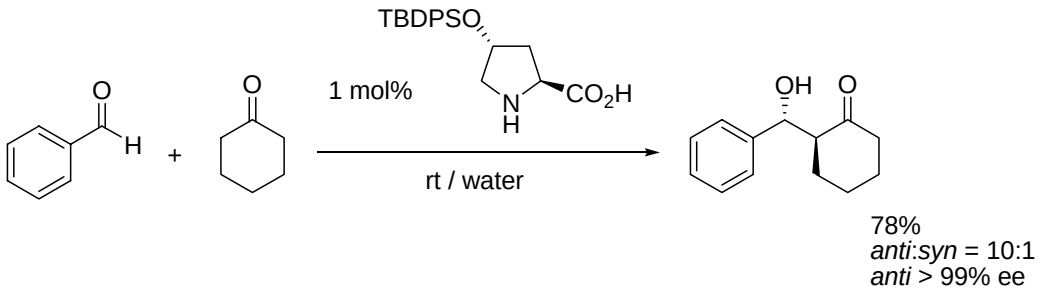


(Dipeptidyl Peptidase IV Inhibitor)

中でも４位置換プロリンは、天然アミノ酸の一種であるヒドロキシプロリンから誘導し易いこともあり、多くの誘導体が合成され、様々な用途に利用されている [5]。例えば医薬では、Spirapril[6]、Fosinopril[7]等が ACE 阻害剤(angiotensin-converting enzyme inhibitors)として開発されている。ま

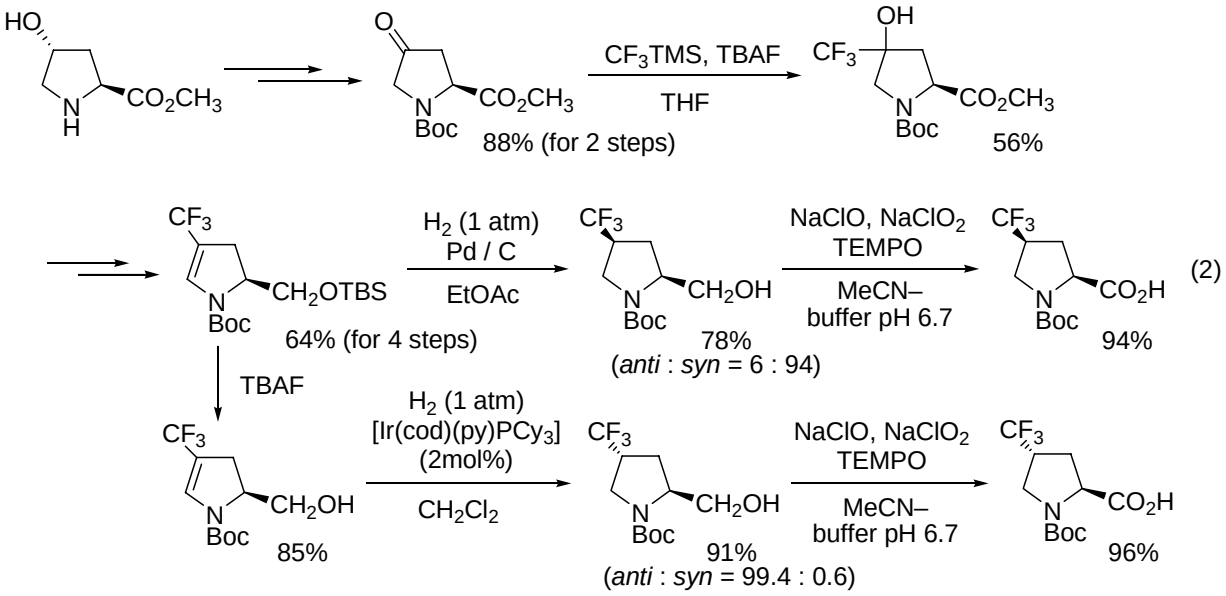
た最近、ヒドロキシプロリン誘導体を不斉触媒に用いたアルドール反応に関しても報告されており(式1)[8]、4 位置換基の有用性が広く認められている。また、プロリンは硬タンパク質のひとつであるコラーゲンのβシート構造を構築しているが、4-ヒドロキシプロリンを組み込むことによってβシート構造をさらに安定化できることが知られ、その効果に関して精力的に研究が行われている[9]。

Scheme 1. Direct Aldol reaction using 4-substituted proline catalyst

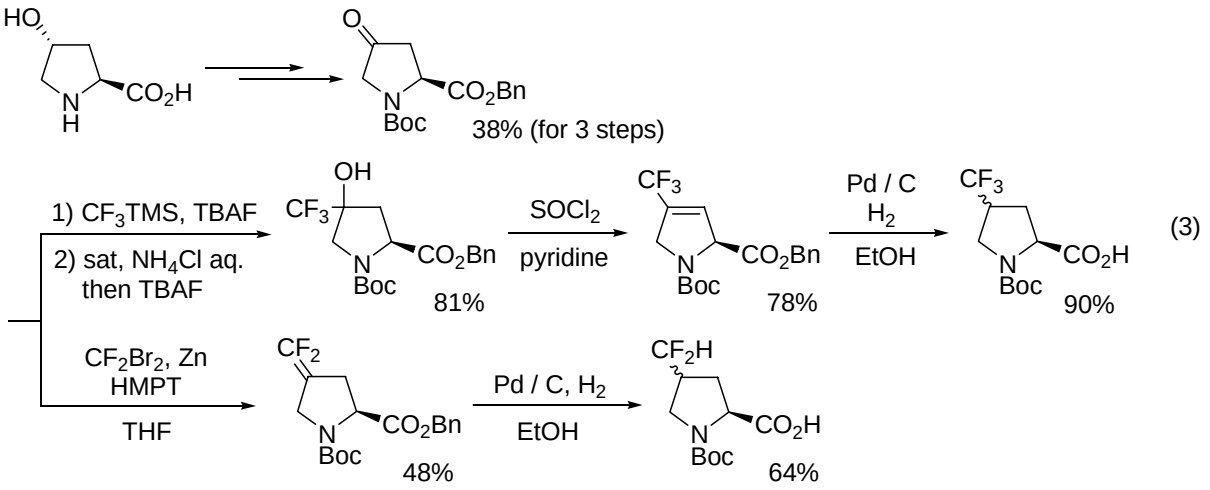


序論でも述べたが、生理活性天然物の一部の官能基をフッ素もしくは含フッ素炭素置換基に置き換えると、代謝の阻害や体内動態、レセプターとの相互作用に変化をもたらすことから、フッ素導入は医農薬品開発における重要なツールの一つとなっている。そのため、4-ヒドロキシプロリンから合成される 4-フルオロプロリン誘導体は生化学、医薬の分野において興味が持たれ、中には既に臨床応用されているものもある[2b]。同様に、含フッ素炭素置換基を有するプロリン誘導体も生理活性物質等への応用が期待されるが、４位にフルオロ炭素置換基を持つプロリンの合成については、最近になって 3 例報告されているのみである[10,11]。

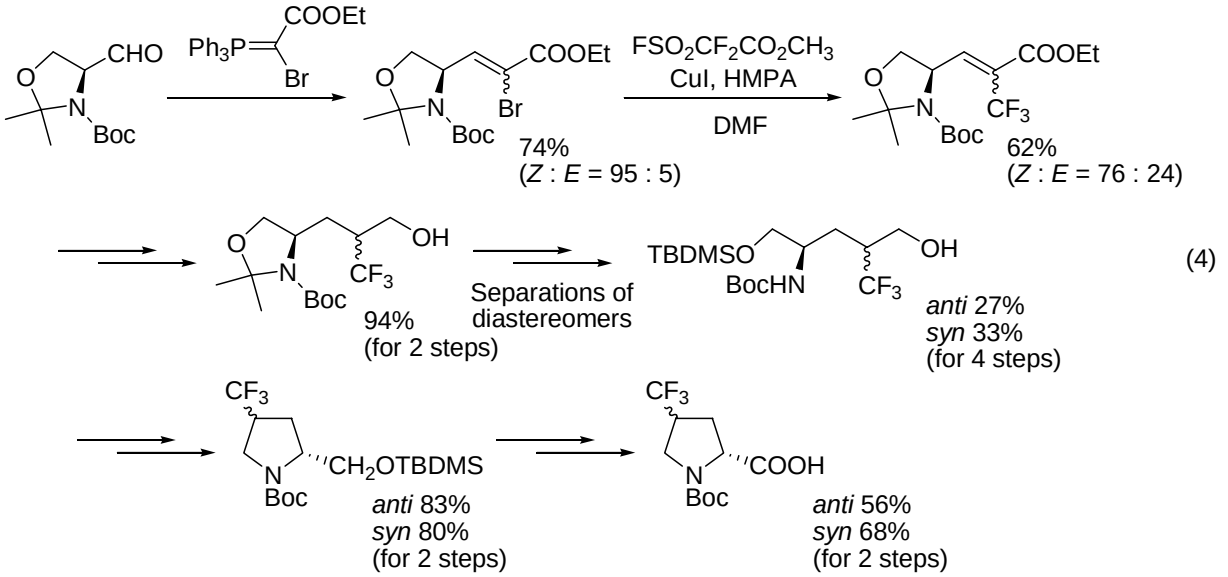
Goodman は、4-ヒドロキシプロリンメチルエステルを出発原料とし、9－10 ステップで 4-(トリフルオロメチル)プロリンへと導いている[10]。CF_3TMS を使用してオキソプロリン誘導体のトリフルオロメチル化を行い、続く脱水反応により 4-(トリフルオロメチル)ピロリンを調製した。この環内二重結合に対し、ピロリンの２位置換基の反対側から水素化を行ない、*syn*-4-(トリフルオロメチル)プロリノールへと誘導し、また一方で、ヒドロキシメチル基を金属触媒へ配位させて水素化を行うことで *anti*-4-(トリフルオロメチル)プロリンも合成している(式2、*syn*-4-CF_3-プロリン;9 steps、総収率 23%、*anti*-4-CF_3-プロリン；10 steps、総収率 23%)。



Qing も同様に、ヒドロキシプロリンから 4-オキソプロリンを調製し、これに CF_3TMS または CF_2Br_2 を用いて、それぞれトリフルオロメチル基、ジフルオロメチレン基を導入している[11a]。また、ジフルオロメチレン基を水素化し、4-(ジフルオロメチル)プロリンも合成している(式 3、4-CF_3-プロリン；6 steps、総収率 22%、4-CF_2H-プロリン；5 steps、総収率 12%)。上記の例に比べ行程数は少ないが、収率は高くなく、還元反応の立体選択性も良くない。



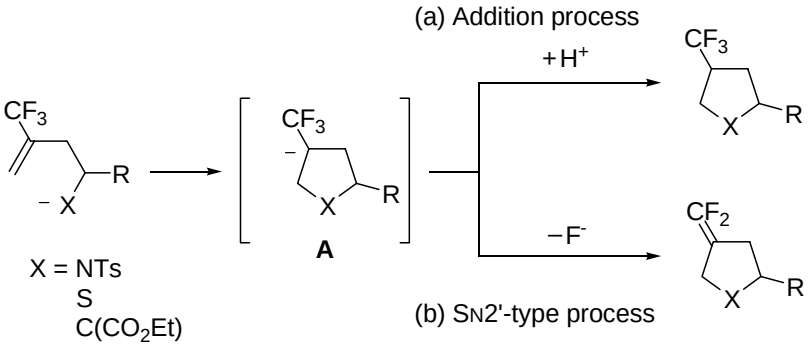
Qing はさらに、L-セリンを出発原料とする 4-(トリフルオロメチル)プロリンの合成に関して報告を行っている[11b]。α-ブロモ-α,β-不飽和エステルのトリフルオロメチル化および不飽和エステル部の還元によりβ-(トリフルオロメチル)アルコールを異性体混合物として得ており、両異性体を分離した後にそれぞれ *anti*-および *syn*-4-(トリフルオロメチル)プロリンへと誘導している (式 4、12 steps、総収率 7.7%)。



(4)

上記の合成報告は、いずれにおいてもアミノ酸を光学活性な出発物質として使用しており、含フッ素光学活性プロリンを容易に誘導できるという点で価値の高い手法であるが、天然原料を用いるために片方の光学異性体のみが入手可能という側面もあり、また合成効率も高くない。そのため、こうした天然物によらない純粋に化学合成による手法で、かつ効率の高い手法の開発もなお求められる。

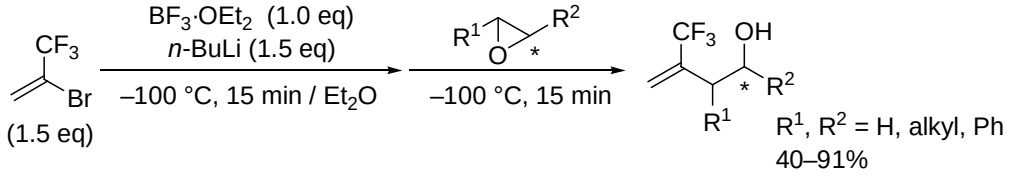
一方序論でも述べたが、当研究室では最近、(トリフルオロメチル)ビニル基への求核反応を分子内反応に応用すると、分子間では反応しにくいヘテロ原子求核種によっても S_N2'型反応が進行することを見出している[12]。また、求核反応における 5-*endo-trig* 環化は Baldwin 則では不利な反応とされているが[13]、(トリフルオロメチル)ビニル基への求核反応はこの 5-*endo-trig* 形式でも進行し、含フッ素炭素置換基を有する種々のヘテロ環および炭素環の構築法を開発している(式 5)[14]。この反応では、プロトン性溶媒中では付加反応が進行し、トリフルオロメチル基を有する環化生成物を与える。一方、プロトン源がない場合には、トリフルオロメチル基上のフッ素の脱離を伴い、ジフルオロメチレン基を有する環状化合物が生成する。これにより、2 種の含フッ素炭素置換基をもつ 5 員環化合物を作り分けることができる。



(5)

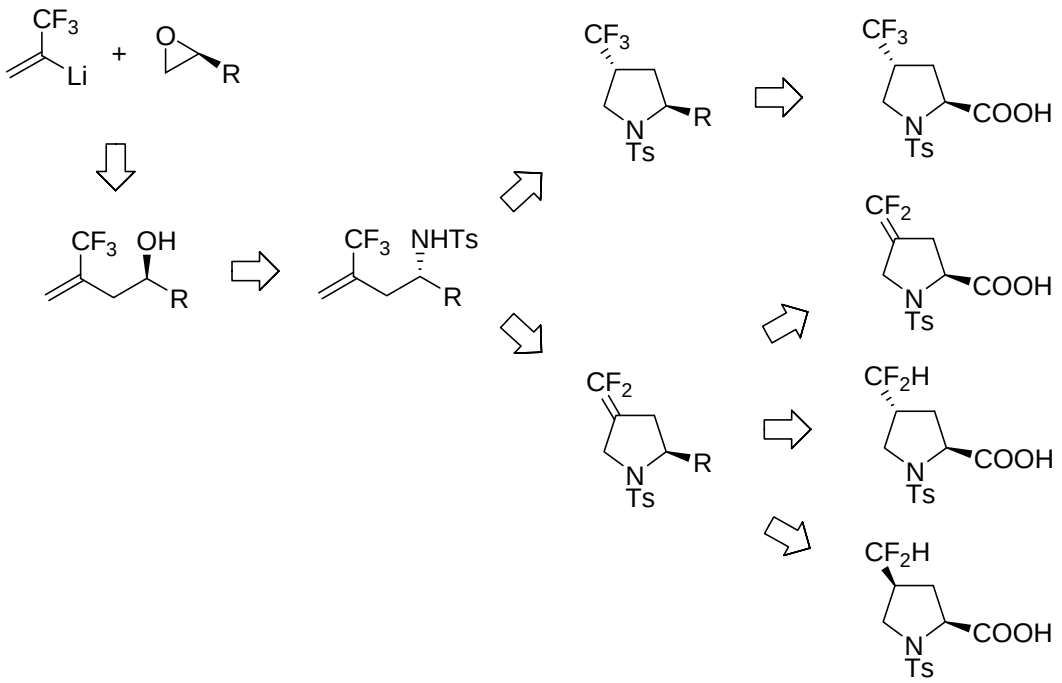
この反応は、(トリフルオロメチル)ビニル化合物が有する末端アルケンの高い求電子性、およびアリル位のフッ素原子の脱離能により促進されている。また、反応中間体 **A** におけるα-アニオンは、トリフルオロメチル基の電子求引効果により安定化されている。これらの効果により通常では困難な 5-*endo*-*trig* 環化反応が進行したものと考えられる。

また、第一章で述べたように筆者は、(トリフルオロメチル)ビニルリチウムにより光学活性オキシランの開環反応を行うことで、光学活性アルコールを得る手法を開発した(式 6)[15]。これを利用すると、式 5 (X = NTs)のピロリジン合成反応における環化原料である[3-(トリフルオロメチル)ホモアリル]トシルアミドを光学活性体として提供することができる。



(6)

以上述べた、(トリフルオロメチル)ビニルリチウムによる光学活性オキシランの開環反応と [3-(トリフルオロメチル)ホモアリル]トシルアミドの求核的 5-*endo*-*trig* 反応を組み合わせることによって、4 位にトリフルオロメチル基およびジフルオロメチレン基を有する様々な 2 位置換光学活性ピロリジン骨格を構築することが可能となる。また、Goodman はピロリンの環内二重結合を面選択的に水素化して *anti*-、*syn*-(トリフルオロメチル)プロリンの合成を行っている(式 2)[10a,16]。同様に式 5 で合成されるピロリジンの *exo*-ジフルオロメチレン基を面選択的水素化することができれば、ジフルオロメチル基を持つ *anti*-、*syn*-両異性体が得られると考えた。これらのピロリジン骨格における 2 位の置換基(R)はオキシランの 2 位の置換基から誘導できるため、ここにあらかじめアリール基やヒドロキシメチル基等、カルボキシ基へ変換可能な置換基を導入しておけば、同一の環化前駆体より短いステップ数で、様々な含フッ素炭素置換基を有するプロリンが合成できると予想した(式 7)。

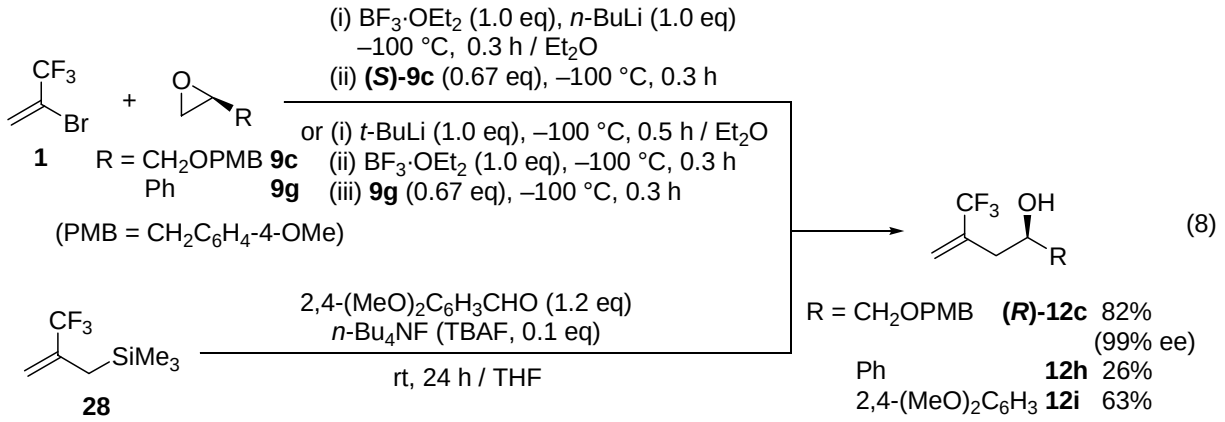


(7)

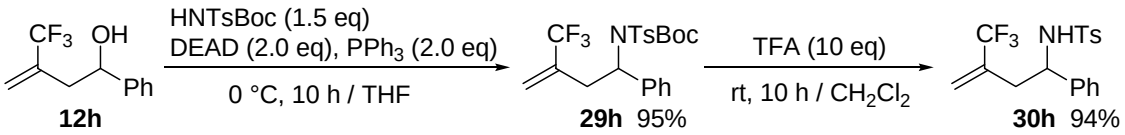
そこで筆者は、各種 4-フルオロ炭素置換プロリンの系統的な合成手法の確立を目指し、トリフルオロメチル基、ジフルオロメチレン基、ジフルオロメチル基を 4 位に持つ光学活性プロリンの合成を試みることにした。

第一節　環化前駆体の合成

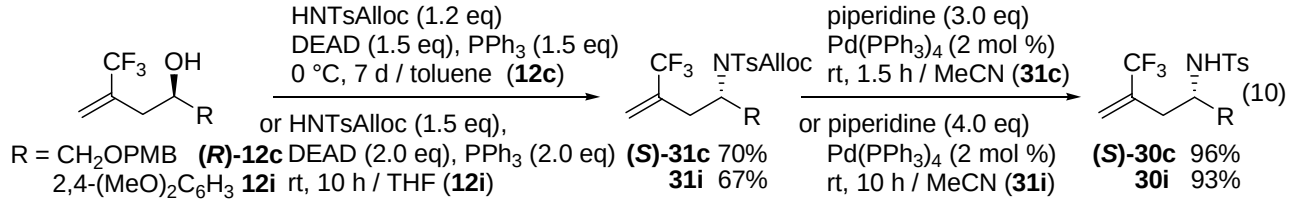
まず 3-(トリフルオロメチル)ホモアリルアルコールの合成を行った。第一章に述べたように、1-(トリフルオロメチル)ビニルリチウムによりオキシランを開環することで目的のアルコールを得ることができる(式 8)。また緒言にも述べたように、オキシランの 2 位の置換基を最終的にカルボキシ基へ変換するため、2 位にヒドロキシメチル基およびフェニル基を有するオキシランを使用して検討を行った。*p*-メトキシベンジル(PMB)エーテルとして保護した光学活性グリシジルアルコール(***S***)-**9c**[17]にこの手法を適用し、86%の収率で光学活性アルコール **12c** を得た。また、ラセミ体の 2-フェニルオキシラン **9g** に対して同様の手法を試みると、26%と低収率であるが目的とするフェニル基を有するホモアリルアルコール **12h** をラセミ体として得ることができた。この 3-(トリフルオロメチル)ホモアリルアルコールは Ishikawa により報告された 2-(トリフルオロメチル)アリルシラン **28** とアルデヒドの反応を用いても合成できる[18,19]。そこで、2,4-ジメトキシベンズアルデヒドを使用し、2,4-ジメトキシフェニル基を有するアルコール **12i** をラセミ体として得た。



得られたホモアリルアルコールは Mitsunobu 反応[20]によりトシルアミドへ変換した。上で述べたアルコール **12** に対してそれぞれ、DEAD、PPh_3 および Boc トシルアミドを作用させたところ、良好な収率で Boc トシルアミド **29** を得ることができた(式 9)。トリフルオロ酢酸を用いて Boc 基の除去を行ったところ、Boc トシルアミド **29h** に関しては良好な収率でトシルアミド **30h** を得ることができたが、**29c** および **29i** においては基質の分解が進行した。そこで、Boc トシルアミドに換えて Alloc トシルアミドを用いて Mitsunobu 反応を行い、ピペリジンおよび触媒量の $Pd(PPh_3)_4$ を用いて Alloc 基の除去を行ったところ、良好な収率で環化前駆体である 3-(トリフルオロメチル)ホモアリルアミド (***S***)-**30c**,**30i** を得ることができた(式 10)。



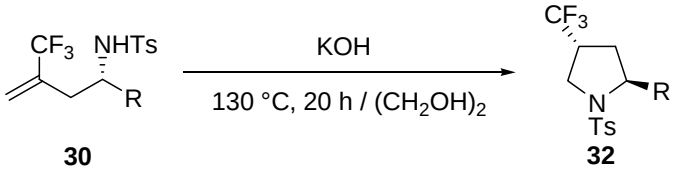
(9)



(10)

第二節　含フッ素炭素置換基を有するピロリジン骨格の構築

続いて、トシルアミド **30** の 5-*endo*-*trig* 環化反応を試みた。まず、プロトン性溶媒であるエチレングリコール中で環化反応を行った(式 11)。光学活性トシルアミド(***S***)-**30c** を KOH 存在下、エチレングリコール中で 130 ℃に加熱すると、付加型の環化が進行し、収率 68%で目的とするトリフルオロメチル基を有するピロリジン(2*S*,4*R*)-**32c** を得ることができた(表 1, entry 1)。生成物は、4 位のトリフルオロメチル基と 2 位の置換基の立体異性体混合物として得られた。この異性体比は 70：30 であり、後で述べる実験により *anti* 体が優先して生成することがわかった。また、HPLC で *anti* 体の光学純度を測定したところ 99% ee であり、環化反応は立体保持で進行していることが確認された。一方、アリール基を有する基質 **30h**,**30i** を用いると 9：1 以上の良好な *anti* 選択性で反応は進行し、ピロリジン化合物 **32h**,**32i** をそれぞれ収率 85%、74%で与えた(entries 2,3)。そこで、トリフルオロメチル基を有するプロリンの合成に関しては、より立体選択的に生成するアリール置換ピロリジン **32h**,**32i** を用いて以後の検討を行うこととした。



(11)

Table 1. Synthesis of 4-(trifluoromethyl)pyrrolidines **32**

Entry	R		KOH (eq)	**32** / % (*anti* : *syn*)	
1	CH_2OPMB	(***S***)-**30c**	5.0	68	(70 : 30, *anti*: 99% ee)
2	Ph	**30h**	5.0	85	(92 : 8)
3	C_6H_3-2,4-$(OMe)_2$	**30i**	1.3	74	(90 : 10)

得られた 4-(トリフルオロメチル)ピロリジン **32c**, **32h**, **32i** はいずれもクロマトグラフィーによる異性体の分離は困難であった。そのため、立体配置の決定を目的として種々基質の検討を行ったところ、4-ブロモフェニル基を有するピロリジン **32j** において異性体の分離ができ、その両異性体の NOESY スペクトルを測定して立体配置を決定した。すなわち、H^2 と H^4 との間に NOE 相関がある異性体を *syn* 体、NOE 相関がない異性体を *anti* 体と同定した。

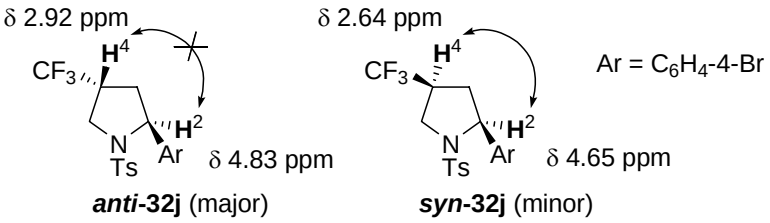


Figure 2. NOESY experiments of 4-(trifluoromethyl)pyrrolidines **32j**.

また、*N*-トシルピロリジン **32j** の配座解析を行ったところ、*syn* 体においては 2 位のフェニル基および 4 位のトリフルオロメチル基の反発により 4 位 H が擬アキシャル配置となり、また *anti* 体では中間の位置を占めることがわかった(Figure 3)。^{1}H NMR における磁気異方性に関して、一般にエクアトリアルプロトンは非遮蔽化円錐部の中にあるためシグナルが低磁場シフトする。そのため、**32j** における 4 位 H の化学シフトは *syn* 体の方が *anti* 体より高磁場側に現れると予想される。実際にピロリジン **32j** の 4 位 H のシグナルは、*syn* 体が高磁場側に現れ、この予想と合致する。この結果から、**32c**,**30h**,**30i** に関して両異性体の化学シフト値を比較して立体化学を推定した(表 2)。これらにより、上記の環化反応で得られたピロリジン **32** はいずれも *anti* 体が主生成物であることがわかった。

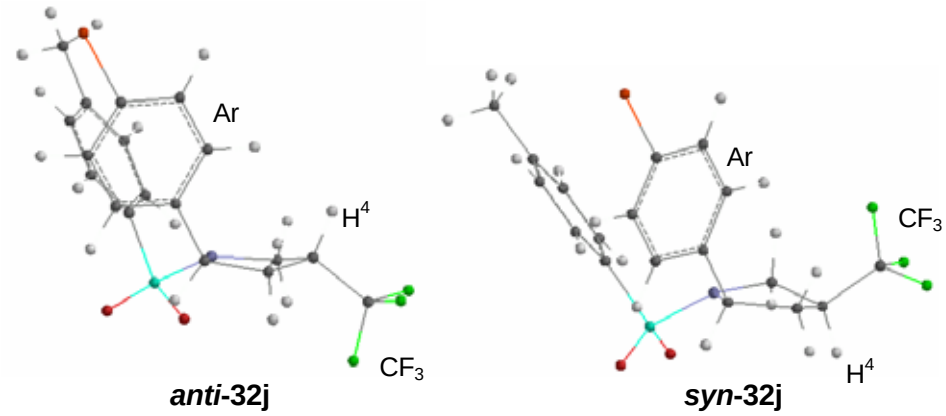
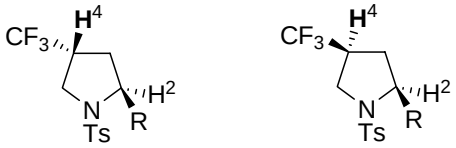


Figure 3. Conformer analysis of **32j** (calculated by PM3).

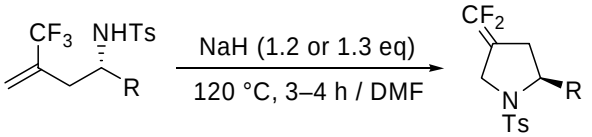
Table 2. ^{1}H NMR chemical shifts of H^4 in 4-(trifluoromethyl)pyrrolidines **32**



***anti*-32** ***syn*-32**

R		H^4 (*anti*)	H^4 (*syn*)	*anti* : *syn*
CH_2OPMB	**32c**	3.10	2.28	70 : 30
C_6H_5	**32h**	2.96	2.63	92 : 8
C_6H_3-2,4-$(OMe)_2$	**32i**	2.90	2.46	90 : 10
C_6H_4-4-Br	**32j**	2.92	2.64	92 : 8

次に、非プロトン性条件下における環化反応を試みた。トシルアミド**(*S*)-30c** に、DMF 中 NaH を加えて 120 ℃に加熱すると、S_N2'型反応が進行して 4 位にジフルオロメチレン基を有する光学活性ピロリジン**(*S*)-33c** が収率 90%で得られた(式 12)。式 11 と同様に、環化反応において光学純度は保持され、ここでもラセミ化しないことが明らかになった。また、フェニル基を有するトシルアミド **30h** に関しても良好に反応は進行し、対応するピロリジン **33h** を 91%の収率で得た。



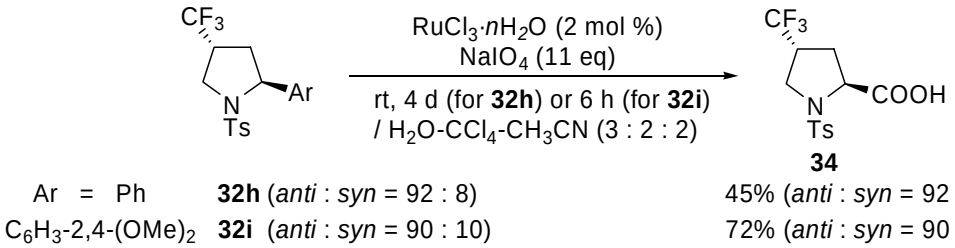
(12)

R = CH_2OPMB **(*S*)-30c** **(*S*)-33c** 90% (99% ee)
Ph **30h** **33h** 91%

第三節　含フッ素炭素置換基を有するプロリンの合成 (1)

前節で *anti* 選択的に得られた 4-(トリフルオロメチル)ピロリジン **32h**,**32i** について、2 位のアリール基を酸化してプロリンへの誘導を試みた。まず、最も立体選択性の良かった 2 位にフェニル基を持つピロリジン **32h** (*anti*：*syn* = 92：8)に、H_2O、CH_3CN、CCl_4の混合溶媒中、$RuCl_3$と $NaIO_4$から系中で発生させた RuO_4を作用させたところ [21]、立体保持で酸化が進行し *anti* 体主生成物のプロリン **34** (*anti*：*syn* = 92：8)が得られた(式 13)。酸化の収率が 45%と低かったため、芳香環部位を電子豊富で酸化の受け易いジメトキシフェニル基に変更した **32i** (*anti*：*syn* = 90：10)を用いて同様の酸化を試みた。その結果、ここでも立体保持で反応が進行し、収率 72%でトリフルオロメチル基を有する *N*-トシルプロリン **34** (*anti*：*syn* = 90：10)に誘導できた。

この合成法では、原料のアリルシランから目的化合物まで５ステップで済み、総収率は 21%であった。ラセミ合成ではあるが、短いステップ数で 4-(トリフルオロメチル)プロリン **34** の合成を達成できた。光学活性プロリンに関しては、Jacobsen の手法により光学活性 2-アリルオキシランを得ることができることから[22]、オキシランの開環収率に改善の余地はあるが、合成することは可能である。



(13)

なお、ここで得られた **34** の立体配置については、前節と同様に ^{1}H NMR における 4 位 H の化学シフトを比較し、低磁場に現れたものを *anti* 異性体、高磁場のものを *syn* 異性体と推定した。また、Goodman は、合成した *N*-Boc-4-(トリフルオロメチル)プロリンの立体配置を X 線結晶解析により決定しているが、この両異性体の 4 位 H の化学シフト値[10a]に関しても、同様の傾向を示すことが確認できた(Figrue 4)。

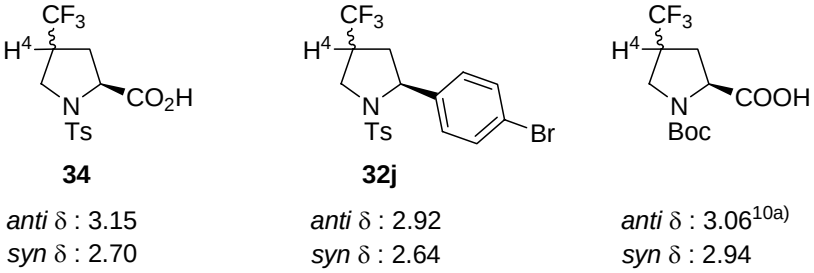
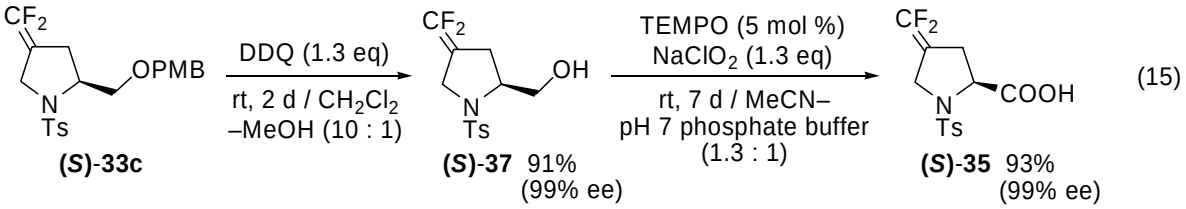


Figure 4. ^{1}H NMR chemical shifts of H^4 in 4-(trifluoromethyl)prolines **34**.

次に、4-(ジフルオロメチレン)プロリンの合成を検討した。まず、4-(ジフルオロメチル)ピロリジン **33h** の 2 位のフェニル基を酸化してカルボキシ基にすることを試みた。ピロリジン **33h** に対して先程と同様に RuO_4 を作用させたところ、フェニル基より先にジフルオロアルケン部位が酸化的に開裂してしまい、目的の 4-(ジフルオロメチレン)プロリン **35** は得られなかった(式 14)。

(14)

そこで、4-ジフルオロメチレン-2-(ヒドロキシルメチル)ピロリジン(***S***)-**37** のヒドロキシメチル基の酸化によりカルボン酸を得ることにした。DDQ を使用して 4-(ジフルオロメチレン)ピロリジン(***S***)-**33c** の PMB 基を除去し、得られたピロリジン(***S***)-**37** に触媒量の TEMPO および再酸化剤として亜塩素酸ナトリウムを作用させた。反応に長時間を要したものの、ジフルオロアルケン部位を損なうことなくヒドロキシメチル基をカルボキシ基へ変換することができ、目的とする 4-ジフルオロメチレン-*N*-トシルプロリン(***S***)-**35** を収率 93%で得ることができた(式 15)[23]。なお、(***S***)-**35** の光学純度は 99% ee であったことから、式 15 の変換だけでなく原料のオキシランからの全てのステップにおいて、ラセミ化は進行していないことがわかった。また、原料のオキシランから 6 ステップ、総収率 42%で(ジフルオロメチレン)プロリン(***S***)-**35** の合成を達成した[24]。



第四節　含フッ素置換基を有するプロリンの合成 (2)：ジフルオロメチレン基の面選択的水素化

最後に、4-(ジフルオロメチレン)ピロリジンから 4-(ジフルオロメチル)プロリンへの誘導を試みた。ジフルオロメチル基はジフルオロメチレン部位の水素化により得ることができるが、原料のピロリジンが 2 位に置換基を有するため、*anti* および *syn* を与える可能性がある。4 位フルオロ炭素置換プロリンを、医農薬等の生理活性物質合成の中間体として利用することを考慮すると、両立体異性体を各々選択的に合成できる還元手法の確立が望まれる。そこで、両方の面選択的な還元を行うために次に示す二つ方法を検討した。すなわち、ピロリジンの 2 位の置換基を利用し、ヒドロキシ基等の極性置換基を金属触媒に配位させながら、極性置換基と同じ面から水素化を行なうことで、*anti* 選択的にジフルオロメチル置換体を得る方法(Figure 5-a)と、ヒドロキシ基に非極性の嵩高い保護基を導入し、その立体障害を利用して反対側の面から水素化を行ない、*syn* 選択的にジフルオロメチル体を得る方法である(Figure 5-b)。

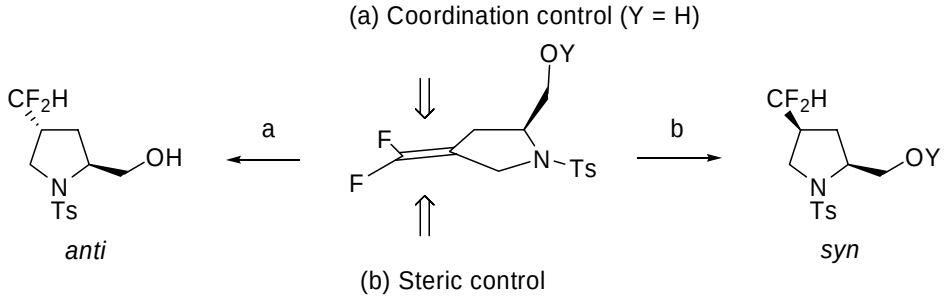
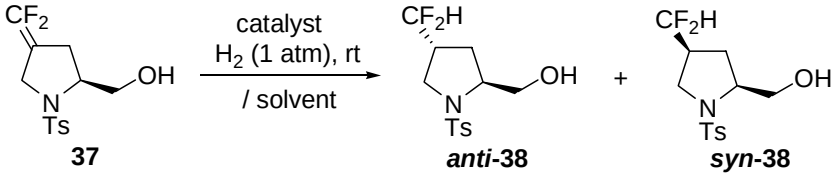


Figure 5. Stereoselective hydrogenation of difluoromethylene group.

まず、(*S*)-4-ジフルオロメチレン-2-ヒドロキシメチル-1-トシルプロリン(***S*)-37** を基質に選び、ヒドロキシ基の金属触媒への配位を利用して *anti* 選択的に(ジフルオロメチル)ピロリジン ***anti*-38** を合成することを試みた(式 16)。



(16)

Table 3. *anti*-Selective hydrogenation of (difluoromethylene)pyrrolidine **37**

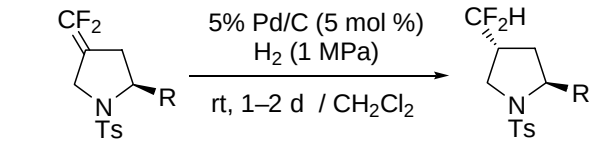
Entry	Catalyst (mol %)	Conditions	**38** / % (*anti* : *syn*)	**37** / %
1	[Ir(cod)Py(PCy_3)]PF_6 (5)	24 h / CH_2Cl_2	trace	>98
2	[Ir(cod)Py(PCy_3)]PF_6 (30)	24 h / CH_2Cl_2	<10 (>98 : 2)	64
3[a)]	[Ir(cod)Py(PCy_3)]PF_6 (30)	24 h / CH_2Cl_2	25 (84 : 16)	15
4	[Rh(nbd)dppb]BF_4 (5)	10 h / CH_2Cl_2	No Reaction	
5	5% Pd / C (5)	1 h / EtOH	88 (47 : 53)	0
6	5% Pd / C (5)	1 h / EtOAc	94 (59 : 41)	0
7	5% Pd / C (5)	5 d / CH_2Cl_2	97 (71 : 29)	0
8	5% Pd / C (50)	6 h / CH_2Cl_2	73 (79 : 21)	0
9	5% Pd / C (50)	6 h / $CHCl_3$	90 (79 : 21)	0

a) H_2 10 MPa

ヒドロキシ基の配位を利用した選択的水素化が報告されている[Ir(cod)Py(PCy_3)]PF_6 [10,16]を 5 mol %用いて**(*S*)-37** の水素化を行なったが、還元反応はほとんど進行しなかった(表 3, entry 1)。触媒量を 30 mol %まで増やすと、ほぼ完全な選択性で *anti* 体が得られたものの、反応は非常に遅く ***anti*-38** は低収率であった(entry 2)。そこで、水素加圧条件下(10 MPa)での反応を試みたが、フルオロメチル基の分解等により回収率が低下し、良好な収率で目的化合物を得ることはできなかった(entry 3)。次

に、ロジウムカチオン性錯体である[Rh(nbd)dppb]BF_4を触媒に用いたが反応は全く進行しないことがわかった(entry 4)。Pd/C を用いて水素化を行ったところ、EtOH や EtOAc 溶媒中ではほとんど選択性が見られなかったが(entries 5,6)、ハロゲン系の溶媒を使用すると、反応は遅いものの期待した *anti* 選択性(*anti*：*syn* = 71：29)で目的とする **38** を得ることができた(entry 7)。そこで反応を加速することを目的に Pd/C を増量したところ、*anti* 選択性が改善されることがわかった(entries 8,9)。これは、触媒を増量するとヒドロキシ基が相互作用可能な金属表面が増え、その結果 *anti* 選択性が向上したものと推測される。得られた 4-(ジフルオロメチル)ピロリジン(***S***)-***anti*-38** の光学異性体比を調べたところ 98% ee であり、水素添加による還元反応においてもラセミ化はほとんど起こらないことが確認された。

また、2 位に COOH 基、COOEt 基を有する 4-(ジフルオロメチレン)ピロリジン **35**,**39** も水素化に際して金属表面と相互作用すると期待された。そこで、Pd/C を使用して水素化を試みたが、*anti* 選択性は見られたものの良好な結果は得られなかった(式 17)。

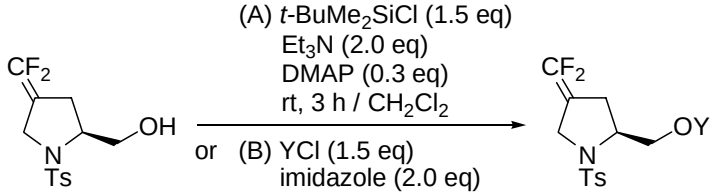


(17)

R = COOH **35**
COOEt **39**

R = COOH **40** 30% (*anti* : *syn* = 70 : 30)
COOEt **41** 25% (*anti* : *syn* = 76 : 24)

つぎに、立体障害を利用した *syn* 選択的水素化の検討を行った。**37** のヒドロキシ基へシリル基を導入することとし(式 18)、嵩高い保護基である *t*-$BuMe_2Si$ 基(**42a**)、*i*-Pr_3Si 基(**42b**)、*t*-$BuPh_2Si$ 基(**42c**)を有する 4-(ジフルオロメチレン)ピロリジンを調製した。



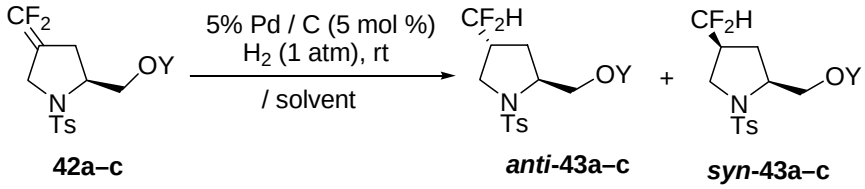
(18)

37

42a : Y = Si*t*-$BuMe_2$ (method A: 94%)
42b : Y = Si*i*-Pr_3 (method B: 93%)
42c : Y = Si*t*-$BuPh_2$ (method B: 69%)

触媒は、ジフルオロメチレン部位の水素化が最も収率良く進行する Pd/C を用いることにした。*t*-$BuMe_2Si$ 基を導入した **42a** に EtOAc 中で水素化を行なうと、予想通り立体障害の少ない面からの水素化が主に進行し、*anti*：*syn* 比は 13：87 と *syn* 体が優先した(表 4, entry 1)。EtOH 中で水素化すると比率は 11：89 まで改善され、*syn* 選択的にジフルオロメチル基を有するピロリジン **43a** を得ることができた(entry 2)。より大きな保護基を導入することで選択性の向上が期待できると考え、

i-Pr_3Si 基を有する **42b** や *t*-$BuPh_2Si$ 基を有する **42c** の水素化を試みたが、反応は進行し難くなり、また選択性も逆に低下した(entries 3,4)。立体配座の解析を行ったところ、*i*-Pr_3Si 基や *t*-$BuPh_2Si$ 基はα面まで張り出すことが示され、適度な大きさの *t*-$BuMe_2Si$ 基を有する **42a** においてより選択性が向上したことがわかった。

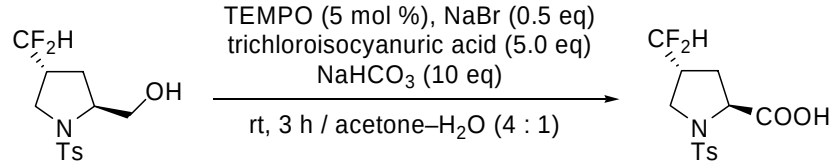


42a–c ***anti*-43a–c** ***syn*-43a–c** (19)

Table 4. *syn*-Selective hydrogenation of (difluoromethylene)pyrrolidines **42a–c**

Entry	Y		solvent	Time	Yield / % (*anti* : *syn*)
1	Si*t*-$BuMe_2$	**42a**	EtOAc	1 h	**43a** 98 (13 : 87)
2	Si*t*-$BuMe_2$	**42a**	EtOH	1 h	**43a** 99 (11 : 89)
3	Si*i*-Pr_3	**42b**	EtOH	6 h	**43b** 92 (20 : 80)
4	Si*t*-$BuPh_2$	**42c**	EtOH	20 h	**43c** 93 (27 : 73)

表 3 の entry 9 と表 4 の entry 2 においてそれぞれ得られた 4-(ジフルオロメチル)ピロリジン ***anti*-38**,***syn*-43a** に対し、ヒドロキシメチル基の酸化を行いプロリンへ変換した。***anti*-38**(*anti*：*syn* = 79：21)に触媒量の TEMPO および再酸化剤としてトリクロロイソシアヌル酸を作用させたところ[25]、立体保持で酸化反応が進行し、良好な収率で目的とする *anti*-ジフルオロメチル-*N*-トシルプロリン ***anti*-40** へと導くことができた(式 20)。原料のオキシランから 7 ステップ、総収率 39%で *anti*-4-(ジフルオロメチル)プロリン(*anti*：*syn* = 79：21)の合成を達成できた。

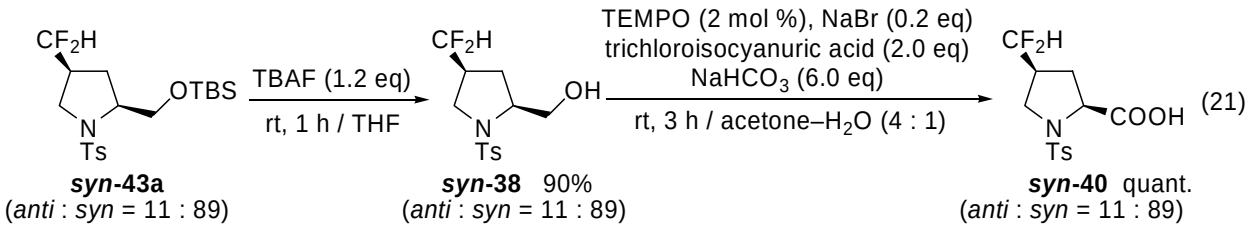


***anti*-38**
(*anti* : *syn* = 79 : 21)

***anti*-40** 96%
(*anti* : *syn* = 79 : 21)

(20)

また、*syn* 体が主生成物である **43a**(*anti*： *syn* = 11 ： 89)の *t*-$BuMe_2Si$ 基を除去した後、同様に TEMPO で酸化すると、*syn*-4-(ジフルオロメチル)プロリン ***syn*-40** へと導くことができた(式 21)。*syn* 体(*anti*：*syn* = 11：89)に関しては、オキシランから 9 ステップ、総収率 40%であった。



これらのジフルオロメチル基を有するプロリン誘導体の立体化学は、シリル誘導体 ***syn*-43a** における NOESY 測定により決定した(Figure 6)。すなわち、ジフルオロメチル基のプロトンと $H^{5\beta}$の間、および $H^{5\alpha}$と H^{2} の間に NOE 相関が確認されたため、これを *syn* 体と同定した。

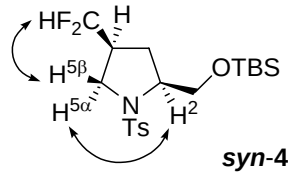


Figure 6. NOESY experiment of *syn*-(difluoromethyl)prolinol ***syn*-43a**.

以上、1-(トリフルオロメチル)ビニルリチウムを用いた光学活性オキシランの開環反応と、(トリフルオロメチル)ビニル基に対する窒素求核種を用いた 5-*endo*-*trig* 環化を組み合わせることにより、4 位にトリフルオロメチル基、ジフルオロメチレン基、ジフルオロメチル基を有する各種プロリン誘導体 **34**, **35**, **40** を合成することに成功した。更に、ジフルオロメチル基を持つプロリン **40** に関しては、*exo*-ジフルオロメチレン基に対する面選択的な水素化を行うことで、***anti*-40** と ***syn*-40** の両異性体をそれぞれ合成することができた。ここで開発した合成法は、ビルディングブロック法を取り入れることで効率の良い手法となっている。また、本手法は、これまで報告された含フッ素置換基を有するプロリン誘導体の合成とは異なり、ヒドロキシプロリン等の生体由来の原料に依存しない合成法を提供するものである。

第一章および第二章では(トリフルオロメチル)ビニル基を有する化合物の合成、およびその応用研究に関して述べた。次章では(トリフルオロメチル)ビニル基の反応性に注目して検討を行った内容に関して述べる。

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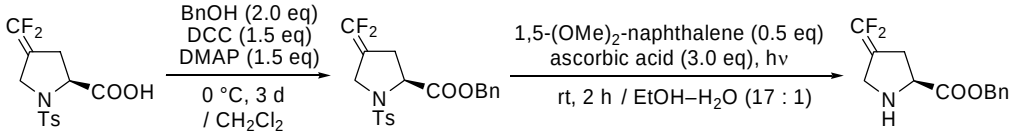

35 **44** 81% **45** 35%

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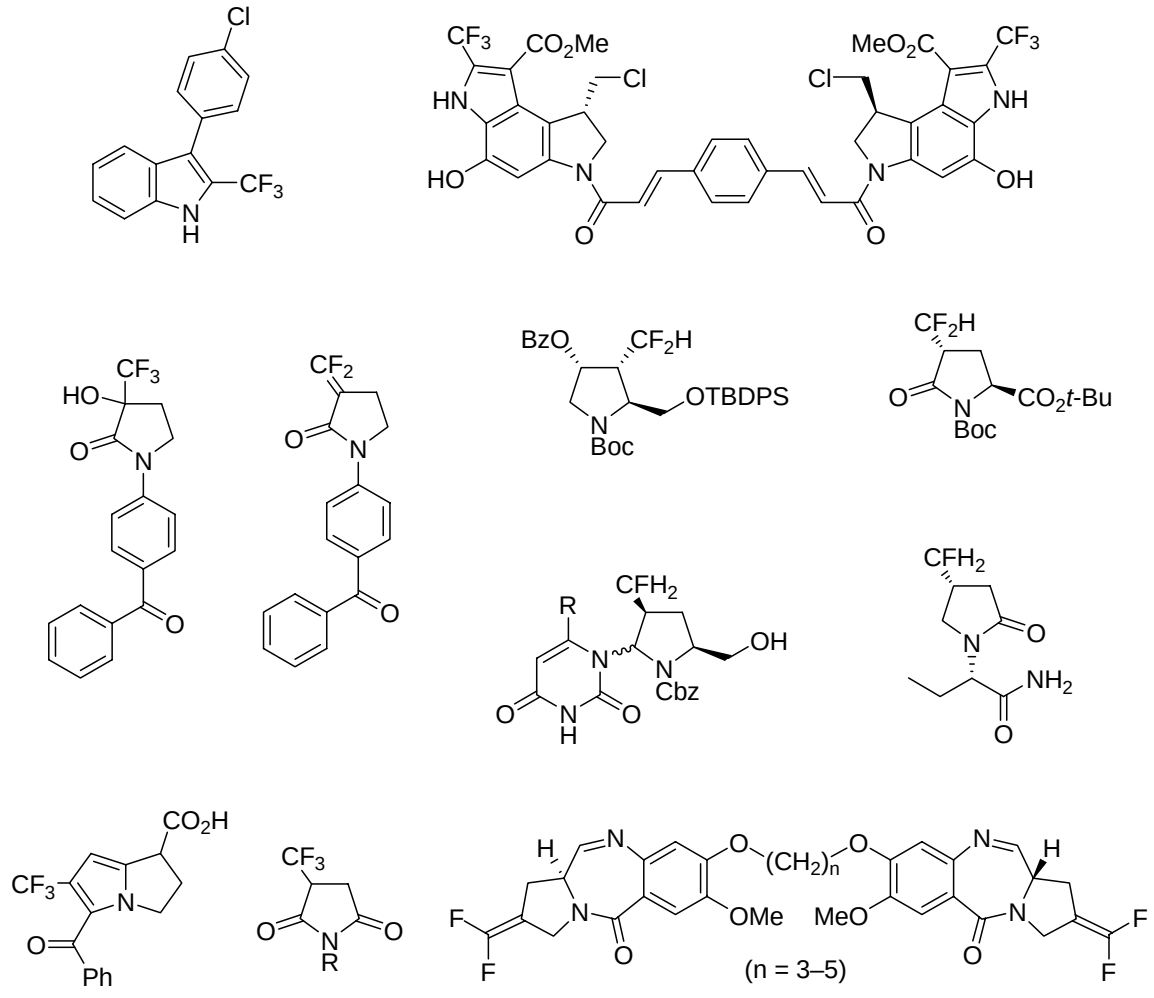
第三章　トリフルオロメチルビニル基を有するオキシム誘導体の 5-*endo* Heck 型反応

緒言

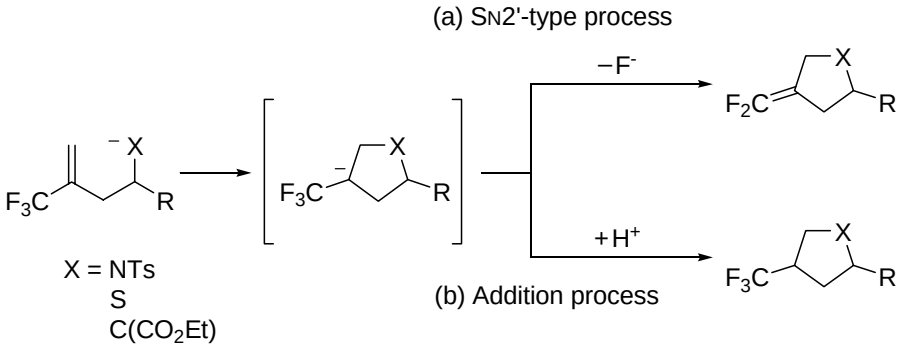
インドールやピロリジンなどの含窒素５員環構造は、多くの生理活性物質や天然物の骨格中に含まれている。生理活性物質にフッ素原子や含フッ素置換基を導入するとその生理活性が大きく変化することから[1]、フッ素原子や含フッ素置換基を有する含窒素 5 員環化合物は医農薬への応用が期待され、現在までに多くの関連する化合物が検討されている。図１に 2000 年以降報告された含フッ素炭素置換基を有する含窒素５員環化合物の一部を示す[2,3]。こうした研究の流れは今後ますます盛んになると考えられ、そのためにはフッ素を含む含窒素 5 員環化合物の新たな合成法の開発が望まれる。

図１　含フッ素置換基を有する含窒素５員環化合物

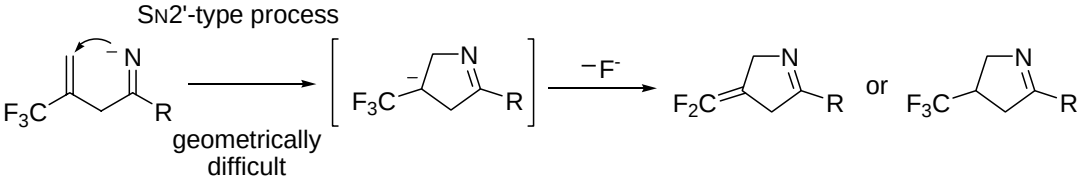


当研究室では、(トリフルオロメチル)ビニル基への求核付加反応を分子内反応に応用すると、分子間では反応しにくいヘテロ原子求核種によっても S_N2'型反応が進行することを見出している[4]。これを 5 員環形成に利用することで、困難とされる 5-*endo-trig* 環化[5]に成功し、含フッ素炭素置換基を有

する種々のヘテロ環および炭素環を構築できることを示した(式 1)[6]。筆者は、さらにこれを第二章で述べたプロリン合成へと展開した。



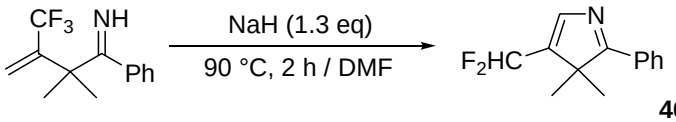
(1)



(2)

この(トリフルオロメチル)ビニル基への求核攻撃を特徴とする 5-*endo-trig*型の反応(式 1)において、アミドの窒素アニオンの代わりにイミンの窒素アニオンを求核種として導入するとピロリンが合成できることになる。これは、環内にイミン部位を有するため、様々な含フッ素ピロリジン誘導体の合成に有用な中間体となる。但しこの環化前駆体は、環を形成する 5 個の原子のうち 4 個までが sp^2 混成軌道を持つため、コンフォメーションの自由度が少ない。従って、その環化は立体的に極めて困難な反応になると予想され、より難易度の高い課題と考えられた(式 2)。

そこで、2-(トリフルオロメチル)アリル=ケトンのイミンを NaH で処理して脱プロトンを行い、対応する窒素アニオンを発生させて、5-*endo-trig* 型の分子内 SN2′型反応を試みた。その結果、目的の環化反応が進行した後に二重結合が異性化した 4-ジフルオロメチル-3*H*-ピロールが少量得られた(式 3)。このことから、sp^2 窒素アニオンの(トリフルオロメチル)ビニル基への求核攻撃は反応性が十分ではなく、5-*endo-trig*形式で環化を行うのは困難であり、その達成には別の手法を必要とすることがわかった。

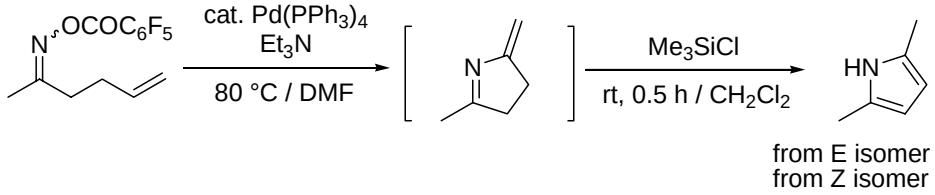


46 9%

(3)

ところで当研究室では、下記のようなアルケン部を有する *O*-ペンタフルオロベンゾイルオキシムの分子内 Heck 反応を報告している[7]。この反応は、C−N 結合形成によりピロール等の含窒素環状化合

物を与えることから、含窒素ヘテロ環合成の有力な合成手法となっている[8]。



(4)

この反応の機構を図 2 に示す。*O*-ペンタフルオロベンゾイルオキシムの N－O 結合が 0 価パラジウム錯体に酸化的付加し、生成したアルキリデンアミノパラジウム種 **A** にアルケンが挿入することで C－N 結合が形成される。最後にヒドリドパラジウム種が脱離することでイミン部が生成し、パラジウムヒドリドから HX が還元的脱離することにより触媒サイクルが成立する。

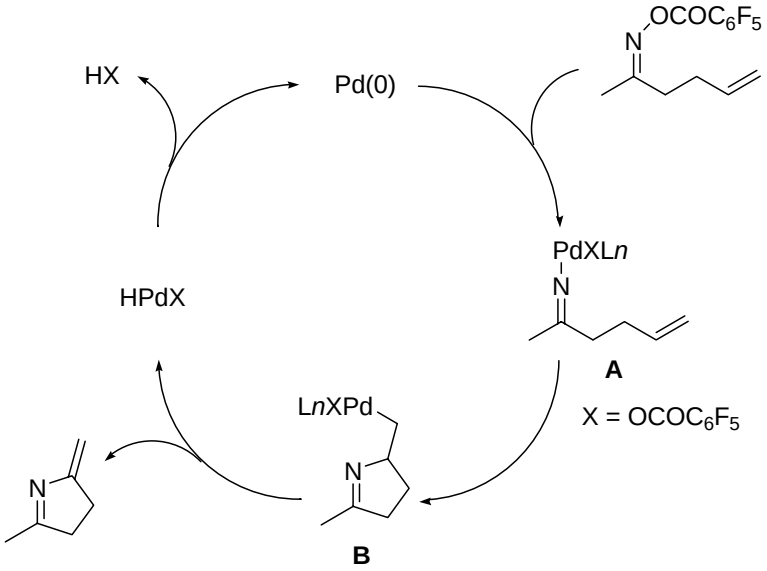
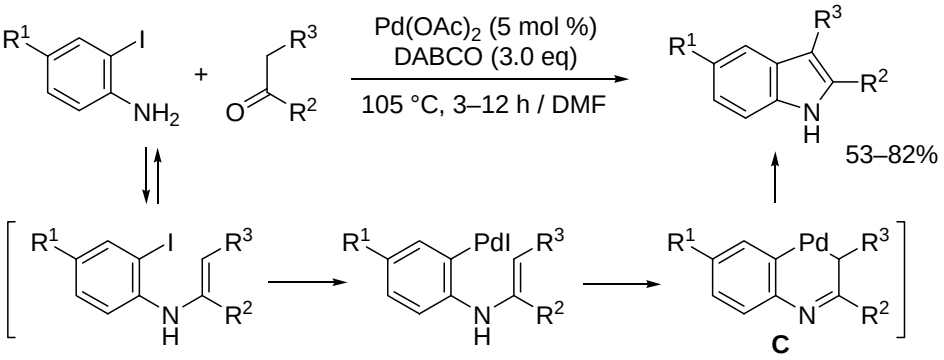
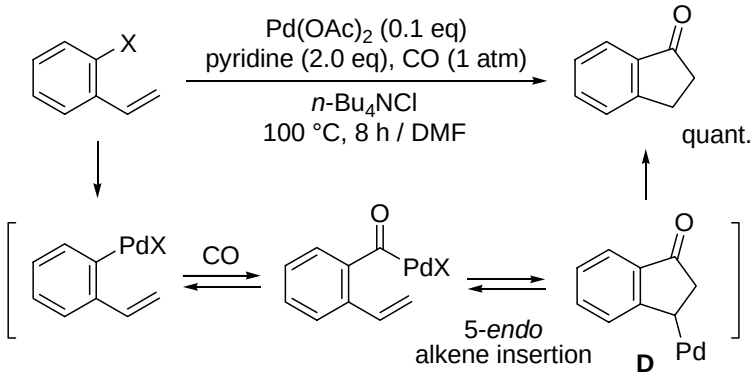


Figure 2. Mechanism.

一般に、分子内 Heck 反応においては上記の例も含めて *exo* 型の環化が進行し易いとされ、中でも 5-*endo* 型の反応例は少ない。例外として、エナミンあるいはビニルエーテル部位を有する化合物の分子内 Heck 反応が挙げられるが、これはパラジウム上の配位子変換で 6 員環パラダサイクル中間体 **C** を形成した後、還元的脱離により C－C 結合が生成しカップリングして、見掛け上 5-*endo* 型の生成物が得られた可能性が指摘されている(式 5)[9]。一方、式 6 のアシルパラジウム中間体 **D** を経る反応は、数少ない 5-*endo* Heck 反応と言える[10]。これはアシル基の電子求引性によりパラジウム原子上が電子不足なため、5-*endo* 形式にもかかわらずアルケン挿入が進行したものと考えられる[11]。

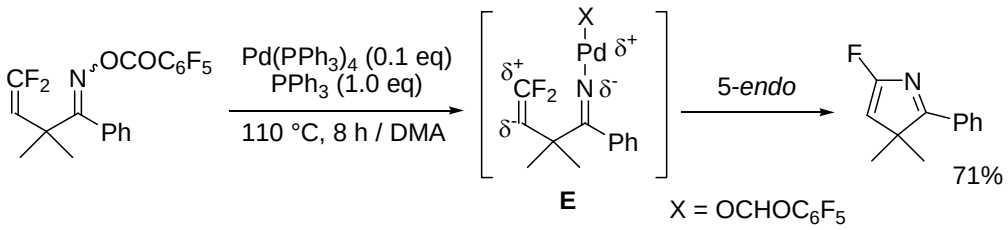


(5)



(6)

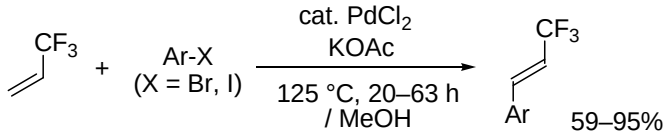
これに対し、最近当研究室では *gem*-ジフルオロアルケンへのアルキリデンアミノパラジウムによる 5-*endo* Heck 型環化反応を開発しており、フルオロピロールの触媒的合成に成功した(式 7)[12)]。この反応は、アルキリデンアミノパラジウム中間体 **E** において、それぞれ分極した *gem*-ジフルオロビニル基の二重結合部と Pd－N 結合部の間の静電的相互作用により促進されたものと考えている。



(7)

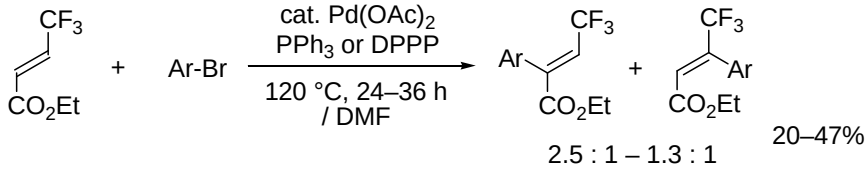
一方、ここで(トリフルオロメチル)ビニル基を有する化合物の Heck 反応に目を向けると、以下のような分子間反応が知られており、位置選択性に関して興味深い知見が得られている。

Ojima は 3,3,3-トリフルオロプロペンとハロゲン化アリールの Heck 反応に関して報告している(式 8)[13d)]。この反応では、トリフルオロメチル基のβ位に選択的にアリール化が進行し、α位での C－C 結合生成は起こらない。



(8)

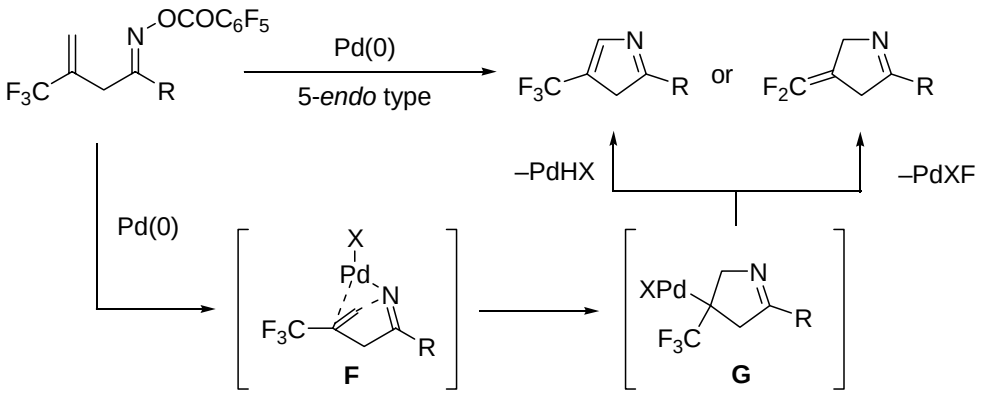
また Kimoto は、β-(トリフルオロメチル)アクリル酸エステルを用いてハロゲン化アリールとの Heck 反応を行い、トリフルオロメチル基のβ位にアリール基が結合した異性体が若干優先して得られることを報告している(式 9)[13a)]。電子求引基を有するアルケンの Heck 反応では、一般に電子求引基のβ位に置換基が導入されることが知られており、アクリル酸エステルではカルボニル基のβ位に C－C 結合生成が進行する[11a)]。ここでは、トリフルオロメチル基の電子求引効果がエトキシカルボニル基のそれに勝ったため、トリフルオロメチル基のβ位をアリール化した生成物が多く得られたものと考えることができる。



(9)

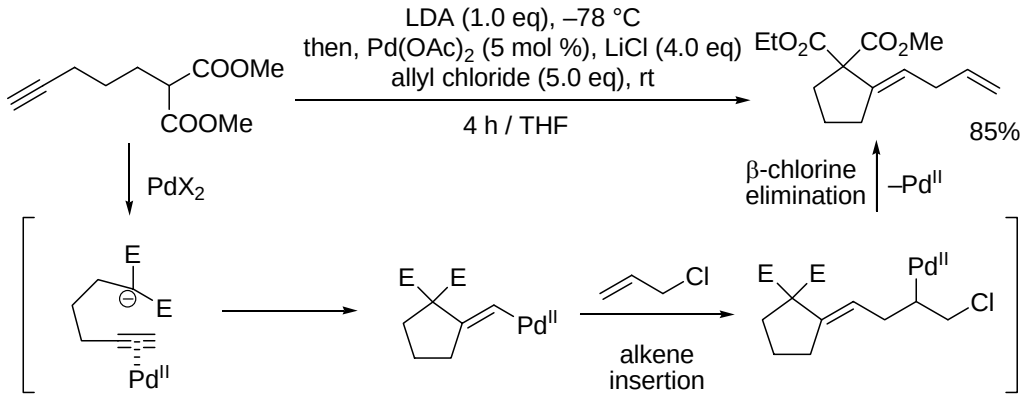
Deeth は 3,3,3-トリフルオロプロペンを含む一置換アルケンとの Heck 反応に関して計算を行い、アルケン挿入の位置選択性に対して定量的な解釈を与えた[13e)]。アルケン挿入段階におけるα置換およびβ置換のそれぞれの遷移状態のエネルギー差を求めることで位置選択性は予測できるが、前駆体アルケン－Pd 錯体におけるアルケン部位の分極を含む電子構造を考慮することによって位置選択性を数値化することができ、トリフルオロプロペンではトリフルオロメチル基のβ位において選択的に炭素―炭素結合が生成するとしている。

以上に挙げた(トリフルオロメチル)ビニル化合物の Heck 反応におけるβ位選択性に関する報告例から、この選択性を発現する原動力の一つであるトリフルオロメチル基の電子求引効果がアルケン挿入を促進できると、例の少ない 5-*endo* 形式の環化を達成でき(式 10)、式 2 に示した困難な 5-*endo* 形式での二重結合同士の結合形成が行え、含フッ素置換基を有するピロリン、ピロールの合成へ展開できると考えた。



(10)

近傍にハロゲンを有するアルケンが二価パラジウム錯体に挿入して生成する Pd 中間体からは、β水素脱離の他にβ-ハロゲン脱離が進行する可能性もある[14]。式 11 にβ-ヘテロ原子脱離を伴う反応を示す。式 10 における(トリフルオロメチル)ビニル化合物の Heck 型反応において、アルケン挿入が進行して、生成する中間体 **G** からはβ-水素脱離の他にβ-フッ素脱離が進行する可能性もあり、これら二つの脱離反応の選択性を見る上で興味深い基質と言える。また、β-フッ素脱離が進行すればジフルオロメチレン基が生成するが、この含フッ素炭素置換基は多様な反応性を示すので[15]、更に複雑な含フッ素化合物の構築に有用である。

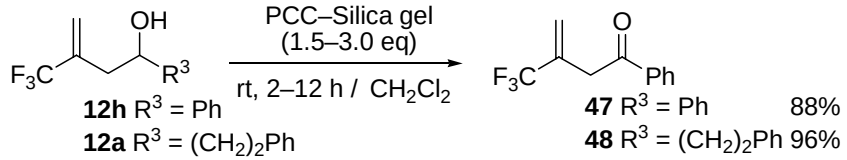


(11)

本章では、(トリフルオロメチル)ビニル基を有する *O*-ペンタフルオロベンゾイルオキシム化合物の 5-*endo* 型分子内 Heck 反応に関して行った研究について述べる。

第一節　環化前駆体の合成

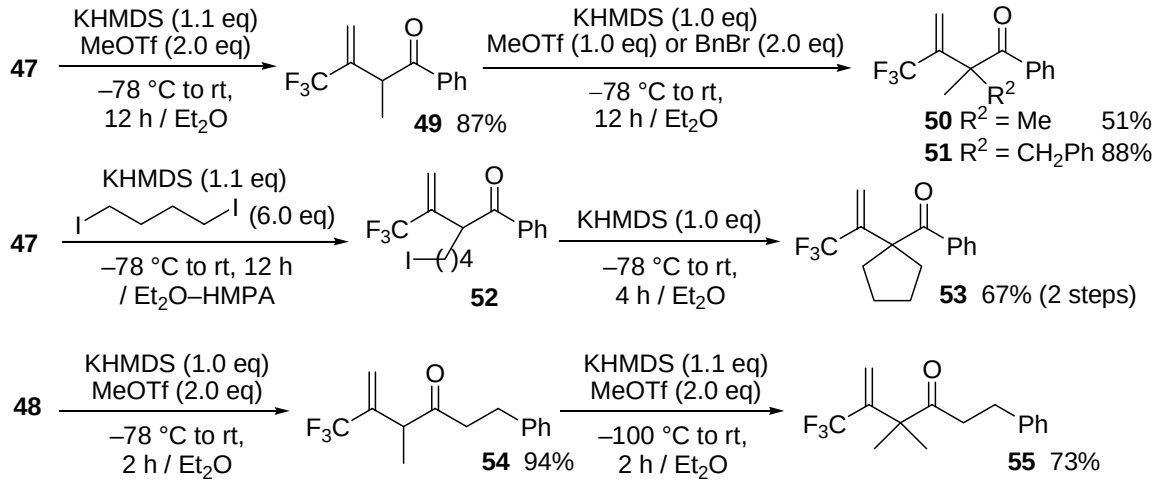
(トリフルオロメチル)ビニル基を有する *O*-ペンタフルオロベンゾイルオキシムを以下の方法で合成した。第一章第二節で述べた 1-(トリフルオロメチル)ビニルリチウム **2** によるオキシランの開環反応[16]、もしくは 2-(トリフルオロメチル)アリルシランのアルデヒドへの付加反応[17]を用いて合成した 3-(トリフルオロメチル)ホモアリルアルコール **12a**,**12h** を PCC で酸化し、ケトン **47**,**48** を得た(式 12)。KHMDS で処理してケトンエノラートを生成し、ハロゲン化アルキルまたはトリフルオロメタンスルホン酸メチルを反応させてα位のアルキル化を行い、α-モノアルキルケトン **49**,**54** やα-ジアルキルケトン **50**,**51**,**53**,**55** を調製した(式 13)。



12h R^3 = Ph
12a R^3 = $(CH_2)_2Ph$

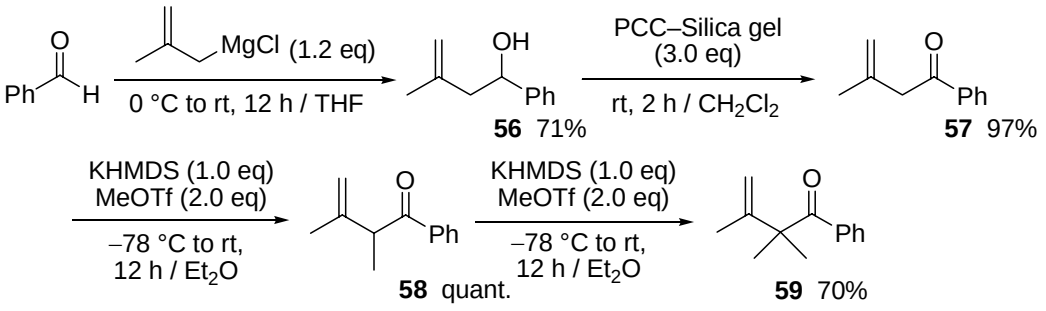
47 R^3 = Ph　88%
48 R^3 = $(CH_2)_2Ph$　96%

(12)



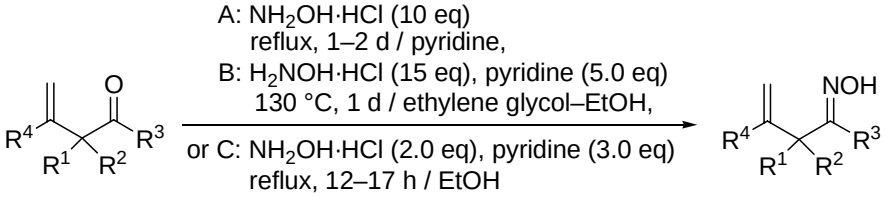
(13)

また、**50** のトリフルオロメチル基の代わりにメチル基を導入した対応するアリル=ケトン **59** も合成した(式 14)。



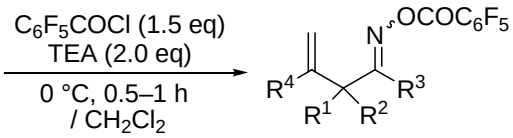
(14)

続いて、ヒドロキシアミンを用いて、上述のケトン **47**,**49**,**50**,**51**,**53**,**55**,**59** をオキシム化し、**60a–g** へ誘導した。最後にオキシムをペンタフルオロベンゾイル化することにより、目的の環化前駆体 *O*-ペンタフルオロベンゾイルオキシム **61a–g** を得た(式 15)。



60a R^1,R^2 = Me, R^3 = Ph, R^4 = CF_3 59% (method A)
60b R^1 = Me, R^2 = CH_2Ph, R^3 = Ph, R^4 = CF_3 51% (method B)
60c R^1,R^2 = -$(CH_2)_4$-, R^3 = Ph, R^4 = CF_3 47% (method B)
60d R^1,R^2 = Me, R^3 = $(CH_2)_2$Ph, R^4 = CF_3 48% (method A)
60e R^1 = H, R^2 = H, R^3 = Ph, R^4 = CF_3 89% (method C)
60f R^1 = H, R^2 = Me, R^3 = Ph, R^4 = CF_3 91% (method C)
60g R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = Me 84% (method A)

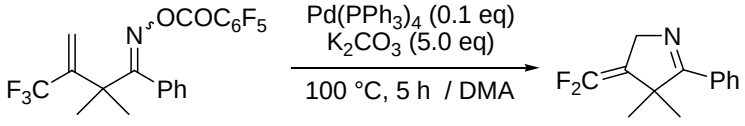
(15)



61a R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = CF_3 82%
61b R^1 = Me, R^2 =CH_2Ph, R^3 = Ph, R^4 = CF_3 76%
61c R^1,R^2 = -$(CH_2)_4$-, R^3 = Ph, R^4 = CF_3 82%
61d R^1,R^2 = Me, R^3 = $(CH_2)_2$Ph, R^4 = CF_3 87%
61e R^1 = H, R^2 = H, R^3 = Ph, R^4 = CF_3 88%
61f R^1 = H, R^2 = Me, R^3 = Ph, R^4 = CF_3 58%
61g R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = Me 34%

第二節　トリフルオロメチルビニル基を有するオキシム誘導体の 5-*endo* Heck 型反応

まず、通常の Heck 反応条件での環化反応を試みた。$Pd(PPh_3)_4$ 触媒と K_2CO_3 を加え、100 ℃に加熱したところ、収率 36%で目的とする 5 員環生成物 **62a** を得ることができた(式 16)。

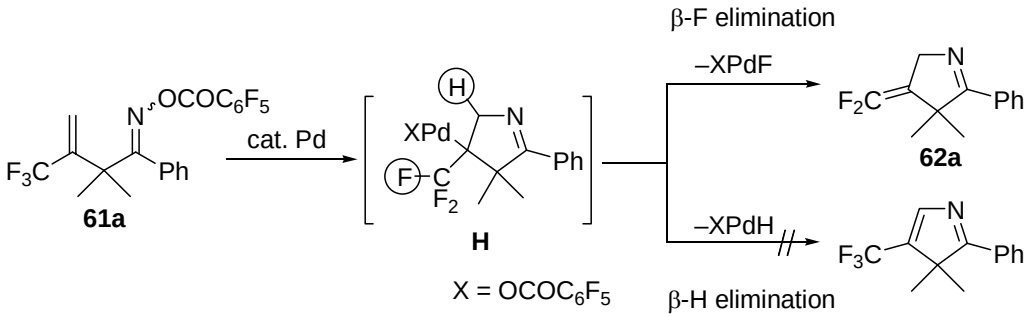


61a　　**62a** 36%

(16)

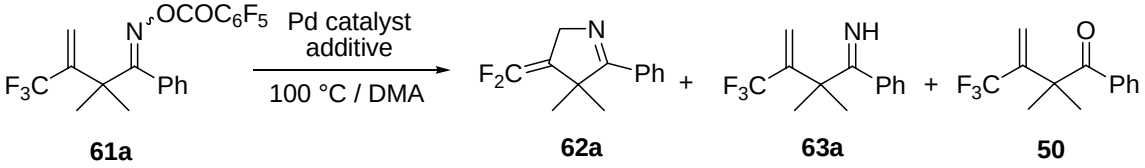
但し生成物 **62a** は、予想された(トリフルオロメチル)ピロールではなく(ジフルオロメチレン)ピロリンであった。すなわち、(トリフルオロメチル)ビニル化合物の分子間 Heck 反応(式 9,10)と異なり、β-水素脱離ではなくβ-フッ素脱離が進行した(式 17)。また、10 mol %の触媒量に対して 36%のピロ

リンが得られたことから、β-フッ素脱離により生成した二価のフッ化パラジウム化合物を 0 価へ還元するのに配位子のトリフェニルホスフィンが作用しているものと考えられる[18]。



(17)

これらを考慮に入れて、還元剤とパラジウム触媒の検討も行った。



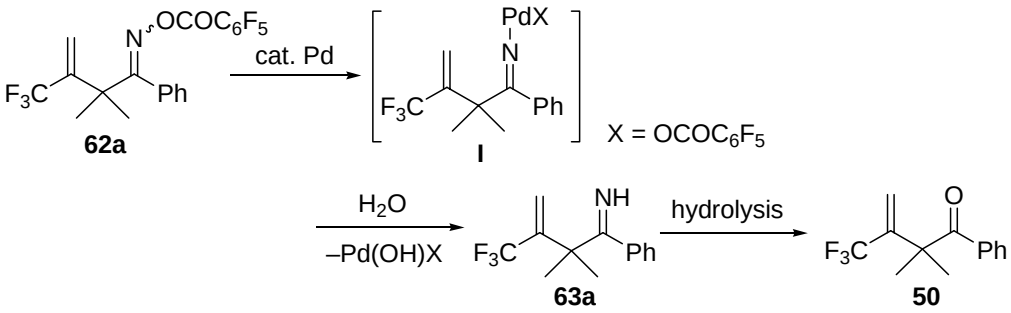
(18)

Table 1.

Entry	Pd catalyst (eq)	Additive (eq)	Time / h	Yield / %			
				62a	**63a**	**50**	**61a**
1	$Pd(PPh_3)_4$ (0.1)	K_2CO_3 (5.0)	5	36			
2	$Pd(PPh_3)_4$ (0.1)	Et_3N (5.0)	11	31		37	
3	$Pd(PPh_3)_4$ (0.1)	PPh_3 (1.0)	1	**60**	8		
4	$Pd(OAc)_2$ (0.1)	PPh_3 (1.0)	1	8	22	16	
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.05)	PPh_3 (1.0)	1	36	28		
6	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.05)	P(*o*-tol)$_3$ (1.0)	4	0			76
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.05)	$P(C_6F_5)_3$ (1.0)	4	0			27
8	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.05)	P(*t*-Bu)$_3$ (1.0)	4.5	0			76

式 16 と同様の反応条件において 1−5 倍モル量の還元剤を加え、反応を行った(式 18, 表 1)。トリエチルアミンを添加したところ、ピロリン **62a** が収率 31%で、またケトン **50** が収率 37%で得られた(entry 2)。ケトン **50** が生成する機構を式 19 に示す。アルキリデンアミノパラジウム中間体 **I** が加水分解を受け、イミンおよび二価 Pd(OH)X が生成する。反応停止後、イミンはさらに加水分解を受

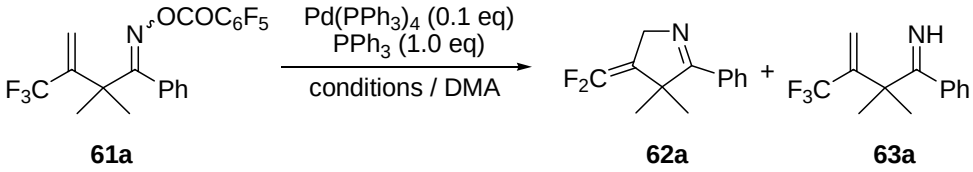
け、ケトンを生成すると考えられる。Entry 2 ではピロリン **62a** とケトン **50** が合計 68%生成しており、トリエチルアミンも二価パラジウムの還元剤として作用したと考えられる。



(19)

続いて、トリフェニルホスフィンを等モル量添加したところ、ピロリン **62a** の収率は 60%まで向上した(entry 3)。この結果から、トリフェニルホスフィンは Pd(II)の還元だけではなく、環化の促進にも影響しているものと思われる。他のパラジウム種 $Pd(OAc)_2$、$Pd_2(dba)_3{\cdot}CHCl_3$やホスフィン配位子 $P(o\text{-}Tol)_3$、$P(C_6F_5)_3$、$P(t\text{-}Bu)_3$を検討したが、良好な結果は得られなかった(entries 4–8)。

続いて、反応温度の検討を行った(式 20, 表 2)。80 ℃で反応を行うとピロリン **62a** の収率は 17%まで低下したので、120 ℃に上げたところ収率はやはり低下した。環化前駆体 **61a** のみを *N,N*-ジメチルアセトアミド中で加熱したところ、120 ℃以上では分解し始め、複数のトリフルオロメチル化合物を生じることが確認できた。これらの結果から、目的の環化には加熱を必要とするが、温度が高すぎると基質が分解して収率の低下を招くことがわかった。



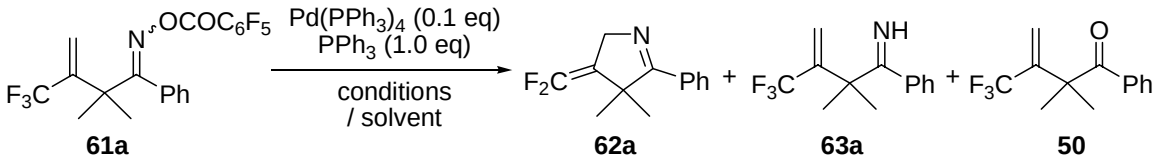
(20)

Table 2.

Entry	Conditions	Yield / %	
		62a	**63a**
1	80 °C, 2 h	17	57
2	100 °C, 1 h	**60**	8
3	120 °C, 40 min	50	17

最後に溶媒の検討を行った(式 21, 表 3)。*N,N*-ジメチルアセトアミド(DMA)と同じアミド系の溶媒

である *N,N*-ジメチルホルムアミド(DMF)や 1,3-ジメチル-2-イミダゾリジノン(DMI)を用いたが、収率の向上には至らなかった(entries 2,3)。エーテル系の溶媒として 1-メトキシ-2-(2-メトキシエトキシ)エタン(diglyme)を用いたが、大部分の原料が回収され、環化体 **62a** は得られなかった(entry 4)。トルエンを用いた場合も、収率の改善には至らなかった(entry 5)。



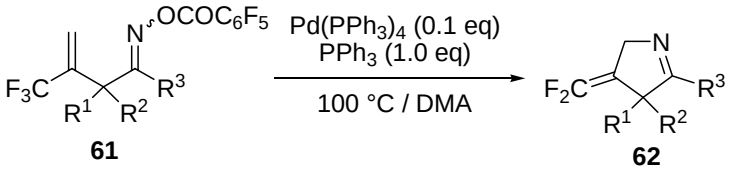
61a **62a** **63a** **50** (21)

Table 3.

Entry	Conditions / Solvent	Yield / %		
		62a	**63a**	**50**
1	100 °C, 1 h / DMA	**60**	8	
2	120 °C, 1.5 h / DMF	5	60	3
3	100 °C, 0.5 h / DMI	38	22	
4	100 °C, 1 h / diglyme	0		
5	reflux, 14 h / toluene	27		10

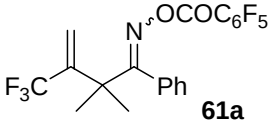
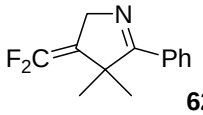
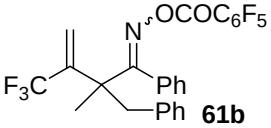
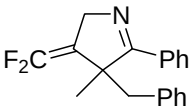
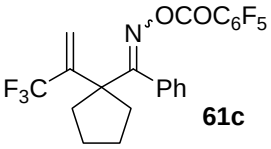
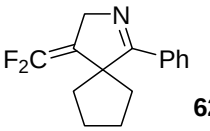
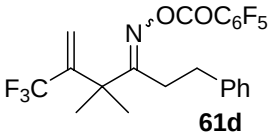
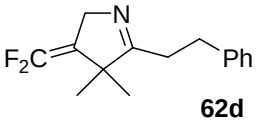
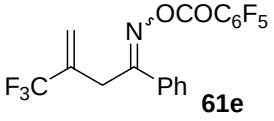
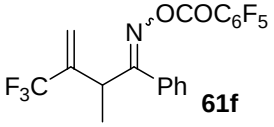
以上の検討の結果、*N,N*-ジメチルアセトアミド中で等モル量のトリフェニルホスフィンと 0.1 倍モル量のテトラキストリフェニルホスフィンパラジウムを 100 ℃で作用させた場合、ピロリン **62a** が最も良い収率で得られた。

続いて、得られた最適条件においてオキシム **61a–f** の反応を行い、基質一般性を調べた(式 22, 表 4)。



61 **62** (22)

Table 4. Synthesis of 4-difluoromethylene-1-pyrrolines **62**

Entry	Oxime	Product	Conditions	Yield / %
1	 **61a**	 **62a**	100 °C 1 h	60
2	 **61b**	 **62b**	100 °C 0.8 h	71
3	 **61c**	 **62c**	100 °C 2.5 h	65
4	 **61d**	 **62d**	100 °C 0.5 h	20[a)]
5	 **61e**	—	110 °C 2 h	—
6	 **61f**	—	80 °C 2 h	—

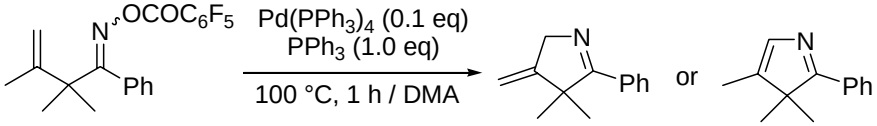
a) Yield deduced from ^{19}F NMR spectrum relative to internal standard ($(CF_3)_2C(C_6H_4$-*p*-$CH_3)_2$).

α 位に 2 つの置換基をもつアリル=フェニル=ケトン *O*-ペンタフルオロベンゾイルオキシム **61b**,**61c** からは、ピロリン **62b**,**62c** を良好な収率で得ることができた(entry 2,3)。一方、アリル=アルキル=ケトンから誘導されたオキシム **61d** を用いて反応を行ったところ、フェネチル基の酸化等の副反応が進行し、環化体 **62d** の収率は 20%であった(entry 4)。続いて、オキシムの α 位が無置換のオキシム **61e** および一置換のオキシム **61f** を用いて Heck 型の反応を行ったが、原料は消失したものの環化体は生成しなかった(entries 5,6)。これは、*gem*-ジアルキル置換基の環化促進効果[19]が失われたためと考えられるが、現在のところ明らかではない。

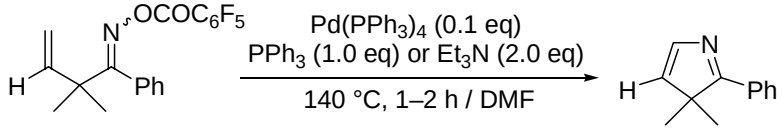
第三節　反応機構の考察

3-ホモアリル=ケトンの *O*-ペンタフルオロベンゾイルオキシムの環化では、5-*exo* 形式で反応が進行することは既に分かっているが[7,8]、今回 2-(トリフルオロメチル)アリル=ケトンの *O*-ペンタフルオロベンゾイルオキシムを用いると 5-*endo* 環化が起こることがわかった。ここで、トリフルオロメチル基の効果を確かめるため、フッ素を含まないアルケンを有するオキシムの環化反応についても検討した。

環化前駆体**61a**のトリフルオロメチル基に代えてメチル基を導入した基質**61g**に対して同様の条件を試みたが、予想されたピロリンやピロールは得られなかった(式 23)。また、トリフルオロメチル基の代わりに水素を有する基質 **61h** に関する Heck 型反応では、環化生成物が得られないことも分かっている(式 24)[11]。このことから、本 Heck 型反応においてトリフルオロメチル基が 5-*endo* 環化を促進する役割を果たしていることが明らかになった。

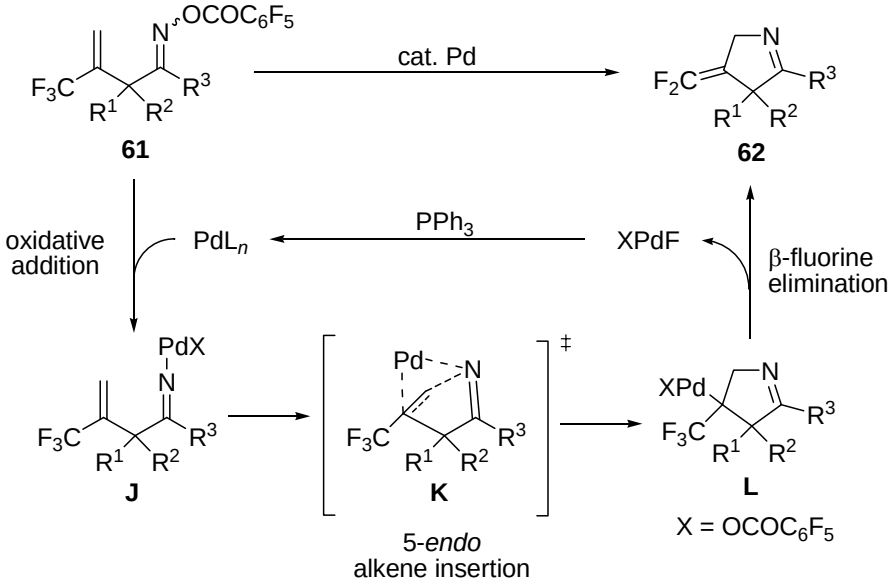


61g　　**64** 0%　　**65** 0%　　(23)



61h　　**66** 0%　　(24)

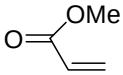
(トリフルオロメチル)ビニル基を有する *O*-ペンタフルオロベンゾイルオキシム **61** の 5-*endo* 型 Heck 型環化の反応機構は、次のように推定される(式 25)。まず、*O*-ペンタフルオロベンゾイルオキシム **61** の N－O 結合が 0 価パラジウム錯体に酸化的付加し、アルキリデンアミノパラジウム(Ⅱ)中間体 **J** が生じる。続いて 5-*endo* 形式でのアルケン挿入により中間体 **L** が生成し、β-フッ素脱離によりフッ化パラジウム(Ⅱ)錯体 XPdF が生成するとともに、ジフルオロメチレン基を有する環状イミン **62** が得られる。生じた二価のフッ化パラジウム錯体は添加したトリフェニルホスフィンにより 0 価に還元され、触媒サイクルが成立する。



(25)

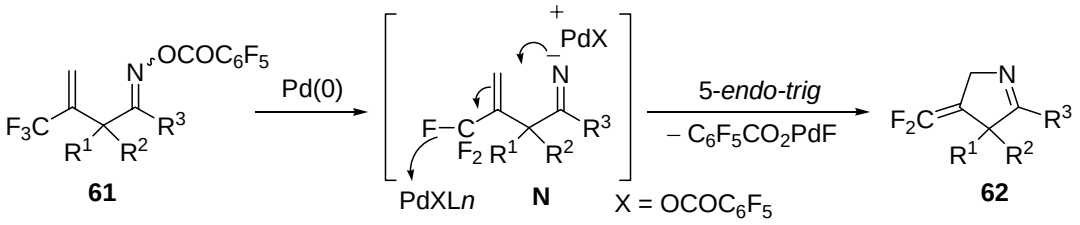
1-(トリフルオロメチル)ビニル基を有するオキシム化合物を用いることで、例の少ない 5-*endo* のアミノ-Heck 型の反応を達成できた理由は次のように考えられる。すなわち、①トリフルオロメチル基によりアルケンの LUMO が低下しており(表 5)、しかもトリフェニルホスフィンが過剰にあり逆供与の起こり易い環境であることから、イミノパラジウム種は(トリフルオロ)ビニル基と相互作用しやすく、また、②トリフルオロメチル基のα-アニオン安定化効果により、アルケン挿入反応の 4 員環遷移状態 **K**、およびアルケン挿入による C－Pd 結合を有する反応中間体 **L** も安定化を受けると考えられる。これらにより、式 2 に示す困難な 5-*endo* 形式で二重結合同士の結合形成反応が進行したものと考えられる。

Table 5. Energy levels of mono-substituted alkenes (MP2/6-31G*)

Substrate	LUMO (eV)	HOMO (eV)
	5.1	–9.6
	3.7	–11.2
	2.8	–10.6

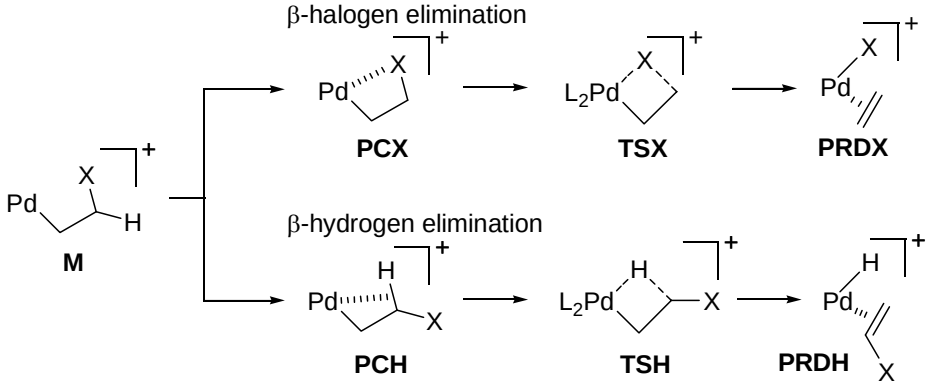
ここまでは、アルケン挿入を含む Heck 型の反応機構によって反応が進行していると考えてきたが、アルキリデンアミノパラジウム(Ⅱ)**N** の窒素原子がアルケン部位の末端炭素に求核付加して進行する S_N2'型の反応機構も考慮する必要がある(式 26)。アルキリデンアミノパラジウム(Ⅱ)中間体 **N** の N－Pd 結合は、通常の有機パラジウム化合物に比べイオン性の強いことが示唆されており [7]、(トリフル

オロメチル)ビニル基への求核攻撃により C－N 結合が生成する可能性もある。しかし、ナトリウムを対カチオンとするイミン窒素のアニオンを用いた S_N2'型反応では良好な結果が得られていないことから(式 3)、本反応ではアルケン挿入による C－N 結合生成(Heck 型反応)が進行していると推測している。



(26)

これまでトリフルオロプロペンの分子間 Heck 反応ではβ-水素脱離のみが知られてきたが[13]、本反応においてはβ-フッ素脱離がβ-水素脱離に優先して進行しており、その理由に興味がもたれる。Lin はβ-ハロゲン化エチルパラジウム化合物において、パラジウムの脱離に到るまでの過程に関して DFT 計算により解析を行っている(Figure 3)[14a]。式 27 に示すようにβ位にハロゲンと水素の両者を有するエチルパラジウム種 **M** より β-水素脱離とβ-ハロゲン脱離の過程を計算したところ、ハロゲン(X)が塩素や臭素の場合は速度論的にも熱力学的にもβ-ハロゲン脱離が起こり易いことが分かった。これに対しフッ素の場合には、β-水素脱離が速度論的に有利であるものの、熱力学的には β-水素脱離生成物 **PRDH** は C－Pd 種 **PCX** および β-フッ素脱離生成物 **PRDX** よりも不安定であり、熱力学支配の条件を設定すればβ-フッ素脱離が進行し得るものと考えられる。



(27)

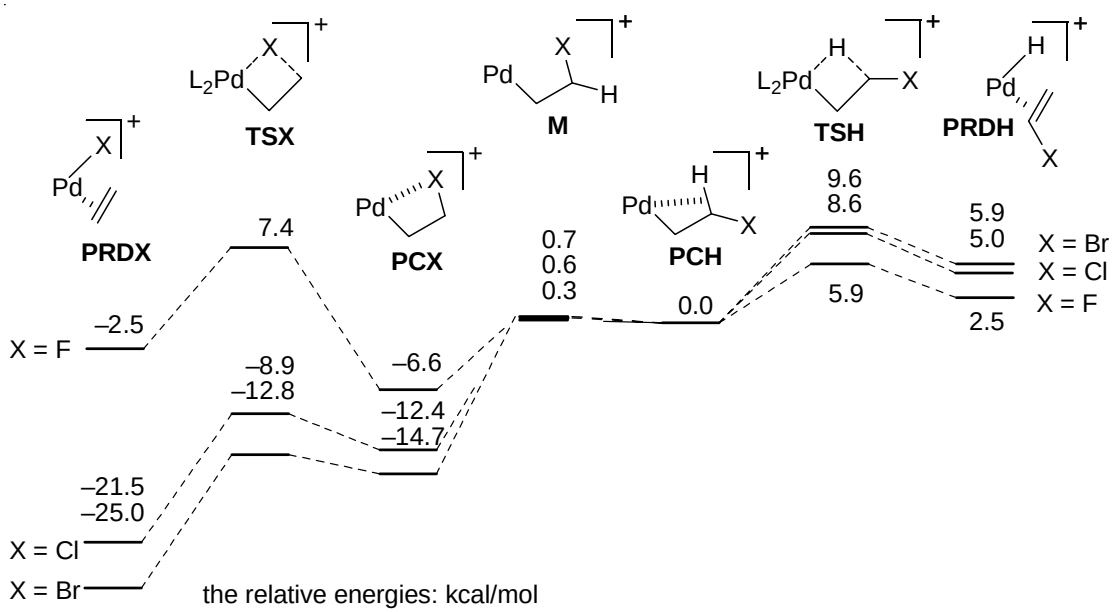


Figure 3. Energy profiles relevant to β-hydrogen and β-halogen eliminations.

また、β-ハロゲン脱離を含む Heck 型の反応という観点からも当反応は稀な例である。一般に、ハロゲン化アリルやビニルは Pd(0)錯体に酸化的付加し易いため[20]、Heck 反応のアルケン成分として用いることは困難である。そのため、Heck 反応における β-ヘテロ原子脱離反応はほとんど知られていない。一方、緒言にも述べたように(トリフルオロメチル)ビニル化合物はアリル位に脱離能を有するフッ素を持つにも関わらず Heck 反応が進行することが知られており、*gem*-ジフルオロアリルパラジウム種(Figure 4)は生成し難いことが分かる。こうした(トリフルオロメチル)ビニル基の特性のため、β-ハロゲン脱離と β-水素脱離が競合する系を初めて構築できたと言える。

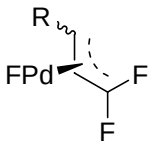


Figure 4.

以上、筆者は(トリフルオロメチル)ビニル基を有する *O*-ペンタフルオロベンゾイルオキシム **61** にトリフェニルホスフィンと触媒量のテトラキストリフェニルホスフィン(0)を作用させることにより、ジフルオロメチレン基を有するピロリン誘導体 **62** の合成法を開発することができた。本反応は、①酸化的付加によるアルキリデンアミノパラジウム種(Ⅱ)**J** の生成、②立体的に困難な 5-*endo* 形式のアルケン挿入反応、③β-水素脱離に優先する β-ハロゲン脱離反応のサイクルを有する極めて稀な触媒反応であり、(トリフルオロメチル)ビニル基の性質により達成することができたものである。

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Experimental section

^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz), and ^{19}F NMR (470 MHz) spectra were recorded in $CDCl_3$ on a Bruker Avance-500 spectrometer. ^{1}H NMR chemical shifts (δ) are given in ppm downfield from Me_4Si. ^{13}C NMR chemical shifts (δ) are given in ppm downfield from Me_4Si, relative to chloroform-*d* (δ = 77.0). ^{19}F NMR chemical shifts (δ_F) are given in ppm downfield from C_6F_6. IR spectra were recorded on a Horiba FT-300S spectrometer. Elemental analyses were performed with a YANAKO MT-6 CHN Corder apparatus. Mass spectra were taken with a JEOL MS-700M spectrometer.

All reactions were carried out under argon. Diethyl ether (Et_2O), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), CH_2Cl_2, and toluene were dried by passing over a column of activated alumina (A-2, Purity) followed by a column of Q-5 scavenger (Engelhard). 1,1,1,3,3,3-Hexafluoropropan-2-ol (HFIP) and ethanol were distilled from sodium, and stored over 3Å molecular sieves. CH_3CN and hexamethylphosphoric triamide (HMPA) were distilled from CaH_2, and stored over 3Å molecular sieves. $CHCl_3$ was passed through an alumina column prior to use. *n*-BuLi (1.5 M in hexane), *s*-BuLi (1.1 M in cyclohexane), *t*-BuLi (1.5 M in pentane) were purchased and used without further purification.

Column chromatography and preparative thin-layer chromatography (PTLC) were performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 and Wako Pure Chemical Industries, Ltd., B5-F), respectively.

The enantiomeric excess was determined by HPLC using an AD-H Daicel column.

第一章第一節

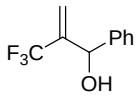
Preparation of 3,3,3-trifluoroprop-1-en-2-yllithium (2)

To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.21 mL, 2.0 mmol) in Et_2O (20 mL) was added a solution of BuLi (2.0 mmol) in Et_2O (3 mL). After stirring for 15 min, a solution of MeOH (0.10 mL, 2.5 mmol) in Et_2O (3 mL) was added slowly. Then the reaction mixture was allowed to warm up to rt, and its ^{19}F NMR spectra was observed, immediately. Signals at 56 (t), 94 (s), 96 (t) ppm were assigned to 1,1-difluoroallene **4**, 2-bromo-3,3,3-trifluoroprop-1-ene **1**, and 3,3,3-trifluoropropene **3**, respectively. Their yields were determined by ^{19}F NMR relative to internal standard ($(CF_3)CTol_2$).

Preparation of 2-(trifluoromethyl)allyl alcohols (5)

To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.21 mL, 2.0 mmol) in Et_2O (10 mL) was added a solution of *s*-BuLi (1.07 M in cyclohexane; 1.87 mL, 2.0 mmol) in Et_2O (2 mL) at –105 °C. After stirring for 10 min, a solution of aldehyde (1.0 mmol) in Et_2O (2 mL) was added dropwise. Then the reaction mixture was allowed to warm up to –50 °C over 2 h. The reaction was quenched with phosphate buffer (pH 7, 10 mL), organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give 2-(trifluoromethyl)allyl alcohol **5**.

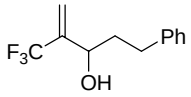
1-Phenyl-2-(trifluoromethyl)prop-2-en-1-ol (5a)



A colorless liquid. 73%.

IR (neat): 3357, 3066, 3035, 2922, 2850, 1321, 1167, 1115, 1022, 957, 698 cm^{-1}. ^1H NMR: δ 2.20–2.22 (1H, m), 5.43 (1H, d, J = 2.9 Hz), 5.80 (1H, q, J_{HF} = 1.4 Hz), 5.93 (1H, q, J_{HF} = 0.7 Hz), 7.33–7.39 (5H, m). ^{13}C NMR: δ 71.3, 119.8 (q, J_{CF} = 5 Hz), 123.1 (q, J_{CF} = 275 Hz), 126.8, 128.6, 128.7, 140.2, 140.8 (q, J_{CF} = 28 Hz). ^{19}F NMR: δ_F 96.5 (br s). HRMS (FAB): calcd for $C_{10}H_{10}F_3O$ ($[M+H]^+$) 203.0684; found 203.0687.

5-Phenyl-2-(trifluoromethyl)pent-1-en-3-ol (5b)

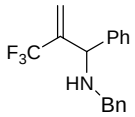


A colorless liquid. 76%.

IR (neat): 3392, 3064, 3028, 2927, 2866, 1409, 1315, 1165, 1115, 1065, 953 cm^{-1}. ^1H NMR: δ1.91 (1H, dddd, J = 13.9, 9.4, 8.6, 5.3 Hz), 2.00 (1H, d, J = 4.2 Hz), 2.01–2.08 (1H, m), 2.70 (1H, ddd, J = 13.8, 9.4, 6.6 Hz), 2.81 (1H, ddd, J = 13.8, 10.0, 5.3 Hz), 4.37 (1H, ddd, J = 8.6, 4.2, 4.2 Hz), 5.74 (1H, m), 5.84 (1H, q, J_{HF} = 1.5 Hz), 7.19 (1H, t, J = 7.6 Hz), 7.20 (2H, d, J = 7.6 Hz), 7.29 (2H, dd, J = 7.6, 7.6 Hz). ^{13}C NMR: δ 31.5, 37.7, 68.4, 119.1 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 275 Hz), 126.0, 128.3, 128.5, 141.2, 141.6 (q, J_{CF} = 28 Hz). ^{19}F NMR: δ_F 96.1 (br s). Anal. Calcd for

$C_{12}H_{13}F_3O$: C, 62.60; H, 5.69. Found: C, 62.53; H, 5.94.

_N_-Benzyl-_N_-(2-trifluoromethyl-1-phenylprop-2-en-1-yl)amine (8a)



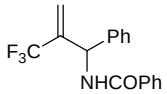
To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.21 mL, 2.0 mmol) and *N*-benzilidene(phenyl)methanamine **7a** (195 mg, 1.0 mmol) in Et_2O (10 mL) was added a solution of *s*-BuLi (1.07 M in cyclohexane; 1.87 mL, 2.0 mmol) in Et_2O (2 mL) at –105 °C. After stirring for 10 min, a solution of $BF_3{\cdot}OEt_2$ (190 mg, 1.5 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was allowed to warm up to –50 °C over 2 h. The reaction was quenched with phosphate buffer (pH 7, 10 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave crude amine (81% ^{19}F NMR yield) as a pale yellow liquid. The residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **8a** (224 mg, 77%) as a pale yellow liquid.

IR (neat): 3084, 3064, 3032, 2839, 1456, 1309, 1219, 1167, 1115, 955, 771 cm^{-1}. ^1H NMR: δ 1.70 (1H, s), 3.72 (1H, d, J = 13.2 Hz), 3.78 (1H, d, J = 13.2 Hz), 4.51 (1H, s), 5.98 (1H, m), 6.03 (1H, s), 7.27–7.41 (10H, m). ^{13}C NMR: δ 51.6, 60.6, 119.5 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 275 Hz), 127.1, 127.6, 127.8, 128.1, 128.4, 128.6, 139.8, 140.5 (q, J_{CF} = 28 Hz), 140.6. ^{19}F NMR: δ_F 95.7 (br s). Anal. Calcd for $C_{17}H_{16}F_3N$: C, 70.09; H, 5.54; N, 4.81. Found: C, 70.02; H, 5.69; N, 4.72.

Preparation of _N_-[2-(trifluoromethyl)allyl]amides (8b–g)

To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (91 μL, 0.88 mmol) in Et_2O (8 mL) was added a solution of *s*-BuLi (1.07 M in cyclohexane; 0.75 mL, 0.80 mmol) in Et_2O (2 mL) at –105 °C. After stirring for 10 min, a solution of *N*-benzoylimine **7b** or *N*-(4-methylbenzenesulfonyl)imine **7c–g** (0.40 mmol) in Et_2O (5–20 mL) was added dropwise. The reaction mixture was allowed to warm up to –50 °C over 2 h. The reaction was quenched with phosphate buffer (pH 7, 10 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give *N*-[2-(trifluoromethyl)allyl]amide **8b–g**.

_N_-[1-phenyl-2-(trifluoromethyl)prop-2-ene-1-yl]benzamide (8b)

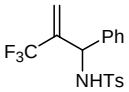


Colorless crystals. 97%.

mp. 153–154 °C. IR (neat): 3313, 3057, 3030, 1637, 1533, 1489, 1219, 1119, 769 cm^{-1}. ^1H NMR: δ 5.61 (1H, s), 5.99 (1H, s), 6.06 (1H, d, J = 7.5 Hz), 6.59 (1H, br d, J = 7.5 Hz), 7.32–7.40 (5H, m), 7.42 (2H, dd, J = 7.4, 7.4 Hz), 7.51 (1H, t, J = 7.4 Hz), 7.77 (2H, d, J = 7.4 Hz). ^{13}C NMR: δ 53.2, 121.3 (q, J_{CF} = 5 Hz), 123.2 (q, J_{CF} = 275 Hz), 127.0, 127.2, 128.4, 128.7, 128.9, 131.9, 133.7, 137.9, 138.7 (q, J_{CF} = 29 Hz), 166.3. ^{19}F NMR: δ_F 96.8 (br s). Anal. Calcd for

$C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; N, 4.59. Found: C, 67.01; H, 4.80; N, 4.57.

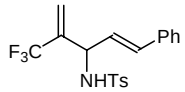
4-Methyl-*N*-[1-phenyl-2-(trifluoromethyl)prop-2-en-1-yl]benzenesulfonamide (8c)



Colorless crystals. 90%.

mp. 111–114 °C. IR (neat): 3261, 3064, 2929, 1435, 1323, 1159, 1115, 1090, 968, 914, 771, 660 cm^{-1}. ^1H NMR: δ 2.41 (3H, s), 5.12 (1H, d, J = 7.2 Hz), 5.43 (1H, d, J = 7.2 Hz), 5.73 (1H, s), 5.88 (1H, s), 7.04 (2H, d, J = 6.5 Hz), 7.18–7.25 (5H, m), 7.63 (2H, d, J = 8.2 Hz). ^{13}C NMR: δ 21.5, 56.5, 121.6 (q, J_{CF} = 5 Hz), 122.8 (q, J_{CF} = 275 Hz), 127.1, 127.2, 128.4, 128.8, 129.5, 136.8, 137.2, 138.0 (q, J_{CF} = 29 Hz), 143.7. ^{19}F NMR: δ_F 96.5 (br s). Anal. Calcd for $C_{17}H_{16}F_3NO_2S$: C, 57.46; H, 4.54; N, 3.94. Found: C, 57.72; H, 4.73; N, 3.74.

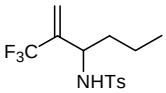
4-Methyl-*N*-{1-[(*E*)-2-phenylethenyl]-2-(trifluoromethyl)prop-2-en-1-yl}benzenesulfonamide (8d)



Colorless crystals. 89%.

mp. 121–123 °C. IR (neat): 3267, 3027, 2926, 1448, 1327, 1157, 1120, 1047, 964, 665 cm^{-1}. ^1H NMR: δ 2.32 (3H, s), 4.77 (1H, dd, J = 7.6, 7.6 Hz), 5.48 (1H, d, J = 7.6 Hz), 5.68 (1H, s), 5.81 (1H, s), 5.86 (1H, dd, J = 15.8, 7.6 Hz), 6.32 (1H, d, J = 15.8 Hz), 7.15 (2H, d, J = 7.6 Hz), 7.20 (2H, d, J = 8.1 Hz), 7.22–7.28 (3H, m), 7.74 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.4, 54.9, 121.6 (q, J_{CF} = 5 Hz), 122.8 (q, J_{CF} = 275 Hz), 124.9, 126.6, 127.3, 128.2, 128.5, 129.6, 133.4, 135.5, 137.2, 137.6 (q, J_{CF} = 29 Hz), 143.7. ^{19}F NMR: δ_F 96.6 (br s). Anal. Calcd for $C_{19}H_{18}F_3NO_2S$: C, 59.83; H, 4.76; N, 3.67. Found: C, 59.58; H, 4.99; N, 3.48.

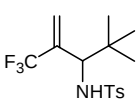
4-Methyl-*N*-[2-(trifluoromethyl)hex-1-en-3-yl]benzenesulfonamide (8e)



Colorless crystals. 77%.

mp. 75–77 °C. IR (neat): 3275, 2964, 2935, 2877, 1323, 1155, 1120, 1092, 661 cm^{-1}. ^1H NMR: δ 0.81 (3H, t, J = 7.3 Hz), 1.16–1.28 (1H, m), 1.30–1.41 (1H, m), 1.51 (1H, dddd, J = 9.0, 9.0, 9.0, 5.2 Hz), 1.60 (1H, dddd, J = 9.0, 9.0, 9.0, 5.8 Hz), 2.42 (3H, s), 3.99 (1H, ddd, J = 9.0, 9.0, 5.2 Hz), 5.51 (1H, s), 5.63 (1H, s), 5.73 (1H, d, J = 9.0 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 13.2, 18.6, 21.4, 37.3, 53.1, 120.6 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 275 Hz), 127.1, 129.5, 137.3, 138.4 (q, J_{CF} = 28 Hz), 143.5. ^{19}F NMR: δ_F 96.5 (br s). Anal. Calcd for $C_{14}H_{18}F_3NO_2S$: C, 52.32; H, 5.65; N, 4.36. Found: C, 52.21; H, 5.71; N, 4.18.

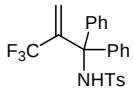
4-Methyl-*N*-[4,4-dimethyl-2-(trifluoromethyl)pent-1-en-3-yl]benzenesulfonamide (8f)



Colorless crystals. 96%.

mp. 153–154 °C. IR (neat): 3275, 2981, 2908, 2871, 1454, 1331, 1171, 1120, 1070, 685 cm^{-1}. ^{1}H NMR: δ 0.92 (9H, s), 2.41 (3H, s), 3.78 (1H, d, J = 9.7 Hz), 5.53 (1H, s), 5.70 (1H, s), 5.95 (1H, d, J = 9.7 Hz), 7.26 (2H, d, J = 8.3 Hz), 7.72 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.5, 26.3, 35.6, 60.3, 123.0 (q, J_{CF} = 275 Hz), 123.6 (q, J_{CF} = 6 Hz), 127.3, 129.4, 137.1, 138.3 (q, J_{CF} = 29 Hz), 143.4. ^{19}F NMR: δ_F 98.7 (br s). Anal. Calcd for $C_{15}H_{20}F_3NO_2S$: C, 53.72; H, 6.01; N, 4.18. Found: C, 53.76; H, 6.16; N, 3.93.

4-Methyl-*N*-[1,1-diphenyl-2-(trifluoromethyl)prop-2-en-1-yl]benzenesulfonamide (8g)



Colorless crystals. 76%.

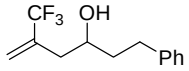
mp. 166–167 °C. IR (neat): 3292, 3064, 3030, 1404, 1311, 1155, 1120, 1028, 769, 546 cm^{-1}. ^{1}H NMR: δ 2.35 (3H, s), 5.66 (1H, s), 5.99 (1H, s), 6.18 (1H, s), 7.01 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz), 7.17 (4H, dd, J = 6.4, 6.4 Hz), 7.21–7.26 (6H, m). ^{13}C NMR: δ 21.4, 71.4, 123.5 (q, J_{CF} = 277 Hz), 124.6 (q, J_{CF} = 5 Hz), 126.7, 127.6, 128.1, 128.9, 129.7, 138.4, 139.1, 142.5 (q, J_{CF} = 27 Hz), 142.6. ^{19}F NMR: δ_F 104.1 (br s). Anal. Calcd for $C_{23}H_{20}F_3NO_2S$: C, 64.02; H, 4.67; N, 3.25. Found: C, 64.21; H, 4.87; N, 3.07.

第一章第二節

Oxirane ring opening with 3,3,3-trifluoroprop-1-en-2-yllithium (2)

To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.47 mL, 4.5 mmol) and $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) in Et_2O (15 mL) was added dropwise a solution of *n*-BuLi (2.67 M in hexane; 1.69 mL, 4.5 mmol) in Et_2O (2 mL) at –100 °C. After the mixture was stirred for 15 min, a solution of oxirane **9** (3.0 mmol) in Et_2O (2 mL) was added dropwise. The mixture was stirred for 15 min, and then allowed to warm up to room temperature. The reaction mixture was quenched with phosphate buffer (pH 7, 30 mL) and organic materials were extracted with EtOAc (15 mL × 2). The combined extracts were washed with water (10 mL × 2) and brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give 3-(trifluoromethyl)homoallyl alcohol **12**.

1-Phenyl-5-(trifluoromethyl)hex-5-en-3-ol (12a)

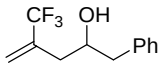


A colorless liquid. 91%.

IR (neat): 3384, 3027, 2929, 1604, 1496, 1454, 1344, 1165, 1117, 947, 748 cm^{-1}. ^{1}H NMR: δ 1.70 (1H, d, J = 4.2 Hz), 1.76–1.88 (2H, m), 2.32 (1H, ddd, J = 15.0, 8.4, 0.9 Hz), 2.44 (1H, ddd, J = 15.0, 4.2, 0.9 Hz), 2.70 (1H, ddd, J = 13.8, 9.6, 6.7 Hz), 2.83 (1H, ddd, J = 13.8, 9.8, 5.8 Hz), 3.85 (1H, ddddd, J = 8.4, 8.4, 4.2, 4.2, 4.2 Hz), 5.46 (1H, q, J_{HF} = 1.2 Hz), 5.79 (1H, q, J_{HF} = 1.5 Hz), 7.18–7.21 (3H, m), 7.27–7.31 (2H, m). ^{13}C NMR: δ 32.0, 38.2, 38.8, 68.7, 121.0 (q,

J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 126.0, 128.4, 128.5, 135.0 (q, J_{CF} = 30 Hz), 141.6. ^{19}F NMR: δ_F 93.5 (br s). Anal. Calcd for $C_{13}H_{15}F_3O$: C, 63.93; H, 6.19. Found: C, 64.19; H, 6.40.

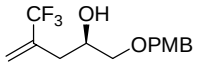
1-Phenyl-4-(trifluoromethyl)pent-4-en-2-ol (12b)



A colorless liquid. 89%.

IR (neat): 3426, 3030, 2924, 1496, 1455, 1418, 1164, 1111, 1080, 946 cm^{-1}. ^{1}H NMR: δ 1.71 (1H, d, J = 4.3 Hz), 2.34 (1H, ddd, J = 15.1, 8.6, 0.8 Hz), 2.43 (1H, ddd, J = 15.1, 4.3, 0.8 Hz), 2.66 (1H, dd, J = 13.6, 8.6 Hz), 2.83 (1H, dd, J = 13.6, 4.3 Hz), 4.00 (1H, ddddd, J = 8.6, 8.6, 4.3, 4.3, 4.3 Hz), 5.52 (1H, q, J_{HF} = 1.3 Hz), 5.81 (1H, q, J_{HF} = 1.4 Hz), 7.20 (2H, d, J = 7.3 Hz), 7.22 (1H, t, J = 7.3 Hz), 7.30 (2H, dd, J = 7.3, 7.3 Hz). ^{13}C NMR: δ 37.3, 43.6, 70.0, 120.8 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 126.7, 128.6, 129.4, 135.0 (q, J_{CF} = 30 Hz), 137.8. ^{19}F NMR: δ_F 93.6 (br s). Anal. Calcd for $C_{12}H_{13}F_3O$: C, 62.60; H, 5.69. Found: C, 62.52; H, 5.86.

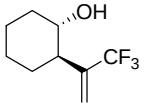
(*R*)-1-(4-Methoxybenzyloxy)-4-(trifluoromethyl)pent-4-en-2-ol [(*R*)-12c]



To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene (**1**, 1.55 mL, 15.0 mmol) and BF_3·OEt_2 (1.89 mL, 15.0 mmol) in Et_2O (40 mL) was added dropwise a solution of *n*-BuLi (2.59 M in hexane; 5.79 mL, 15.0 mmol) in Et_2O (4 mL) at –100 °C. After the mixture was stirred for 15 min, a solution of 2-[(4-methoxybenzyloxy)methyl]oxirane **9c** (98.7% ee, 1.94 g, 10.0 mmol) in Et_2O (4 mL) was added dropwise. The mixture was stirred for 15 min, and then allowed to warm up to rt. The reaction mixture was quenched with phosphate buffer (pH 7, 50 mL), and organic materials were extracted with EtOAc (30 mL × 2). The combined extracts were washed with water (30 mL × 2), brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **(*R*)-12c** (2.37 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ = –2.6 (*c* 1.0, $CHCl_3$). IR (neat): 3446, 2908, 2864, 1612, 1514, 1246, 1165, 1109, 1034, 947, 820 cm^{-1}. ^{1}H NMR: δ 2.32–2.34 (2H, m), 2.56 (1H, br s), 3.35 (1H, dd, J = 9.5, 6.8 Hz), 3.50 (1H, dd, J = 9.5, 3.3 Hz), 3.80 (3H, s), 3.97–4.02 (1H, m), 4.46 (1H, d, J = 11.5 Hz), 4.49 (1H, d, J = 11.5 Hz), 5.49 (1H, q, J_{HF} = 1.2 Hz), 5.77 (1H, q, J_{HF} = 1.3 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 8.7 Hz). ^{13}C NMR: δ 33.6, 55.2, 68.1, 73.0, 73.2, 113.9, 120.6 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 274 Hz), 129.4, 129.7, 134.5 (q, J_{CF} = 30 Hz), 159.4. ^{19}F NMR: δ_F 93.2 (br s). Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.93; H, 5.90. Found: C, 57.91; H, 5.95. HPLC (*i*-PrOH:hexane = 1:50): retention time 19.6 min major peak, 23.9 min minor peak.

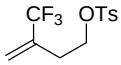
***trans*-2-[1-(Trifluoromethyl)vinyl]cyclohexanol (12d)**



A colorless liquid. 40%.

IR (neat): 3404, 2933, 2860, 1450, 1346, 1296, 1163, 1113, 1063, 937 cm^{-1}. ^1H NMR: δ 1.22–1.34 (4H, m), 1.69–1.72 (1H, m), 1.78–1.82 (1H, m), 1.92–1.94 (1H, m), 2.02 (1H, br s), 2.07–2.10 (1H, m), 2.11–2.16 (1H, m), 3.58 (1H, ddd, J = 10.2, 10.2, 4.3 Hz), 5.49 (1H, s), 5.85 (1H, q, J_{HF} = 1.3 Hz). ^{13}C NMR: δ 24.7, 25.7, 33.0, 34.9, 47.1, 72.6, 118.5 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 274 Hz), 140.8 (q, J_{CF} = 29 Hz). ^{19}F NMR: δ_F 94.0 (br s). HRMS (FAB): calcd for $C_9H_{14}F_3O$ ($[M+H]^+$) 195.0997; found 195.0977.

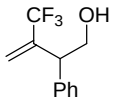
3-(Trifluoromethyl)but-3-enyl 4-methylbenzenesulfonate (12f)



After the ring opening reaction of ethylene oxide **9f** (5 mmol) with 3,3,3-trifluoroprop-1-en-2-yllithium **2**, solvents were partially evaporated to ca. 1/4 volume. Pyridine (5 mL) and tosyl chloride (0.95g, 5.0 mmol) were added to the residue. After the mixture was stirred at room temperature overnight, the reaction was quenched with aqueous HCl (1 M, 30 mL). Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water (10 mL) and brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **12f** (498 mg, 34%) a colorless liquid.

IR (neat): 2970, 2929, 1599, 1358, 1171, 1117, 978, 908 cm^{-1}. ^1H NMR: δ 2.45 (3H, s), 2.57 (2H, t, J = 6.6 Hz), 4.17 (2H, t, J = 6.6 Hz), 5.42 (1H, q, J_{HF} = 1.3 Hz), 5.76 (1H, br s), 7.36 (2H, d, J = 8.4 Hz), 7.78 (2H, d, J = 8.4 Hz). ^{13}C NMR: δ 21.5, 29.1, 67.1, 121.1 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 274 Hz), 127.8, 129.9, 132.6, 133.0 (q, J_{CF} = 30 Hz), 145.1. ^{19}F NMR: δ_F 93.1 (br s). Anal. Calcd for $C_{12}H_{13}F_3O_3S$: C, 48.97; H, 4.45. Found: C, 49.17; H, 4.68.

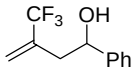
2-Phenyl-3-(trifluoromethyl)but-3-en-1-ol (12g)



To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (1.24 mL, 12 mmol) and 2-phenyloxirane **9g** (0.91 mL, 8.0 mmol) in Et_2O (40 mL) were added dropwise $BF_3{\cdot}OEt_2$ (1.52 mL, 12 mmol) and then a solution of *n*-BuLi (2.71 M in hexane; 4.43 mL, 12 mmol) in Et_2O (4 mL) at –100 °C. The reaction mixture was stirred for 15 min and then allowed to warm up to rt. The reaction was quenched with phosphate buffer (pH 7, 40 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with water (30 mL) and brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **12g** (564 mg, 33 %) as a colorless liquid.

IR (neat): 3377, 3031, 2933, 2887, 1495, 1454, 1414, 1309, 1167, 1117, 1059, 949 cm^{-1}. ^1H NMR: δ 1.57 (1H, br s), 3.78 (1H, dd, J = 6.8, 6.8 Hz), 3.93–4.01 (2H, m), 5.58 (1H, q, J_{HF} = 1.1 Hz), 5.96 (1H, q, J_{HF} = 1.4 Hz), 7.26–7.30 (3H, m), 7.34–7.37 (2H, m). ^{13}C NMR: δ 47.4, 65.0, 119.7 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 275 Hz), 127.5, 128.1, 128.8, 138.2, 138.6 (q, J_{CF} = 28 Hz). ^{19}F NMR: δ_F 94.2 (br s). HRMS (FAB): calcd for $C_{11}H_{12}F_3O$ ($[M+H]^+$) 217.0840; found 217.0857.

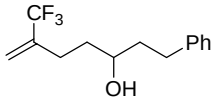
1-Phenyl-3-(trifluoromethyl)but-3-en-1-ol (12h)



To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.51 mL, 4.9 mmol) in Et_2O (15 mL) was added dropwise *t*-BuLi (1.47 M in pentane; 3.1 mL, 4.5 mmol) at –100 °C. After the reaction mixture was stirred for 30 min, $BF_3{\cdot}OEt_2$ (0.57 mL, 4.5 mmol) in Et_2O (3 mL) was added. After being stirred for 5 min, 2-phenyloxirane **9g** (360 mg, 3.0 mmol) in Et_2O (3 mL) was added. The reaction mixture was stirred for 15 min and then allowed to warm up to room temperature. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water (20 mL) and brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **12h** (166 mg, 26%) as a colorless liquid.

IR (neat): 3388, 3064, 3033, 2927, 1346, 1165, 1111, 1045, 947, 756, 698 cm^{-1}. ^1H NMR: δ 2.26 (1H, br s), 2.55 (1H, dd, J = 15.1, 4.9 Hz), 2.62 (1H, ddd, J = 15.1, 8.7, 1.0 Hz), 4.84 (1H, m), 5.38 (1H, q, J_{HF} = 1.2 Hz), 5.74 (1H, q, J_{HF} = 1.4 Hz), 7.27–7.34 (5H, m). ^{13}C NMR: δ 39.6, 71.9, 121.3 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 125.8, 127.9, 128.5, 134.6 (q, J_{CF} = 30 Hz), 143.2. ^{19}F NMR: δ_F 93.6 (br s).

1-Phenyl-6-(trifluoromethyl)hept-6-en-3-ol (14)



To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.31 mL, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) in Et_2O (5 mL) was added dropwise a solution of *n*-BuLi (2.67 M in hexane, 1.1 mL, 3.0 mmol) in Et_2O (2 mL) at –100 °C. After the mixture was stirred for 15 min, a solution of 2-phenethyloxetane **13** (158 mg, 0.97 mmol) in Et_2O (2 mL) was added dropwise. The mixture was stirred for 15 min and warmed to –78 °C over 2 h. After the mixture was allowed to warm up to rt, the reaction was quenched with phosphate buffer (pH 7, 15 mL). Organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with water (15 mL) and brine (15 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **14** (206 mg, 82%) as a colorless liquid.

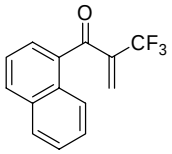
IR (neat): 3354, 3028, 2927, 2862, 1496, 1454, 1323, 1165, 1113, 939 cm^{-1}. ^1H NMR: δ 1.48 (1H, br s), 1.61–1.83 (4H, m), 2.25 (1H, ddd, J = 15.7, 10.5, 5.9 Hz), 2.41 (1H, ddd, J = 15.7, 10.7, 5.0 Hz), 2.69 (1H, ddd, J = 13.7, 9.3, 6.9 Hz), 2.80 (1H, ddd, J = 13.7, 9.4, 6.1 Hz), 3.66 (1H, dddd, J = 8.2, 8.2, 4.1, 4.1 Hz), 5.31 (1H, q, J_{HF} = 1.4 Hz), 5.66 (1H, q, J_{HF} = 1.3 Hz), 7.18–7.21 (3H, m), 7.26–7.31 (2H, m). ^{13}C NMR: δ 25.7, 32.0, 35.2, 39.1, 70.5, 117.7 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 274 Hz), 125.9, 128.4, 128.5, 138.2 (q, J_{CF} = 29 Hz), 141.7. ^{19}F NMR: δ_F 93.3 (br s). Anal. Calcd for $C_{14}H_{17}F_3O$: C, 65.10; H, 6.63. Found: C, 65.08; H, 6.86.

第一章第三節

General procedure for the preparation of α,β-unsaturated α-trifluoromethyl-ketones (16)

To a solution of $BF_3{\cdot}OEt_2$ (127 μL, 1.0 mmol) and 2-bromo-3,3,3-trifluoroprop-1-ene **1** (0.41 mL, 4.0 mmol) in Et_2O (10 mL) was added a solution of *n*-BuLi (1.52 M in hexane; 1.27 mL, 2.0 mmol) in Et_2O (3 mL) at –100 °C. After stirring for 10 min, a solution of *N*,*N*-dimethylcarboxamide **15** (1.0 mmol) in Et_2O (5 mL) was added. The reaction mixture was allowed to warm up to –50 °C over 2 h. Phosphate buffer (pH 7, 10 mL) was added to quench the reaction, and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give α,β-unsaturated α-trifluoromethyl-ketone **16**.

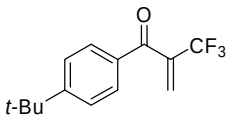
1-(1-Naphthyl)-2-(trifluoromethyl)prop-2-en-1-one (16a)



A pale brown liquid. 55%.

IR (neat): 3059, 1668, 1508, 1340, 1132, 1055, 793 cm^{-1}. ^1H NMR: δ 6.14 (1H, q, J_{HF} = 1.6 Hz), 6.67 (1H, s), 7.50 (1H, dd, *J* = 8.2, 7.2 Hz), 7.56 (1H, dd, *J* = 7.4, 7.4 Hz), 7.59 (1H, dd, *J* = 7.4, 7.4 Hz), 7.62 (1H, d, *J* = 7.2 Hz), 7.91 (1H, d, *J* =7.4 Hz), 8.02 (1H, d, *J* = 8.2 Hz), 8.18 (1H, d, *J* = 7.4 Hz). ^{13}C NMR: δ 121.8 (q, J_{CF} = 276 Hz), 124.1, 125.1, 126.8, 127.9, 128.4, 128.5, 130.5, 132.6, 133.7 (q, J_{CF} = 5 Hz), 133.7, 134.2, 139.4 (q, J_{CF} = 29 Hz), 192.7. ^{19}F NMR: δ_F 96.9 (br s). HRMS (FAB): calcd for $C_{14}H_{10}F_3O$ ($[M+H]^+$) 251.0684; found 251.0691.

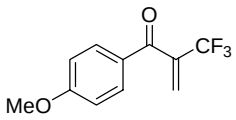
1-(4-*tert*-Butylphenyl)-2-(trifluoromethyl)prop-2-en-1-one (16b)



A colorless liquid. 65%.

IR (neat): 2966, 2871, 1670, 1602, 1352, 1128, 1103, 978 cm^{-1}. ^1H NMR: δ 1.35 (9H, s), 6.11 (1H, s), 6.57 (1H, s), 7.51 (2H, d, *J* = 8.5 Hz), 7.78 (2H, d, *J* = 8.5 Hz). ^{13}C NMR: δ 31.0, 35.2, 121.7 (q, J_{CF} = 275 Hz), 125.7, 129.6 (q, J_{CF} = 5 Hz), 129.7, 133.4, 137.6 (q, J_{CF} = 30 Hz), 157.7, 190.4. ^{19}F NMR: δ_F 97.0 (br s). Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.62; H, 5.90. Found: C, 65.90; H, 6.18.

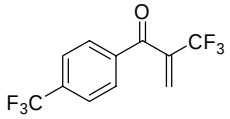
1-(4-Methoxyphenyl)-2-(trifluoromethyl)prop-2-en-1-one (16c)



A pale brown liquid. 57%.

IR (neat): 3012, 2966, 2844, 1662, 1597, 1350, 1252, 1119, 976 cm^{-1}. ^{1}H NMR: δ 3.89 (3H, s), 6.03 (1H, q, J_{HF} = 0.8 Hz), 6.51 (1H, q, J_{HF} = 1.1 Hz), 6.97 (2H, d, J = 8.9 Hz), 7.84 (2H, d, J = 8.9 Hz). ^{13}C NMR: δ 55.5, 113.9, 121.7 (q, J_{CF} = 275 Hz), 128.5 (q, J_{CF} = 5 Hz), 128.7, 132.1, 137.5 (q, J_{CF} = 31 Hz), 164.2, 189.3. ^{19}F NMR: δ_F 97.2 (br s). Anal. Calcd for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found: C, 57.55; H, 4.12.

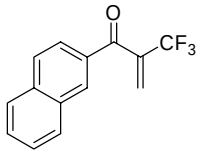
2-(Trifluoromethyl)-1-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (16d)



A pale yellow liquid. 24%.

IR (neat): 2920, 2850, 1682, 1323, 1169, 1126, 1066, 982 cm^{-1}. ^{1}H NMR: δ 6.17 (1H, m), 6.70 (1H, m), 7.78 (2H, d, J = 8.1 Hz), 7.91 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 121.4 (q, J_{CF} = 275 Hz), 123.4 (q, J_{CF} = 274 Hz), 125.8 (q, J_{CF} = 4 Hz), 129.8, 131.7 (q, J_{CF} = 5 Hz), 134.9 (q, J_{CF} = 33 Hz), 137.4 (q, J_{CF} = 31 Hz), 139.0, 189.8. ^{19}F NMR: δ_F 96.9 (3F, br s), 98.5 (3F, br s). HRMS (FAB): calcd for $C_{11}H_7F_6O$ ($[M+H]^+$) 269.0401; found 269.0388.

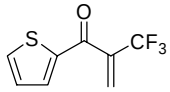
1-(2-Naphthyl)-2-(trifluoromethyl)prop-2-en-1-one (16e)



A pale brown liquid. 61%.

IR (neat): 3062, 1664, 1626, 1342, 1132, 1105, 985, 771 cm^{-1}. ^{1}H NMR: δ 6.18 (1H, m), 6.64 (1H, m), 7.58 (1H, dd, J = 7.5, 7.5 Hz), 7.64 (1H, dd, J = 7.5, 7.5 Hz), 7.88–7.97 (4H, m), 8.30 (1H, s). ^{13}C NMR: δ 121.7 (q, J_{CF} = 275 Hz), 124.6, 127.2, 127.8, 128.8, 129.0, 129.6, 130.1 (q, J_{CF} = 5 Hz), 131.9, 132.1, 133.3, 135.7, 137.7 (q, J_{CF} = 30 Hz), 190.7. ^{19}F NMR: δ_F 97.1 (br s). HRMS (FAB): calcd for $C_{14}H_{10}F_3O$ ($[M+H]^+$) 251.0684; found 251.0662. Anal. Calcd for $C_{14}H_9F_3O$: C, 67.20; H, 3.63. Found: C, 67.09; H, 3.86.

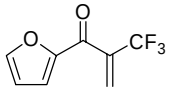
1-Thiophen-2-yl-2-(trifluoromethyl)prop-2-en-1-one (16f)



A pale brown liquid. 65%.

IR (neat): 3111, 2920, 1651, 1630, 1410, 1360, 1115, 1055, 723 cm^{-1}. ^{1}H NMR: δ 6.28 (1H, q, J_{HF} = 0.7 Hz), 6.53 (1H, s), 7.19 (1H, dd, J = 5.0, 3.9 Hz), 7.69 (1H, dd, J = 3.9, 1.1 Hz), 7.79 (1H, dd, J = 5.0, 1.1 Hz). ^{13}C NMR: δ 121.4 (q, J_{CF} = 274 Hz), 128.3, 128.5 (q, J_{CF} = 5 Hz), 135.1, 136.0, 137.6, (q, J_{CF} = 31 Hz), 142.4, 182.0. ^{19}F NMR: δ_F 97.2 (br s). Anal. Calcd for $C_8H_5F_3OS$: C, 46.60; H, 2.44. Found: C, 46.44; H, 2.71.

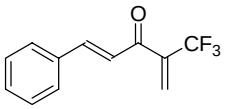
1-Furan-2-yl-2-(trifluoromethyl)prop-2-en-1-one (16g)



A pale brown liquid. 51%.

IR (neat): 3140, 2920, 1660, 1464, 1394, 1354, 1128, 985, 764 cm^{-1}. ^{1}H NMR: δ 6.52 (1H, q, J_{HF} = 0.7 Hz), 6.58 (1H, m), 6.62 (1H, dd, J = 3.6, 1.7 Hz), 7.29 (1H, dd, J = 3.6, 0.7 Hz), 7.71 (1H, dd, J = 1.7, 0.7 Hz). ^{13}C NMR: δ 112.6, 121.2, 121.4 (q, J_{CF} = 275 Hz), 129.9 (q, J_{CF} = 5 Hz), 136.9 (q, J_{CF} = 30 Hz), 148.1, 151.3, 176.4. ^{19}F NMR: δ_F 97.2 (br s). HRMS (FAB): calcd for $C_8H_6F_3O_2$ ($[M+H]^+$) 191.0320; found 191.0323.

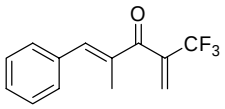
(*E*)-1-Phenyl-4-(trifluoromethyl)penta-1,4-dien-3-one (16h)



Colorless crystals. 38%.

IR (neat): 3064, 3030, 1674, 1604, 1362, 1142, 1045 cm^{-1}. ^{1}H NMR: δ 6.49 (1H, q, J_{HF} = 0.8 Hz), 6.56 (1H, q, J_{HF} = 1.2 Hz), 7.15 (1H, d, J = 16 Hz), 7.40–7.44 (3H, m), 7.56–7.61 (2H, m), 7.77 (1H, d, J = 16 Hz). ^{13}C NMR: δ 121.1, 122.0 (q, J_{CF} = 275 Hz), 128.6, 129.0, 129.8 (q, J_{CF} = 5 Hz), 131.1, 134.0, 138.6 (q, J_{CF} = 30 Hz), 146.4, 185.0. ^{19}F NMR: δ_F 97.5 (br s). Anal. Calcd for $C_{12}H_9F_3O$: C, 63.72; H, 4.01. Found: C, 63.50; H, 4.07.

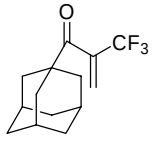
(*E*)-2-Methyl-1-phenyl-4-(trifluoromethyl)penta-1,4-dien-3-one (16i)



A colorless liquid. 66%.

IR (neat): 3057, 3030, 2960, 2875, 1653, 1616, 1342, 1219, 1169, 1126, 1026, 771 cm^{-1}. ^{1}H NMR: δ 2.17 (3H, d, J = 1.3 Hz), 6.01 (1H, q, J_{HF} = 1.1 Hz), 6.40 (1H, q, J_{HF} = 1.2 Hz), 7.36–7.47 (6H, m). ^{13}C NMR: δ 13.3, 121.6 (q, J_{CF} = 275 Hz), 127.4 (q, J_{CF} = 6 Hz), 128.6, 129.3, 129.9, 135.0, 136.5, 137.7 (q, J_{CF} = 30 Hz), 144.1, 193.1. ^{19}F NMR: δ_F 97.3 (br s). HRMS (FAB): calcd for $C_{13}H_{12}F_3O$ ($[M+H]^+$) 241.0840; found 241.0843.

1-(1-Adamantyl)-2-(trifluoromethyl)prop-2-en-1-one (16j)



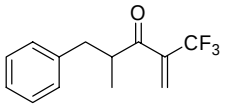
Compound **16j** was prepared according to the general procedure by using 2-bromo-3,3,3-trifluoropropen-1-en (2.0 eq), *n*-BuLi (1.0 eq) and $BF_3{\cdot}OEt_2$ (1.3 eq).

A pale yellow liquid. 73%.

IR (neat): 2906, 2854, 1693, 1456, 1335, 1311, 1167, 1134, 1113, 1001, 966 cm^{-1}. ^{1}H NMR: δ 1.70 (3H, br d, J = 11.8 Hz), 1.76 (3H, br d, J = 11.8 Hz), 1.90 (6H, d, J = 2.6 Hz), 2.08 (3H, br s), 5.79 (1H, m), 6.14 (1H, m). ^{13}C NMR:

δ 27.8, 36.2, 38.1, 47.4, 121.3 (q, J_{CF} = 275 Hz), 122.9 (q, J_{CF} = 6 Hz), 137.9 (q, J_{CF} = 31 Hz), 204.5. ^{19}F NMR: δ_F 97.9 (br s). HRMS (FAB): calcd for $C_{14}H_{18}F_3O$ ([M+H]$^+$) 259.1310; found 259.1302.

4-Methyl-5-phenyl-2-(trifluoromethyl)pent-1-en-3-one (16k)

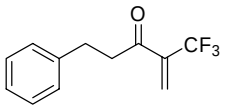


Compound **16k** was prepared according to the general procedure by using BF_3·OEt_2 (1.3 eq).

A colorless liquid. 78%.

IR (neat): 3032, 2978, 2937, 1695, 1454, 1327, 1140, 1002, 773 cm^{-1}. ^{1}H NMR: δ 1.15 (3H, d, J = 7.0 Hz), 2.63 (1H, dd, J = 13.6, 7.0 Hz), 3.04 (1H, dd, J = 13.6, 7.0 Hz), 3.37 (1H, ddq, J = 7.0, 7.0, 7.0 Hz), 6.32 (1H, m), 6.39 (1H, m), 7.14 (2H, d, J = 7.3 Hz), 7.20 (1H, t, J = 7.3 Hz), 7.27 (2H, dd, J = 7.3, 7.3 Hz). ^{13}C NMR: δ 17.0, 39.2, 43.8, 121.7 (q, J_{CF} = 275 Hz), 126.4, 128.5, 129.0, 130.1 (q, J_{CF} = 4 Hz), 137.9 (q, J_{CF} = 29 Hz), 139.1, 199.3. ^{19}F NMR: δ_F 96.9 (br s). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.46; H, 5.41. Found: C, 64.41; H, 5.60.

5-Phenyl-2-(trifluoromethyl)penta-1-en-3-one (16l)



Compound **16l** was prepared according to the general procedure by using BF_3·OEt_2 (1.3 eq).

A pale yellow liquid. 42%.

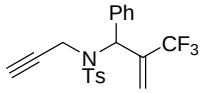
IR (neat): 3032, 1697, 1373, 1329, 1140, 1063, 995, 771 cm^{-1}. ^{1}H NMR: δ 2.97 (2H, t, J = 7.5 Hz), 3.04 (2H, t, J = 7.5 Hz), 6.43 (1H, m), 6.48 (1H, m), 7.18–7.23 (3H, m), 7.29 (2H, dd, J = 7.1, 7.1 Hz). ^{13}C NMR: δ 29.4, 40.8, 121.8 (q, J_{CF} = 275 Hz), 126.3, 128.3, 128.6, 130.4 (q, J_{CF} = 6 Hz), 138.0 (q, J_{CF} = 30 Hz), 140.4, 194.1. ^{19}F NMR: δ_F 97.0 (br s). HRMS (FAB): calcd for $C_{12}H_{12}F_3O$ ([M+H]$^+$) 229.0840; found 229.0829.

第一章第四節

Preparation of *N*-propargyl-*N*-[2-(trifluoromethyl)allyl]amides (23)

To a solution of *N*-(4-methylbenzenesulfonyl)-2-(trifluoromethyl)allylamide **8** (0.4 mmol) in DMF (2 mL) was added sodium hydride (55%, in mineral oil; 26 mg, 0.6 mmol) at rt. After stirring for 5 min, propargyl bromide (0.8 mmol) was added. The reaction mixture was stirred for 12 h, and quenched with phosphate buffer (pH 7, 10 mL). Organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 3:1) to give **23**.

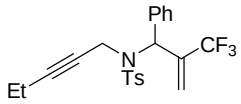
4-Methyl-*N*-[1-phenyl-2-(trifluoromethyl)-2-propen-1-yl]-*N*-prop-2-yn-1-ylbenzenesulfonamide (23a)



A pale yellow liquid. 92%.

IR (neat): 3294, 3066, 3032, 2925, 1338, 1159, 1107, 1057, 899, 814, 661 cm^{-1}. ^1H NMR: δ 2.08 (1H, t, J = 2.5 Hz), 2.42 (3H, s), 3.77 (1H, dd, J = 18.5, 2.5 Hz), 4.17 (1H, dd, J = 18.5, 2.5 Hz), 5.90 (1H, s), 5.92 (1H, m), 6.08 (1H, m), 7.13 (2H, dd, J = 7.5, 1.8 Hz), 7.26–7.29 (5H, m), 7.71 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.5, 34.9, 60.5, 72.8, 79.0, 122.9 (q, J_{CF} = 275 Hz), 123.8 (q, J_{CF} = 5 Hz), 127.6, 128.5, 128.6, 129.1, 129.4, 134.4, 136.9, 137.0 (q, J_{CF} = 27 Hz), 143.7. ^{19}F NMR: δ_F 96.4 (br s). HRMS (FAB): calcd for $C_{20}H_{19}F_3NO_2S$ ($[M+H]^+$) 394.1089; found 394.1084.

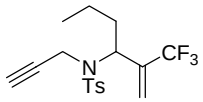
4-Methyl-*N*-[1-phenyl-2-(trifluoromethyl)-2-propen-1-yl]-*N*-pent-2-yn-1-ylbenzenesulfonamide (23b)



A colorless liquid. 90%.

IR (neat): 3030, 2978, 2939, 2875, 1456, 1338, 1317, 1157, 1124, 1090, 1051, 902, 773 cm^{-1}. ^1H NMR: δ 0.94 (3H, t, J = 7.5 Hz), 1.97 (2H, qdd, J = 7.5, 2.1, 2.1 Hz), 2.41 (3H, s), 3.80 (1H, dt, J = 18.3, 2.1 Hz), 4.12 (1H, dt, J = 18.3, 2.1 Hz), 5.91 (1H, s), 5.94 (1H, s), 6.08 (1H, s), 7.13–7.17 (2H, m), 7.23–7.28 (5H, m), 7.71 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 12.1, 13.2, 21.4, 35.5, 60.4, 74.5, 86.5, 123.0 (q, J_{CF} = 276 Hz), 123.8 (q, J_{CF} = 5 Hz), 127.6, 128.3, 128.4, 129.2×2, 134.7, 137.3 (q, J_{CF} = 29 Hz), 137.4, 143.4. ^{19}F NMR: δ_F 96.5 (br s). HRMS (FAB): calcd for $C_{22}H_{23}F_3NO_2S$ ($[M+H]^+$) 422.1402; found 422.1398.

4-Methyl-*N*-[2-(trifluoromethyl)hex-1-en-3-yl]-*N*-prop-2-yn-1-ylbenzenesulfonamide (23c)



A colorless liquid. 84%.

IR (neat): 3275, 2964, 2875, 1338, 1311, 1159, 1126, 1088, 1045, 681, 656 cm^{-1}. ^1H NMR: δ 0.88 (3H, t, J = 7.5 Hz), 1.20–1.35 (2H, m), 1.77 (1H, dddd, J = 14.0, 9.4, 6.6, 6.6 Hz), 1.91 (1H, dddd, J = 14.0, 8.4, 8.4, 5.8 Hz), 2.14 (1H, t, J = 2.5 Hz), 2.42 (3H, s), 3.77 (1H, dd, J = 18.9, 2.5 Hz), 4.14 (1H, dd, J = 18.9, 2.5 Hz), 4.78 (1H, dd, J = 8.4, 6.6 Hz), 5.72 (1H, s), 6.04 (1H, s), 7.28 (2H, d, J = 8.4 Hz), 7.78 (2H, d, J = 8.4 Hz). ^{13}C NMR: δ 13.4, 19.7, 21.5, 32.4, 33.1, 55.6, 72.5, 79.4, 122.7 (q, J_{CF} = 6 Hz), 122.9 (q, J_{CF} = 275 Hz), 127.7, 129.3, 135.5 (q, J_{CF} = 29 Hz), 137.3, 143.6. ^{19}F NMR: δ_F 95.3 (br s). HRMS (FAB): calcd for $C_{17}H_{21}F_3NO_2S$ ($[M+H]^+$) 360.1245; found 360.1259.

Pauson-Khand reaction of *N*-propargyl-*N*-[2-(trifluoromethyl)allyl]amides (23)

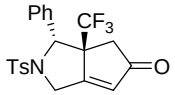
To a solution of **23** (0.339 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (140 mg, 0.41 mmol), and the solution was stirred for 30 min at rt. The solvent was removed under reduced pressure, and then acetonitrile (15 mL) was added. After heating the solution at 60 °C for 2–3 h, the solvent was removed under reduced pressure. The residue was purified

by column chromatography (hexane–EtOAc, 3 : 1) to give cyclopentnenone **24**.

2-(4-Methylbenzenesulfonyl)-3-phenyl-3a-trifluoromethyl-2,3,3a,4-tetrahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (24a)

81% (*anti* : *syn* = 94 : 6).

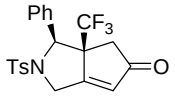
Major product (*anti* isomer).



A pale yellow liquid.

IR (neat): 3032, 2943, 2868, 1730, 1348, 1147, 1059, 912, 802, 667, 563, 542 cm^{-1}. ^1H NMR: δ 1.58 (1H, d, J = 18.0 Hz), 2.37 (1H, d, J = 18.0 Hz), 2.40 (3H, s), 4.41 (1H, d, J = 15.0 Hz), 4.58 (1H, d, J = 15.0 Hz), 5.34 (1H, s), 6.32 (1H, s), 6.75–6.82 (1H, m), 7.11–7.23 (2H, m), 7.23 (2H, d, J = 8.1 Hz), 7.29 (1H, t, J = 7.4 Hz), 7.34–7.41 (1H, m), 7.57 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.5, 41.4, 47.8, 62.2 (q, J_{CF} = 26 Hz), 64.0, 125.1 (br s), 125.9 (q, J_{CF} = 284 Hz), 127.2, 127.5 (br s), 128.8, 129.0 (br s), 129.2 (br s), 129.6, 131.5, 135.0, 136.8, 143.9, 168.3, 203.1.
^{19}F NMR: δ_F 87.6 (br s). HRMS (FAB): calcd for $C_{21}H_{19}F_3NO_3S$ ($[M+H]^+$) 422.1038; found 422.1050.

Minor product (*syn* isomer).



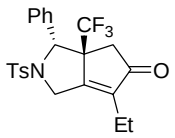
A pale yellow liquid.

IR (neat): 3066, 3033, 2922, 2852, 1732, 1354, 1165, 1092, 1032 cm^{-1}. ^1H NMR: δ 2.43 (3H, s), 2.47 (1H, d, J = 17.8 Hz), 2.72 (1H, d, J = 17.8 Hz), 4.45 (1H, s), 4.57 (1H, d, J = 16.0 Hz), 4.69 (1H, d, J = 16.0 Hz), 6.13 (1H, s), 7.07–7.18 (1H, m), 7.27 (2H, d, J = 8.3 Hz), 7.28–7.35 (3H, m), 7.54 (2H, d, J = 8.3 Hz), 7.54–7.64 (1H, m). ^{13}C NMR: δ 21.6, 43.5, 49.3, 62.4 (q, J_{CF} = 26 Hz), 71.0, 124.9 (q, J_{CF} = 285 Hz), 127.9, 128.1 (br s)×2, 128.8, 129.8, 130.0, 133.3, 133.7, 144.6, 168.9, 202.9. ^{19}F NMR: δ_F 94.0 (br s). HRMS (FAB): calcd for $C_{21}H_{19}F_3NO_3S$ ($[M+H]^+$) 422.1038; found 422.1010.

6-Ethyl-2-(4-methylbenzenesulfonyl)-3-phenyl-3a-trifluoromethyl-2,3,3a,4-tetrahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (24b)

85% (*anti* : *syn* = 83 : 17).

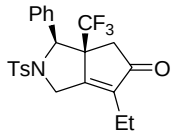
Major product (*anti* isomer).



A pale yellow liquid.

IR (neat): 2976, 2939, 1726, 1864, 1348, 1186, 1147, 1093, 1041 cm^{-1}. ^1H NMR: δ 1.08 (3H, t, J = 7.5 Hz), 1.53 (1H, d, J = 18.1 Hz), 2.24 (1H, dq, J = 15.0, 7.5 Hz), 2.33 (1H, dq, J = 15.0, 7.5 Hz), 2.37 (1H, d, J = 18.1 Hz), 2.41 (3H, s), 4.32 (1H, d, J = 14.6 Hz), 4.59 (1H, d, J = 14.6 Hz), 5.30 (1H, s), 6.72–6.79 (1H, br d), 7.12–7.21 (2H, m), 7.24 (2H, d, J = 8.0 Hz), 7.28 (1H, t, J = 7.4 Hz), 7.33–7.40 (1H, m), 7.60 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 12.1, 17.6, 21.5, 40.9, 46.8, 60.3 (q, J_{CF} = 26 Hz), 64.0, 125.0 (br s), 126.2 (q, J_{CF} = 284 Hz), 127.2, 127.5 (br s), 128.6, 128.9 (br s), 129.2 (br s), 129.5, 135.0, 137.2, 143.8, 145.5, 159.6, 203.3. ^{19}F NMR: δ_F 87.3 (br s). HRMS (FAB): calcd for $C_{23}H_{23}F_3NO_3S$ ($[M+H]^+$) 450.1351; found 450.1332.

Minor product (*syn* isomer).



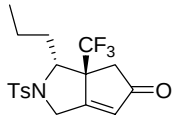
A pale yellow liquid.

IR (neat): 2974, 2937, 1724, 1684, 1354, 1259, 1159, 1090, 1026, 700, 661 cm^{-1}. ^1H NMR: δ 0.98 (3H, t, J = 7.5 Hz), 2.13 (1H, dq, J = 14.8, 7.5 Hz), 2.22 (1H, dq, J = 14.8, 7.5 Hz), 2.42 (3H, s), 2.43 (1H, d, J = 17.9 Hz), 2.71 (1H, d, J = 17.9 Hz), 4.38 (1H, s), 4.50 (1H, d, J = 15.7 Hz), 4.65 (1H, d, J = 15.7 Hz), 7.05–7.18 (1H, br s), 7.26 (2H, d, J = 8.2 Hz), 7.28–7.33 (3H, m), 7.55 (2H, d, J = 8.2 Hz), 7.56–7.67 (1H, br s). ^{13}C NMR: δ 12.0, 17.5, 21.5, 43.0, 48.3, 60.6 (q, J_{CF} = 26 Hz), 71.2, 125.2 (q, J_{CF} = 285 Hz), 127.1 (br s), 127.9, 128.1 (br s), 128.6, 129.8, 133.3, 134.1, 143.9, 144.5, 160.8, 203.2. ^{19}F NMR: δ_F 93.8 (br s). HRMS (FAB): calcd for $C_{23}H_{23}F_3NO_3S$ ($[M+H]^+$) 450.1351; found 450.1360.

2-(4-Methylbenzenesulfonyl)-3-propyl-3a-trifluoromethyl-2,3,3a,4-tetrahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (24c)

71% (*anti* : *syn* = 86 : 14).

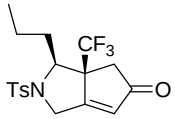
Major product (*anti* isomer).



A pale yellow liquid.

IR (neat): 2962, 2875, 1732, 1346, 1149, 1092, 1036, 665 cm^{-1}. ^1H NMR: δ 0.94 (3H, t, J = 7.3 Hz), 1.16–1.31 (2H, m), 1.57 (1H, dddd, J = 14.7, 14.7, 9.5, 5.5 Hz), 1.85–1.93 (1H, m), 2.43 (1H, d, J = 17.7 Hz), 2.45 (3H, s), 2.61 (1H, d, J = 17.7 Hz), 4.05 (1H, d, J = 15.2 Hz), 4.08 (1H, dd, J = 9.5, 2.8 Hz), 4.37 (1H, d, J = 15.2 Hz), 6.29 (1H, s), 7.35 (2H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 13.5, 18.6, 21.5, 35.6, 40.8, 47.2, 59.9, 60.2 (q, J_{CF} = 26 Hz), 125.8 (q, J_{CF} = 284 Hz), 127.4, 129.7, 130.4, 134.3, 144.1, 169.9, 203.5. ^{19}F NMR: δ_F 86.9 (br s). HRMS (FAB): calcd for $C_{18}H_{21}F_3NO_3S$ ($[M+H]^+$) 388.1194; found 388.1199.

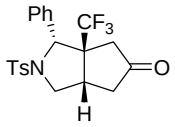
Minor product (*syn* isomer).



A pale yellow liquid.

IR (neat): 2964, 2931, 2877, 1732, 1348, 1161, 1090, 1032, 771 cm^{-1}. ^1H NMR: δ 0.88 (3H, t, J = 7.0 Hz), 1.22–1.32 (1H, m), 1.32–1.44 (1H, m), 1.81 (1H, br q, J = 10.2 Hz), 2.23 (1H, d, J = 18.0 Hz), 2.45 (3H, s), 2.45–2.52 (1H, m), 2.76 (1H, d, J = 18.0 Hz), 3.26 (1H, br d, J = 11.8 Hz), 4.39 (1H, d, J = 16.4 Hz), 4.47 (1H, d, J = 16.4 Hz), 6.07 (1H, s), 7.34 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 14.0, 19.6, 21.6, 32.1, 44.1, 49.1, 59.6 (q, J_{CF} = 26 Hz), 67.8, 125.5 (q, J_{CF} = 286 Hz), 127.3, 129.4, 130.0, 134.5, 144.4, 169.2, 203.4. ^{19}F NMR: δ_F 93.3 (br s). HRMS (FAB): calcd for $C_{18}H_{21}F_3NO_3S$ ($[M+H]^+$) 388.1194; found 388.1209.

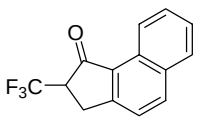
2-(4-Methylbenzenesulfonyl)-1-phenyl-6a-(trifluoromethyl)hexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (25)



To a solution of 2-(4-methylbenzenesulfonyl)-3-phenyl-3a-(trifluoromethyl)-2,3,3a,4-tetrahydrocyclopenta[*c*]-pyrrol-5(1*H*)-one **24a** (major isomer, 53 mg, 0.125 mmol) in MeOH (2 mL) was added 5% Pd/C (10 mg), and the solution was stirred for 15 min at rt under H_2 (1 atm). After H_2 was replaced by argon, solid materials were removed through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane–EtOAc, 3:2) to give cyclopentanone **25** (54 mg, quant.) as colorless crystals.

mp. 151–155 °C. IR (neat): 3064, 3035, 2925, 1753, 1352, 1155, 1032, 665, 573 cm^{-1}. ^1H NMR: δ 2.00 (1H, d, J = 19.6 Hz), 2.18 (1H, d, J = 19.6 Hz), 2.33 (1H, dd, J = 19.4, 6.2 Hz), 2.45 (3H, s), 2.59 (1H, dd, J = 19.4, 9.2 Hz), 2.92 (1H, dddd, J = 9.2, 6.2, 6.2, 6.2 Hz), 3.50 (1H, dd, J = 11.2, 6.2 Hz), 3.84 (1H, dd, J = 11.2, 6.2 Hz), 5.07 (1H, s), 7.22 (2H, d, J = 7.2 Hz), 7.28–7.36 (5H, m), 7.67 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.6, 40.6, 41.6, 41.7, 53.5, 60.4 (q, J_{CF} = 25 Hz), 65.9, 127.0, 127.7 (q, J_{CF} = 281 Hz), 127.8, 128.5, 128.9, 129.7, 133.6, 137.4, 144.3, 211.4. ^{19}F NMR: δ_F 87.5 (br s). Anal. Calcd for $C_{21}H_{20}F_3NO_3S$: C, 59.56; H, 4.76; N, 3.31. Found: C, 59.68; H, 5.02; N, 3.03.

2-Trifluoromethyl-2,3-dihydrocyclopenta[*a*]naphthalene-1-one (26a)

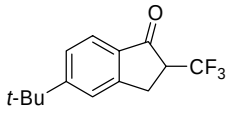


To a solution of 1-(1-naphthyl)-2-(trifluoromethyl)prop-2-en-1-one **16a** (71 mg, 0.29 mmol) in HFIP (1 mL) was added TfOH (0.27 mL, 3 mmol) at rt. After stirring for 1 h, the reaction was quenched with phosphate buffer (pH 7, 5 mL). Organic materials were extracted with EtOAc (10 mL × 2). The combined extracts were washed with brine (5 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give 1-indanone **26a** (52 mg, 73 %) as colorless crystals.

mp. 102–104 °C. IR (neat): 3059, 2945, 1705, 1574, 1514, 1439, 1344, 1250, 1184, 1153, 1088, 955 cm^{-1}. ^1H NMR: δ

3.34–3.43 (1H, m), 3.48–3.57 (2H, m), 7.53 (1H, d, J = 8.4 Hz), 7.60 (1H, dd, J = 7.8, 7.8 Hz), 7.71 (1H, dd, J = 7.8, 7.8 Hz), 7.91 (1H, d, J = 7.8 Hz), 8.10 (1H, d, J = 8.4 Hz), 9.09 (1H, d, J = 7.8 Hz). ^{13}C NMR: δ 27.9 (q, J_{CF} = 2 Hz), 50.1 (q, J_{CF} = 27 Hz), 123.3, 123.9, 125.0 (q, J_{CF} = 279 Hz), 127.2, 128.3, 129.3, 129.6, 130.1, 132.8, 137.1, 155.7, 197.1. ^{19}F NMR: δ_F 93.9 (d, J_{HF} = 9 Hz). Anal. Calcd for $C_{14}H_9F_3O$: C, 67.20; H, 3.63. Found: C, 67.18; H, 3.83.

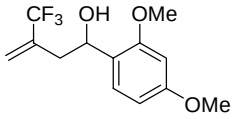
5-*tert*-Butyl-2-trifluoromethyl-2,3-dihydroinden-1-one (26b)



To a solution of 1-(4-*tert*-butylphenyl)-2-(trifluoromethyl)prop-2-en-1-one **16b** (727 mg, 2.84 mmol) in HFIP (7 mL) was added TfOH (2.5 mL, 28 mmol) at rt. After stirring for 3 d, the reaction was quenched with phosphate buffer (pH 7, 20 mL). Organic materials were extracted with EtOAc (15 mL × 2). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give 1-indanone **26b** (636 mg, 87 %) as colorless crystals.

mp. 59–60 °C. IR (neat): 2966, 2871, 1720, 1608, 1350, 1254, 1174, 1157, 1109 cm^{-1}. ^{1}H NMR: δ 1.37 (9H, s), 3.26–3.33 (1H, m), 3.39–3.46 (2H, m), 7.49 (1H, d, J = 8.2 Hz), 7.51 (1H, s), 7.75 (1H, d, J = 8.2 Hz). ^{13}C NMR: δ 27.6 (q, J_{CF} = 2 Hz), 31.1, 35.6, 49.9 (q, J_{CF} = 27 Hz), 123.0, 124.3, 125.0 (q, J_{CF} = 279 Hz), 126.0, 133.5 (q, J_{CF} = 2 Hz), 152.4, 160.4, 196.4. ^{19}F NMR: δ_F 94.0 (d, J_{FH} = 9 Hz). Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.62; H, 5.90. Found: C, 65.69; H, 6.05.

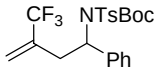
1-(2,4-Dimethoxyphenyl)-3-(trifluoromethyl)but-3-en-1-ol (12i)



To a mixture of trimethyl-2-(trifluoromethyl)prop-2-en-1-ylsilane **28** (273 mg, 1.50 mmol), 2,4-dimethoxybenzaldehyde (299 mg, 1.80 mmol), and MS 4A (0.10 g) in THF (5 mL) was added a solution of tetrabutylammonium fluoride (TBAF, 1 M in THF; 0.15 mL, 0.15 mmol) at 0 °C. After the mixture was stirred for 1 d at rt, the reaction was quenched by phosphate buffer (pH 7, 10 mL). The mixture was filtered through a pad of Celite, and organic materials were extracted with EtOAc (10 mL × 2). The combined extracts were washed with water (10 mL × 2), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **12i** (261 mg, 63%) as a colorless liquid.

IR (neat): 3429, 3005, 2941, 2839, 1612, 1589, 1506, 1466, 1290, 1157, 1113, 1036 cm^{-1}. ^1H NMR: δ 2.53–2.70 (3H, m), 3.81 (3H, s), 3.84 (3H, s), 5.02 (1H, dd, J = 6.8, 6.8 Hz), 5.43 (1H, q, J_{HF} = 1.0 Hz), 5.74 (1H, q, J_{HF} = 1.2 Hz), 6.47 (1H, s), 6.48 (1H, dd, J = 8.6, 2.4 Hz), 7.21 (1H, d, J = 8.6 Hz). ^{13}C NMR: δ 37.5, 55.3, 55.4, 68.7, 98.7, 104.1, 120.4 (q, J_{CF} = 6 Hz), 123.6, 123.7 (q, J_{CF} = 274 Hz), 127.6, 135.2 (q, J_{CF} = 30 Hz), 157.5, 160.3. ^{19}F NMR: δ_F 93.3 (br s). HRMS (FAB): calcd for $C_{13}H_{16}F_3O_3$ ($[M+H]^+$) 277.1052; found 277.1045.

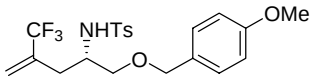
***tert*-Butyl *N*-(4-Methylbenzenesulfonyl)-*N*-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]carbamate (29h)**



To a solution of **12h** (512 mg, 2.37 mmol), PPh_3 (1.24 g, 4.73 mmol), and *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate (945 mg, 3.48 mmol) in THF (15 mL) was added DEAD (40% in toluene; 0.82 ml, 4.7 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 10 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **29h** (1.12 g, 95%) as a colorless liquid.

IR (neat): 3018, 2981, 2933, 1728, 1599, 1354, 1169, 1151, 1122 cm^{-1}. ^1H NMR: δ 1.26 (9H, s), 2.40 (3H, s), 3.22 (1H, dd, J = 15.5, 6.5 Hz), 3.39 (1H, dd, J = 15.5, 8.7 Hz), 5.50 (1H, s), 5.83 (1H, s), 5.93 (1H, dd, J = 8.7, 6.5 Hz), 7.20 (2H, d, J = 8.1 Hz), 7.31 (1H, t, J = 7.4 Hz), 7.35 (2H, dd, J = 7.4, 7.4 Hz), 7.45 (2H, d, J = 7.4 Hz), 7.53 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.5, 27.7, 31.9, 58.9, 84.6, 121.5 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 272 Hz), 127.8, 128.1, 128.3, 128.4, 128.9, 134.7 (q, J_{CF} = 30 Hz), 138.6, 144.1, 150.8, 171.1. ^{19}F NMR: δ_F 93.3 (br s). Anal. Calcd for $C_{23}H_{26}F_3NO_4S$: C, 58.84; H, 5.58; N, 2.98. Found: C, 58.60; H, 5.71; N, 2.79.

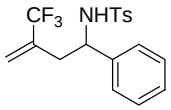
(*S*)-*N*-[1-(4-Methoxybenzyloxy)-4-(trifluoromethyl)pent-4-en-2-yl]-4- methylbenzenesulfonamide [(*S*)-30c]



To a solution of **(*S*)-31c** (1.82 g, 3.45 mmol) and piperidine (1.02 mL, 10.3 mmol) in CH_3CN (40 mL) was added $Pd(PPh_3)_4$ (8.0 mg, 0.069 mmol) at rt. After the mixture was stirred for 1.5 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **(*S*)-30c** (1.47 g, 96%) as a colorless liquid.

$[\alpha]_D^{25}$ = –33 (*c* 1.0, $CHCl_3$). IR (neat): 3278, 2958, 2910, 2864, 1612, 1514, 1419, 1331, 1247, 1161, 1119 cm^{-1}. ^1H NMR: δ 2.37 (1H, dd, *J* = 14.8, 7.1 Hz), 2.41 (3H, s), 2.43 (1H, dd, *J* = 14.8, 7.8 Hz), 3.22 (1H, dd, *J* = 9.5, 3.9 Hz), 3.33 (1H, dd, *J* = 9.5, 3.5 Hz), 3.55 (1H, ddddd, *J* = 8.2, 7.8, 7.4, 3.9, 3.5 Hz), 3.81 (3H, s), 4.27 (1H, d, *J* = 11.4 Hz), 4.30 (1H, d, *J* = 11.4 Hz), 5.03 (1H, d, *J* = 8.6 Hz), 5.29 (1H, q, J_{HF} = 1.1 Hz), 5.63 (1H, q, J_{HF} = 1.5 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 7.15 (2H, d, *J* = 8.7 Hz), 7.25 (2H, d, *J* = 8.7 Hz), 7.70 (2H, d, *J* = 8.7 Hz). ^{13}C NMR: δ 21.5, 32.7, 51.9, 55.2, 69.5, 72.9, 113.8, 121.6 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 274 Hz), 127.0, 129.4, 129.5, 129.6, 133.9 (q, J_{CF} = 30 Hz), 137.7, 143.4, 159.4. ^{19}F NMR: δ_F 93.5 (br s). HRMS (FAB): calcd for $C_{21}H_{25}F_3NO_4S$ ($[M+H]^+$) 444.1456; found 444.1453. HPLC (*i*-PrOH:hexane = 1:30): retention time 32.5 min major peak, 30.9 min minor peak.

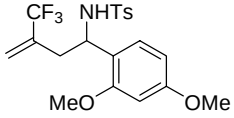
4-Methyl-*N*-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (30h)



To a solution of **29h** (934 mg, 1.99 mmol) in CH_2Cl_2 (15 mL) was added CF_3CO_2H (1.53 ml, 20.6 mmol) at rt. The reaction mixture was stirred at rt for 10 h. The reaction was quenched with sat. aqueous Na_2CO_3 (20 mL), and organic materials were extracted with CH_2Cl_2 (15 mL × 3). The combined extracts were washed with brine (10 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **30h** (688 mg, 94%) as colorless crystals.

IR (neat): 3269, 3064, 3030, 2927, 1456, 1325, 1159, 1120, 912 cm^{-1}. ^1H NMR: δ 2.37 (3H, s), 2.58 (1H, dd, *J* = 15.3, 7.2 Hz), 2.71 (1H, dd, *J* = 15.3, 7.8 Hz), 4.49 (1H, ddd, *J* = 7.8, 7.3, 7.2 Hz), 4.91 (1H, br d), 5.19 (1H, s), 5.63 (1H, s), 7.02–7.04 (2H, m), 7.14 (2H, d, *J* = 8.2 Hz), 7.17–7.19 (3H, m), 7.54 (2H, d, *J* = 8.2 Hz). ^{13}C NMR: δ 21.4, 37.6, 56.5, 121.9 (q, J_{CF} = 5 Hz), 123.3 (q, J_{CF} = 272 Hz), 126.6, 127.1, 127.8, 128.6, 129.3, 133.4 (q, J_{CF} = 30 Hz), 137.2, 139.5, 143.2. ^{19}F NMR: δ_F 93.4 (3F, s). Anal. Calcd for $C_{18}H_{18}F_3NO_2S$: C, 58.52; H, 4.91; N, 3.79. Found: C, 58.56; H, 5.08; N, 3.80.

***N*-[1-(2,4-Dimethoxyphenyl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (30i)**

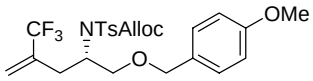


To a solution of **31i** (1.47 g, 2.86 mmol) and piperidine (1.13 mL, 11.4 mmol) in CH_3CN (40 mL) was added $Pd(PPh_3)_4$ (66.0 mg, 57 μmol) at rt. After the mixture was stirred for 12 h, water (10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL),

brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **30i** (1.15 g, 93%) as colorless crystals.

IR (neat): 3276, 3003, 2939, 2839, 1614, 1508, 1325, 1157, 1115, 1034 cm^{-1}. ^1H NMR: δ 2.32 (3H, s), 2.61 (1H, dd, *J* = 15.4, 6.9 Hz), 2.75 (1H, dd, *J* = 15.4, 7.8 Hz), 3.71 (3H, s), 3.73 (3H, s), 4.49 (1H, ddd, *J* = 9.9, 7.8, 6.9 Hz), 5.23 (1H, s), 5.48 (1H, d, *J* = 9.9 Hz), 5.62 (1H, s), 6.18 (1H, d, *J* = 2.3 Hz), 6.21 (1H, dd, *J* = 8.2, 2.3 Hz), 6.70 (1H, d, *J* = 8.2 Hz), 7.04 (2H, d, *J* = 8.2 Hz), 7.45 (2H, d, *J* = 8.2 Hz). ^{13}C NMR: δ 21.3, 35.4, 55.1, 55.3, 55.5, 98.7, 103.8, 119.0, 121.2 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 272 Hz), 126.9, 128.9, 130.1, 134.0 (q, J_{CF} = 30 Hz), 137.5, 142.6, 157.3, 160.5. ^{19}F NMR: δ_F 93.2 (br s). Anal. Calcd for $C_{20}H_{22}F_3NO_4S$: C, 55.93; H, 5.16; N, 3.26. Found: C, 55.91; H, 5.20; N, 3.05.

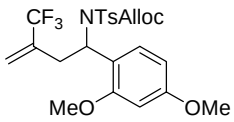
(*S*)-Allyl *N*-[1-(4-Methoxybenzyloxy)-4-(trifluoromethyl)pent-4-en-2-yl]-*N*-(4-methylbenzenesulfonyl)-carbamate [(*S*)-31c]



To a solution of DEAD (2.2 M in toluene; 4.09 mL, 9.00 mmol) in toluene (80 mL) was added triphenylphosphine (2.36 g, 9.00 mmol) at 0 ºC. After the mixture was stirred for 1 h, allyl *N*-(4-methylbenzenesulfonyl)carbamate (1.84 g, 7.20 mmol) and **(*R*)-12c** (1.74 g, 6.00 mmol) were added. The reaction mixture was stirred at 0 ºC for 7 d, and hexane (40 mL) was added. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **(*S*)-31c** (2.22 g, 70%) as a colorless liquid.

$[\alpha]_D^{25}$ = +5.6 (*c* 1.0, $CHCl_3$). IR (neat): 2956, 2870, 1732, 1354, 1250, 1169, 1119 cm^{-1}. ^1H NMR: δ 2.38 (3H, s), 2.62 (1H, dd, *J* = 15.0, 5.8 Hz), 2.89 (1H, dd, *J* = 15.0, 8.9 Hz), 3.60 (1H, dd, *J* = 9.3, 5.8 Hz), 3.82 (3H, s), 3.91 (1H, dd, *J* = 9.3, 8.9 Hz), 4.37 (1H, d, *J* = 11.3 Hz), 4.47 (1H, d, *J* = 11.3 Hz), 4.51 (2H, ddd, *J* = 5.9, 1.3, 1.3 Hz), 5.03 (1H, dddd, *J* = 8.9, 8.9, 5.8, 5.8 Hz), 5.18 (1H, ddt, *J* = 10.3, 1.3, 1.3 Hz), 5.19 (1H, ddt, *J* = 17.4, 1.3, 1.3 Hz), 5.51 (1H, s), 5.71 (1H, ddt, *J* = 17.4, 10.3, 5.9 Hz), 5.84 (1H, q, J_{HF} = 1.3 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 7.11 (2H, d, *J* = 8.3 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.82 (2H, d, *J* = 8.3 Hz). ^{13}C NMR: δ 21.5, 30.2, 55.2, 57.4, 67.4, 69.0, 72.5, 113.6, 119.3, 121.9 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 274 Hz), 128.8, 129.0, 129.4, 129.8, 130.8, 134.1 (q, J_{CF} = 30 Hz), 136.6, 144.2, 151.6, 159.2. ^{19}F NMR: δ_F 93.1 (br s). HRMS (FAB): calcd for $C_{25}H_{29}F_3NO_6S$ ($[M+H]^+$) 528.1668; found 528.1658. HPLC (*i*-PrOH:hexane = 1:50): retention time 20.1 min major peak, 18.9 min minor peak.

Allyl *N*-[1-(2,4-Dimethoxyphenyl)-3-(trifluoromethyl)but-3-en-1-yl]-*N*-(4-methylbenzenesulfonyl)carbamate (31i)



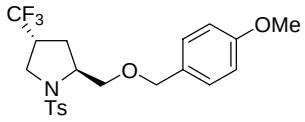
To a solution of PPh_3 (403 mg, 1.54 mmol), allyl *N*-(4-methylbenzenesulfonyl)carbamate (294 mg, 1.15 mmol), and **12i** (213 mg, 0.769 mmol) in THF (8 mL) was added DEAD (2.2 M in toluene; 0.70 mL, 1.54 mmol) at 0 ºC. After the reaction mixture was stirred at rt for 12 h, hexane (10 mL) was added. The mixture was filtered through a pad of

Celite. The solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **31i** (267 mg, 67%) as a colorless liquid.

IR (neat): 2943, 1732, 1614, 1508, 1362, 1252, 1163, 1111, 1032, 937, 615 cm^{-1}. ^1H NMR: δ 2.35 (3H, s), 3.23 (1H, dd, J = 14.4, 6.8 Hz), 3.40 (3H, s), 3.40–3.46 (1H, m), 3.84 (3H, s), 4.63 (2H, d, J = 5.9 Hz), 5.23 (1H, dd, J = 10.4, 1.2 Hz), 5.28 (1H, dd, J = 17.2, 1.2 Hz), 5.55 (1H, s), 5.82 (1H, s), 5.81–5.88 (1H, m), 5.95 (1H, dd, J = 6.8, 6.8 Hz), 6.23 (1H, d, J = 2.3 Hz), 6.56 (1H, dd, J = 8.6, 2.3 Hz), 7.07 (2H, d, J = 8.2 Hz), 7.18–7.29 (2H, m), 7.40 (1H, d, J = 8.6 Hz). ^{13}C NMR: δ 21.4, 32.0, 54.9, 55.0, 55.4, 67.6, 97.9, 103.6, 116.9, 119.1, 121.4 (q, J_{CF} = 3 Hz), 123.6 (q, J_{CF} = 274 Hz), 128.4, 128.5, 130.2, 131.2, 134.3 (q, J_{CF} = 30 Hz), 136.8, 143.7, 152.9, 158.7, 160.9. ^{19}F NMR: δ_F 93.4 (br s). HRMS (FAB): calcd for $C_{24}H_{27}F_3NO_6S$ ($[M+H]^+$) 514.1511; found 514.1489.

第二章第二節

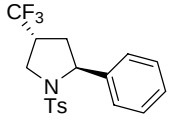
(2*R*,4*S*)-2-[(4-Methoxybenzyloxy)methyl]-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine [(2*R*,4*S*)-32c]



To a solution of **(*S*)-30c** (102 mg, 0.229 mmol) in ethylene glycol (2.0 mL) was added KOH powder (64 mg, 1.15 mmol) at rt. After the reaction mixture was stirred at 130 °C for 20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **(2*R*,4*S*)-32c** (69 mg, 68%, *anti*:*syn* = 70:30) as a colorless liquid.

IR (neat): 2954, 2862, 1612, 1514, 1348, 1248, 1163, 1034, 818, 667 cm^{-1}. ^1H NMR: (***anti*-7a**) δ 1.67 (1H, ddd, J = 12.7, 10.8, 8.9 Hz), 2.06 (1H, dd, J = 12.7, 5.6 Hz), 2.44 (3H, s), 3.05–3.15 (1H, m), 3.19 (1H, dd, J = 9.6, 9.6 Hz), 3.54 (1H, dd, J = 9.6, 6.3 Hz), 3.63 (1H, dd, J = 9.6, 3.2 Hz), 3.67 (1H, dd, J = 9.6, 8.1 Hz), 3.81 (3H, s), 3.85–3.93 (1H, m), 4.43 (1H, d, J =11.5 Hz), 4.46 (1H, d, J = 11.5 Hz), 6.89 (2H, d, J = 8.5 Hz), 7.22 (2H, d, J = 8.5 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz). ^{13}C NMR: (***anti*-7a**) δ 21.5, 28.7, 41.4 (q, J_{CF} = 29 Hz), 47.9, 55.2, 58.9, 72.5, 73.2, 113.8, 126.1 (q, J_{CF} = 277 Hz), 127.4, 129.3, 129.8, 130.0, 134.1, 143.9, 159.3. ^{19}F NMR: (***anti*-7a**) δ_F 90.8 (d, J_{FH} = 8 Hz). HRMS (FAB): calcd for $C_{21}H_{25}F_3NO_4S$ ($[M+H]^+$) 444.1456; found 444.1440. The ee value of ***anti*-7a** was determined to be 99% by HPLC (*i*-PrOH:hexane = 1:30, ***anti*-7a**: retention time 18.2 min major peak, 20.6 min minor peak; ***syn*-7a**: retention time 18.2 min major peak, 22.2 min minor peak).

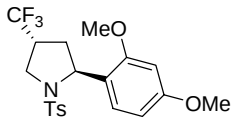
1-(4-Methylbenzenesulfonyl)-2-phenyl-4-(trifluoromethyl)pyrrolidine (32h)



To a solution of **30h** (146 mg, 0.395 mmol) in ethylene glycol (3 mL) was added KOH powder (111 mg, 1.97 mmol) at rt. After the reaction mixture was stirred at 130 °C for 10 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **32h** (124 mg, 85%, *anti*:*syn* = 92:8) as colorless crystals.

IR (neat): 3030, 2983, 2881, 1452, 1400, 1348, 1157, 1120 cm^{-1}. ^1H NMR: (***anti*-32h**) δ 2.05 (2H, dd, J = 8.6, 5.4 Hz), 2.44 (3H, s), 2.88–3.06 (1H, m), 3.50 (1H, dd, J = 10.5, 8.8 Hz), 3.85 (1H, dd, J = 10.5, 8.3 Hz), 4.94 (1H, dd, J = 5.4, 5.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz). (***syn*-32h**) δ 2.42 (3H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, dd, J = 9.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.54 (2H, d, J = 8.2 Hz). ^{13}C NMR: (***anti*-32h**) δ 21.6, 34.8, 40.9 (q, J_{CF} = 29 Hz), 47.7, 62.6, 125.9, 126.1 (q, J_{CF} = 275 Hz), 127.5, 127.7, 128.6, 129.7, 134.2, 141.1, 143.9. ^{19}F NMR: (***anti*-32h**) δ_F 91.1 (d, J_{FH} = 8 Hz,). (***syn*-32h**) δ_F 91.3 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{18}H_{18}F_3NO_2S$: C, 58.52; H, 4.91; N, 3.79. Found: C, 58.43; H, 5.00; N, 3.59.

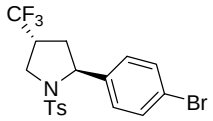
***rel*-(2*R*,4*S*)-2-(2,4-Dimethoxyphenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (32i)**



To a solution of **30i** (88 mg, 0.21 mmol) in ethylene glycol (3 mL) was added KOH powder (15 mg, 0.27 mmol) at rt. After the reaction mixture was stirred at 130 °C for 20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL × 3), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give **32i** (65 mg, 74%, *anti*:*syn* = 90:10) as a colorless liquid.

IR (neat): 3001, 2958, 2839, 1614, 1589, 1506, 1340, 1161, 1034 cm^{-1}. ^1H NMR: (***anti*-32i**) δ 1.89–2.01 (2H, m), 2.44 (3H, s), 2.84–2.95 (1H, m), 3.42 (1H, dd, J = 9.8, 9.8 Hz), 3.75 (3H, s), 3.80 (3H, s), 3.84 (1H, dd, J = 9.8, 9.8 Hz), 5.11 (1H, d, J = 8.0 Hz), 6.40 (1H, s), 6.45 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz). (***syn*-32i**) δ 2.08 (2H, m), 2.41 (3H, s), 2.46 (1H, m), 3.55 (1H, dd, J = 9.9, 9.9 Hz), 3.62 (3H, s), 3.80 (3H, s), 3.95 (1H, dd, J = 9.9, 9.9 Hz), 4.86 (1H, dd, J = 7.6, 7.6 Hz), 6.28 (1H, s), 6.44 (1H, J = 8.4 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.1 Hz). ^{13}C NMR: (***anti*-32i**) δ 21.5, 33.3, 41.0 (q, J_{CF} = 29 Hz), 47.8, 55.1, 55.3, 58.7, 98.6, 103.5, 121.8, 126.2 (q, J_{CF} = 256 Hz), 127.4, 127.8, 129.6, 134.4, 143.6, 156.6, 160.5. ^{19}F NMR: (***anti*-32i**) δ_F 91.3 (d, J_{FH} = 8 Hz). (***syn*-32i**) δ_F 91.4 (d, J_{FH} = 8 Hz). HRMS (FAB): calcd for $C_{20}H_{23}F_3NO_4S$ ($[M+H]^+$) 430.1300; found 430.1284.

***rel*-(2*R*,4*S*)-2-(4-Bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (32j)**

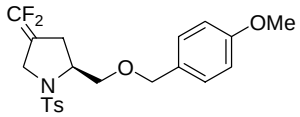


To a solution of *N*-[1-(4-bromophenyl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (207 mg, 0.462 mmol) in ethylene glycol (6 mL) was added KOH powder (129 mg, 2.3 mmol) at rt. After the reaction mixture was stirred at 130 °C for 20 h, phosphate buffer (pH 7, 20 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL × 3), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **32j** (***anti***, 146 mg, 70%; ***syn***, 13 mg, 6%) as colorless crystals.

(***anti*–32j**) mp. 119–120 °C. IR (neat): 3030, 2910, 1489, 1400, 1350, 1163, 1122, 914 cm^{-1}. ^1H NMR: δ 2.01 (1H, ddd, J = 12.9, 7.2, 3.3 Hz), 2.08 (1H, ddd, J = 12.9, 9.9, 8.2 Hz), 2.45 (3H, s), 2.86–2.99 (1H, m), 3.47 (1H, dd, J = 10.6, 8.6 Hz), 3.85 (1H, dd, J = 10.6, 8.2 Hz), 4.83 (1H, dd, J = 8.2, 3.3 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.6, 34.8 (q, J_{CF} = 2 Hz), 40.8 (q, J_{CF} = 29 Hz), 47.8 (q, J_{CF} = 3 Hz), 62.1, 121.6, 126.0 (q, J_{CF} = 276 Hz), 127.5, 127.7, 129.8, 131.7, 134.0, 140.2, 144.1. ^{19}F NMR: δ_F 91.1 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{18}H_{17}BrF_3NO_2S$: C, 48.23; H, 3.82; N, 3.12. Found: C, 48.04; H, 3.84; N, 2.87.

(***syn*–32j**) IR (neat): 2960, 2910, 1489, 1404, 1360, 1271, 1161, 912 cm^{-1}. ^1H NMR: δ 1.99 (1H, ddd, J = 13.3, 11.0, 9.4 Hz), 2.44 (3H, s), 2.52 (1H, ddd, J = 13.3, 7.5, 7.5 Hz), 2.58–2.71 (1H, m), 3.58 (1H, dd, J = 11.5, 9.7 Hz), 3.94 (1H, dd, J = 11.5, 8.2 Hz), 4.65 (1H, dd, J = 9.4, 7.5 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.6, 36.2, 41.6 (q, J_{CF} = 30 Hz), 48.5 (q, J_{CF} = 3 Hz), 63.0, 121.7, 125.6 (q, J_{CF} = 276 Hz), 127.4, 128.2, 129.8, 131.6, 134.6, 139.7, 144.1. ^{19}F NMR: δ_F 91.2 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{18}H_{17}BrF_3NO_2S$: C, 48.23; H, 3.82; N, 3.12. Found: C, 48.30; H, 3.90; N, 2.90.

(*S*)-4-Difluoromethylene-2-[(4-methoxybenzyloxy)methyl]-1-[(4-methylbenzene)sulfonyl]pyrrolidine [(*S*)-33c]

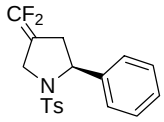


To a solution of **(*S*)-30c** (1.28 g, 2.89 mmol) in DMF (30 mL) was added NaH (55% dispersion in mineral oil; 151 mg, 3.47 mmol) at 0 ºC. After being stirred for 10 min, the mixture was heated at 120 ºC for 4 h. The reaction was quenched with phosphate buffer (pH 7, 40 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with water (30 mL × 4), brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **(*S*)-33c** (1.10 g, 90%) as a colorless liquid.

$[\alpha]_D^{25}$ = –13.1 (*c* 1.0, $CHCl_3$). IR (neat): 2931, 2860, 1782, 1512, 1348, 1248, 1163, 1093, 1036, 816 cm^{-1}. ^1H NMR: δ 2.12–2.21 (1H, m), 2.41 (3H, s), 2.47 (1H, br d, J = 15.5 Hz), 3.38 (1H, dd, J = 9.4, 8.1 Hz), 3.63 (1H, dd, J = 9.4, 4.0 Hz), 3.79 (3H, s), 3.95 (1H, br d, J = 14.0 Hz), 3.99 (1H, br d, J = 14.0 Hz), 3.99–4.03 (1H, m), 4.43 (2H, s), 6.87 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.4, 27.8, 46.9 (d, J_{CF} = 4 Hz), 55.1, 59.2, 71.6, 72.9, 85.6 (dd, J_{CF} = 25, 23 Hz), 113.7, 127.2, 129.1, 129.7, 129.9, 134.8, 143.8, 149.9

(dd, J_{CF} = 284, 284 Hz), 159.2. ^{19}F NMR: δ_F 71.3 (1F, d, J_{FF} = 55 Hz), 74.2 (1F, d, J_{FF} = 55 Hz). HRMS (FAB): calcd for $C_{21}H_{24}F_2NO_4S$ ([M+H]$^+$) 424.1394; found 424.1390. HPLC (*i*-PrOH:hexane = 1:30): retention time 20.4 min major peak, 22.7 min minor peak.

4-Difluoromethylene-1-(4-methylbenzene)sulfonyl-2-phenylpyrrolidine (33h)

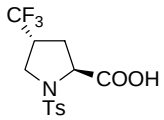


To a solution of **30h** (658 mg, 1.78 mmol) in DMF (15 mL) was added NaH (60% dispersion in mineral oil; 92 mg, 2.3 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min and then 120 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **33h** (564 mg, 91%) as colorless crystals.

IR (neat): 3064, 3032, 2927, 2866, 1782, 1350, 1273, 1219, 1161, 1093, 1058 cm^{-1}. ^{1}H NMR: δ 2.42 (3H, s), 2.54 (1H, br d, *J* = 15.0 Hz), 2.70 (1H, m), 4.13 (1H, dm, *J* = 14.5 Hz), 4.19 (1H, dm, *J* = 14.5 Hz), 4.95 (1H, ddd, *J* = 8.2, 3.1, 1.5 Hz), 7.22– 7.31 (7H, m), 7.57 (2H, d, *J* = 8.3 Hz). ^{13}C NMR: δ 21.5, 33.9, 47.0 (d, J_{CF} = 4 Hz), 63.2, 85.4 (dd, J_{CF} = 25, 22 Hz), 126.2, 127.4, 127.7, 128.5, 129.6, 134.8, 140.8, 143.7, 149.8 (dd, J_{CF} = 283, 283 Hz). ^{19}F NMR: δ_F 72.0 (1F, ddd, J_{FF} = 54 Hz, J_{HF} = 3, 3 Hz), 74.5 (1F, d, J_{FF} = 54 Hz). Anal. Calcd for $C_{18}H_{17}F_2NO_2S$; C, 61.88; H, 4.90; N, 4.01. Found: C, 61.81; H, 4.95; N, 3.74.

第二章第三節

***rel*-(2*R*,4*S*)-1-(4-Methylbenzenesulfonyl)-4-(trifluoromethyl)proline (34)**

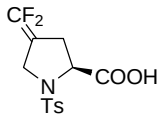


To a suspension of $NaIO_4$ (457 mg, 2.14 mmol) in CH_3CN (1 mL) and H_2O (1.5 mL) was added a solution of **32i** (84 mg, 0.19 mmol) in CCl_4 (1.0 mL) and then $RuCl_3 \cdot H_2O$ (0.8 mg, 4 μmol) at rt. The reaction mixture was stirred for 6 h at rt, and then water was added to quench the reaction. Organic materials were extracted with Et_2O (15 mL × 3). The combined extracts were washed with aqueous NaOH (1 M; 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **34** (47 mg, 72 %, *anti*:*syn* = 90:10) was obtained as colorless crystals.

IR (neat): 3238, 2956, 2926, 1732, 1400, 1350, 1271, 1161, 1128, 1039 cm^{-1}. ^{1}H NMR: (***anti*-34**) δ 2.13 (1H, ddd, *J* = 13.4, 9.2, 9.2 Hz), 2.34 (1H, ddd, *J* = 13.4, 8.0, 2.7 Hz), 2.46 (3H, s), 3.15 (1H, ddddq, J_{HF} = 8.0 Hz, *J* = 9.2, 8.0, 8.0, 8.0 Hz), 3.37 (1H, dd, *J* = 9.9, 8.0 Hz), 3.78 (1H, dd, *J* = 9.9, 8.0 Hz), 4.41 (1H, dd, *J* = 9.2, 2.7 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 7.76 (2H, d, *J* = 8.4 Hz), 8.04 (1H, br s). (***syn*-34**) δ 2.27 (1H, ddd, *J* = 13.5, 8.9, 7.4 Hz), 2.46 (3H, s), 2.51 (1H, ddd, *J* = 13.5, 8.2, 8.2 Hz), 2.62–2.76 (1H, m), 3.45 (1H, dd, *J* = 11.4, 10.4 Hz), 3.77 (1H, dd, *J* = 11.4, 8.6 Hz),

4.47 (1H, dd, J = 8.2, 7.4 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 8.04 (1H, br s). ^{13}C NMR: (***anti*-34**) δ 21.6, 30.0, 41.6 (q, J_{CF} = 30 Hz), 47.1, 59.9, 125.7 (q, J_{CF} = 276 Hz), 127.5, 130.0, 133.8, 144.5, 175.8. ^{19}F NMR: (***anti*-34**) δ_F 90.9 (d, J_{FH} = 8 Hz). (***syn*-34**) δ_F 91.5 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.38; H, 4.25; N, 3.89.

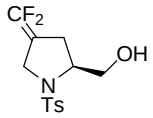
(*S*)-4-Difluoromethylene-1-(4-methylbenzenesulfonyl)proline [(*S*)-35]



To a solution of **(*S*)-37** (144 mg, 0.475 mmol) in CH_3CN (4.8 mL) and phosphate buffer (pH 7, 3.6 mL) were added 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3.7 mg, 24 μmol) and $NaClO_2$ (80 %; 70 mg, 0.62 mmol). The reaction mixture was stirred for 7 d at rt. After aqueous HCl (1 M, 2 mL) was added to the mixture, organic materials were extracted with Et_2O (10 mL × 4). The combined extracts were washed with aqueous Na_2CO_3 (10%; 10 mL × 2), and then the combined aqueous layer was acidified with conc. aqueous HCl (2 mL). Organic materials were extracted again by Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **(*S*)-35** (141 mg, 93%) was obtained as a colorless liquid.

$[\alpha]_D^{25}$ = –13.7 (*c* 1.0, $CHCl_3$). IR (neat): 3228, 2927, 2879, 1783, 1724, 1350, 1275, 1161, 1095, 1063, 771cm^{-1}. ^{1}H NMR: δ 2.45 (3H, s), 2.70–2.75 (2H, m), 4.04–4.12 (2H, m), 4.53 (1H, ddd, J = 8.4, 4.1, 1.6 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.62 (1H, br s), 7.75 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.5, 29.6, 46.5 (d, J_{CF} = 3 Hz), 60.2, 84.6 (dd, J_{CF} = 25, 25 Hz), 127.4, 130.0, 134.5, 144.4, 150.1 (dd, J_{CF} = 286, 286 Hz), 175.6. ^{19}F NMR: δ_F 73.1 (1F, d, J_{FF} = 52 Hz), 75.5 (1F, d, J_{FF} = 52 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_4S$ ([M+H]$^+$) 318.0613; found 318.0601. The ee value was determined to be 99% by HPLC (*i*-PrOH:hexane = 1:10, retention time 12.0 min major peak, 9.1 min minor peak).

(*S*)-4-Difluoromethylene-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine [(*S*)-37]



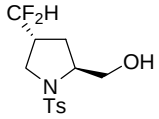
To a solution of **(*S*)-33c** (141 mg, 0.333 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (0.15 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 98.2 mg, 0.433 mmol) at rt. After being stirred for 2 d, the reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 2:1) to give **(*S*)-37** (92 mg, 91%) as a pale yellow liquid.

$[\alpha]_D^{25}$ = +45.5 (*c* 1.0, $CHCl_3$). IR (neat): 3529, 2954, 2924, 2854, 1782, 1344, 1271, 1161 cm^{-1}. ^{1}H NMR: δ 2.23–2.31 (1H, m), 2.39 (1H, br d, J = 14.5 Hz), 2.45 (3H, s), 2.52 (1H, br s), 3.65 (1H, dd, J = 11.5, 5.8 Hz), 3.70 (1H, dd, J = 11.5, 4.7 Hz), 3.79–3.86 (1H, m), 3.96 (1H, br d, J = 14.1 Hz), 4.08 (1H, br d, J = 14.1 Hz), 7.35 (2H, d, J = 7.9 Hz), 7.73 (2H, d, J = 7.9 Hz). ^{13}C NMR: δ 21.5, 27.5, 47.5 (d, J_{CF} = 3 Hz), 61.8, 64.4, 84.9 (dd, J_{CF} = 23, 23 Hz), 127.5, 130.0, 133.7, 144.3, 149.9 (dd, J_{CF} = 283, 283 Hz). ^{19}F NMR: δ_F 71.7 (1F, ddd, J_{FF} = 54 Hz, J_{FH} = 3, 3 Hz), 74.4 (1F, dd, J_{FF} = 54 Hz, J_{FH} = 1 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_3S$ ([M+H]$^+$) 304.0820; found 304.0828. The ee

value was determined to be 99% by HPLC (*i*-PrOH:hexane = 1:10, retention time 12.9 min major peak, 10.9 min minor peak).

第二章第四節

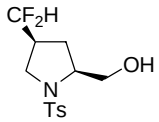
***rel*-(2*R*,4*S*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*anti*-38)**



To a solution of **37** (19.2 mg, 63 μmol) in $CHCl_3$ (5 mL) was added Pd/C (5%, 67 mg, 32 μmol). The mixture was stirred under H_2 (1 atm) at rt for 6 h. The mixture was filtered through a pad of Celite. Removal of the solvent under reduced pressure gave **38** (90% NMR yield, *anti*:*syn* = 79:21) as a pale yellow liquid.

IR (neat): 3521, 2952, 2881, 1597, 1398, 1336, 1155, 1087, 1024, 665 cm^{-1}. ^1H NMR: δ 1.67 (1H, ddd, J = 12.9, 8.8, 8.8 Hz), 1.95–2.00 (1H, m), 2.46 (3H, s), 2.71 (1H, br s), 2.71–2.84 (1H, m), 3.16 (1H, dd, J = 10.1, 8.2 Hz), 3.61–3.73 (3H, m), 3.80 (1H, dd, J = 10.9, 2.9 Hz), 5.38 (1H, ddd, J_{HF} = 56.1, 56.1 Hz, J = 4.8 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.4, 28.5, 41.0 (t, J_{CF} = 8 Hz), 48.5 (t, J_{CF} = 4 Hz), 61.0, 65.2, 116.1 (t, J_{CF} = 240 Hz), 127.6, 129.9, 133.3, 144.2. ^{19}F NMR: δ_F 40.5 (1F, ddd, J_{FF} = 285 Hz, J_{FH} = 56, 14 Hz), 41.4 (1F, ddd, J_{FF} = 285 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ($[M+H]^+$) 306.0977; found 306.0966.

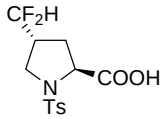
***rel*-(2*R*,4*R*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*syn*-38)**



To a solution of **43a** (86 mg, 0.204 mmol, *anti*:*syn* = 11:89) in THF (3 mL) was added TBAF (1 M in THF; 0.25 mL, 0.25 mmol) at rt. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **38** (56 mg, 90%, *anti*:*syn* = 11:89) as a colorless liquid.

IR (neat): 3521, 2954, 2885, 1597, 1338, 1219, 1157, 1089, 1026, 771 cm^{-1}. ^1H NMR: δ 1.75–1.86 (1H, m), 1.93–2.12 (2H, m), 2.46 (3H, s), 2.89 (1H, br s), 3.39 (1H, dd, J = 11.8, 8.6 Hz), 3.58 (1H, dd, J = 11.8, 7.8 Hz), 3.61–3.73 (2H, m), 3.87 (1H, br d, J = 10.5 Hz), 5.69 (1H, ddd, J_{HF} = 56.2, 56.2 Hz, J = 5.4 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.5, 28.7, 41.0 (t, J_{CF} = 22 Hz), 49.2 (t, J_{CF} = 4 Hz), 61.8, 64.8, 116.2 (t, J_{CF} = 240 Hz), 127.5, 130.1, 133.6, 144.3. ^{19}F NMR: δ_F 41.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ($[M+H]^+$) 306.0975; found 306.0978.

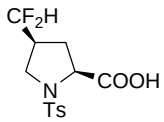
***rel*-(2*R*,4*S*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)proline (*anti*-40)**



To a solution of ***anti*-38** (19.8 mg, 65 μmol, *anti*:*syn* = 79:21) in acetone (2 mL) were added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (3.6 mg, 35 μmol), TEMPO (0.56 mg, 3.6 μmol), and trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with H_2O (5 mL). Organic materials were extracted with Et_2O (5 mL × 3). The combined extracts were washed with aqueous NaOH (1 M, 5 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M), and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, ***anti*-40** (19.8 mg, 96%, *anti*:*syn* = 79:21) was obtained as colorless crystals.

IR (neat): 3534, 2954, 2924, 2852, 1732, 1340, 1159, 1090, 1034 cm^{-1}. ^1H NMR: δ 1.98 (1H, ddd, J = 13.3, 9.5, 9.2 Hz), 2.30 (1H, ddd, J = 13.3, 6.8, 2.8 Hz), 2.46 (3H, s), 2.81–2.93 (1H, m), 3.29 (1H, dd, J = 10.0, 8.2 Hz), 3.69 (1H, dd, J = 10.0, 8.0 Hz), 4.38 (1H, dd, J = 9.2, 2.8 Hz), 5.60 (1H, td, J_{HF} = 55.3 Hz, J = 4.4 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.76 (2H, d, J = 8.5 Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.2 (t, J_{CF} = 3 Hz), 41.7 (t, J_{CF} = 22 Hz), 47.4 (t, J_{CF} = 5 Hz), 60.2, 115.8 (t, J_{CF} = 241 Hz), 127.7, 130.2, 134.3, 144.6, 176.2. ^{19}F NMR: δ_F 40.2 (1F, ddd, J_{FF} = 287 Hz , J_{FH} = 55, 13 Hz), 41.0 (1F, ddd, J_{FF} = 287 Hz , J_{FH} = 55, 11 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_4S$ ($[M+H]^+$) 320.0768; found 320.0742.

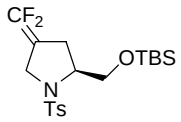
***rel*-(2*R*,4*R*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)proline (*syn*-40)**



To a solution of ***syn*-38** (54 mg, 0.18 mmol, *anti*:*syn* = 11:89) in acetone (2 mL) was added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (4 mg, 0.03 mmol), TEMPO (0.56 mg, 3.6 μmol), and then trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with water (5 mL). Organic materials were extracted with Et_2O (5 mL × 3), and the combined extracts were washed with aqueous NaOH (1 M, 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M), and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, ***syn*-40** (57 mg, 100 %, *anti*:*syn* = 11:89) was obtained as colorless crystals.

IR (neat): 3546, 3220, 2964, 1733, 1340, 1219, 1161, 1035 cm^{-1}. ^1H NMR: δ 2.19 (1H, ddd, J = 13.5, 6.4, 6.1 Hz), 2.35 (1H, ddd, J = 13.5, 9.0, 8.8 Hz), 2.41–2.50 (1H, m), 2.46 (3H, s), 3.47 (1H, dd, J = 11.1, 6.5 Hz), 3.54 (1H, dd, J = 11.1, 7.6 Hz), 4.32 (1H, dd, J = 9.0, 6.1 Hz), 5.79 (1H, ddd, J_{HF} = 56.1, 56.1 Hz, J = 6.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.4 (t, J_{CF} = 3 Hz), 42.3 (t, J_{CF} = 22 Hz), 48.3 (t, J_{CF} = 4 Hz), 60.0, 116.1 (t, J_{CF} = 240 Hz), 127.9, 130.3, 133.9, 144.8, 176.3. ^{19}F NMR: δ_F 40.9 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 11 Hz), 42.3 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 13 Hz). Anal. Calcd for $C_{13}H_{15}F_2NO_4S$: C, 48.90; H, 4.73; N, 4.39. Found: C, 48.99; H, 4.85; N, 4.12.

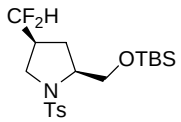
2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (42a)



To a solution of **37** (81 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) was added *t*-$BuMe_2SiCl$ (61 mg, 0.41 mmol), NEt_3 (54 mg, 0.54 mmol), and 4-dimethylaminopyridine (DMAP, 10 mg, 0.08 mmol) at rt. The reaction mixture was stirred at rt for 3 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **42a** (105 mg, 94%) as a colorless liquid.

IR (neat): 2954, 2929, 2858, 1782, 1350, 1271, 1163, 1093, 837, 777, 665 cm^{-1}. ^1H NMR: δ 0.04 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 2.14–2.22 (1H, m), 2.44 (3H, s), 2.49 (1H, br d, J = 15.3 Hz), 3.56 (1H, dd, J = 10.1, 7.1 Hz), 3.75 (1H, dd, J = 10.1, 3.6 Hz), 3.92–3.98 (2H, m), 4.01 (1H, br d, J = 13.8 Hz), 7.32 (2H, d, J = 8.2 Hz), 7.72 (2H, d, J = 8.2 Hz). ^{13}C NMR: δ –5.6, –5.6, 18.1, 21.5, 25.7, 27.4, 47.2 (d, J_{CF} = 4 Hz), 61.1, 65.5, 86.1 (dd, J_{CF} = 26, 22 Hz), 127.3, 129.8, 135.1, 143.8, 149.9 (dd, J_{CF} = 284, 284 Hz). ^{19}F NMR: δ_F 70.7 (1F, ddddd, J_{FF} = 57 Hz, J_{FH} = 3, 3, 3, 3 Hz), 73.6 (1F, dd, J_{FF} = 56 Hz, J_{FH} = 2 Hz). HRMS (FAB): calcd for $C_{19}H_{30}F_2NO_3SSi$ ($[M+H]^+$) 418.1684; found 418.1683.

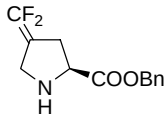
***rel*-(2*R*,4*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidine 43a)**



To a solution of **42a** (75 mg, 0.18 mmol) in EtOH (3 mL) was added Pd/C (5%, 19 mg, 9.0 μmol). The mixture was stirred under H_2 (1 atm) at rt for 1 h. The mixture was filtered through a pad of Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **43a** (73 mg, 98%, *anti*:*syn* = 11:89) as a colorless liquid.

IR (neat): 2954, 2929, 2858, 1348, 1254, 1161, 1090, 1036, 835 cm^{-1}. ^1H NMR: (***syn*-43a**) δ 0.08 (6H, s), 0.89 (9H, s), 1.92 (1H, ddd, J = 13.4, 8.6, 6.1 Hz), 2.00 (1H, ddd, J = 13.4, 8.0, 8.0 Hz), 2.02–2.12 (1H, m), 2.44 (3H, s), 3.30 (1H, dd, J = 11.7, 8.6 Hz), 3.56 (1H, dd, J = 11.7, 7.5 Hz), 3.72–3.79 (2H, m), 3.84 (1H, dd, J = 9.9, 3.0 Hz), 5.69 (1H, ddd, J_{HF} = 56.3, 56.3 Hz, J = 5.6 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz). (***anti*-43a**) δ 0.08 (6H, s), 0.89 (9H, s), 2.02–2.12 (2H, m), 2.44 (3H, s), 2.78–2.89 (1H, m), 3.11 (1H, dd, J = 9.7, 8.6 Hz), 3.66 (1H, dd, J = 9.7, 6.5 Hz), 3.72–3.79 (3H, m), 5.43 (1H, ddd, J_{HF} = 57.8, 57.8 Hz, J = 5.2 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz). ^{13}C NMR: (***syn*-43a**) δ –5.5, –5.4, 18.2, 21.5, 25.8, 28.4 (dd, J_{CF} = 5, 3 Hz), 41.8 (t, J_{CF} = 22 Hz), 49.0 (dd, J_{CF} = 7, 4 Hz), 60.8, 65.8, 116.5 (t, J_{CF} = 241 Hz), 127.4, 129.9, 134.8, 143.8. ^{19}F NMR: (***syn*-43a**) δ_F 41.8 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.9 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{19}H_{32}F_2NO_3SSi$ ($[M+H]^+$) 420.1840; found 420.1853.

Benzyl 4-(Difluoromethylene)pyrrolidine-2-carboxylate (45)

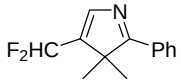


After a solution of benzyl 4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxylate (37 mg, 90 μmol), 1,5-dimethoxynaphthalene (8.8 mg, 47 μmol) and ascorbic acid (49 mg, 280 μmol) in H_2O (1.1 mL) and EtOH (19 mL) was degassed with argon, the solution was irradiated with high-pressure Hg lamp at rt for 2 h through a Pyrex tube. Aqueous HCl (1 M, 1 mL) was added, and the solvent was removed under reduced pressure. Aqueous HCl (1 M, 5 mL) was added to the residue, and the aqueous solution was washed with Et_2O (5 mL). After the aqueous layer was brought to alkaline pH with conc aqueous Na_2CO_3 (5 mL), organic materials were extracted by Et_2O (5 mL × 3). The combined extracts were washed with brine (5 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **45** (8.0 mg, 35%) was obtained as a colorless liquid.

IR (neat): 3035, 2925, 2856, 1783, 1743, 1265, 1219, 1186, 771 cm^{-1}. ^1H NMR: δ 1.92 (1H, br s), 2.58–2.64 (1H, m), 2.78–2.85 (1H, m), 3.56 (1H, br d, J = 13.7 Hz), 3.74 (1H, br d, J = 13.7 Hz), 3.93 (1H, dd, J = 7.6, 6.0 Hz), 5.18 (2H, s), 7.32–7.41 (5H, m). ^{13}C NMR: δ 30.3, 45.5, 60.3, 67.0, 88.0, 128.2, 128.5, 128.7, 135.4, 149.7 (dd, J_{CF} =128, 128 Hz), 173.3. ^{19}F NMR: δ_F 71.7 (1F, dq, J_{FF} = 59 Hz, J_{FH} = 3 Hz), 72.9 (1F, dq, J_{FF} = 59 Hz, J_{FH} = 3 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_2$ ($[M+H]^+$) 254.0993; found 254.0985.

第三章第一節

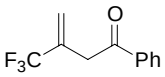
4-Difluoromethyl-3,3-dimethyl-2-phenyl-3*H*-pyrrole (46)



To a solution of 2,2-dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-imine (80 mg, 0.33 mmol) in DMF (3 mL) was added NaH (55% dispersion in mineral oil; 18.8 mg, 0.43 mmol), and the mixture was stirred at 0 °C for 20 min. After the reaction mixture was stirred at 90 °C for 1.5 h, the reaction was quenched with phosphate buffer (pH 7, 10 mL), and organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was observed by ^{19}F NMR (9%, NMR yield). The residue was purified by column chromatography (hexane–Et_2O, 4:1) to give **46** (6.0 mg, 7%) as a pale yellow liquid.

IR (neat): 3060, 2981, 2937, 2873, 1614, 1510, 1053, 1005, 777, 696 cm^{-1}. ^1H NMR: δ 1.57 (6H, s), 6.55 (1H, t, J_{HF} = 54 Hz), 7.33 (1H, t, J_{HF} = 3.5 Hz), 7.45–7.51 (3H, m), 8.01–8.06 (2H, m). ^{13}C NMR: δ 22.4, 56.5, 112.8 (t, J_{CF} = 235 Hz), 128.0, 128.6, 130.9, 132.3, 140.5 (t, J_{CF} = 22 Hz), 142.8 (t, J_{CF} = 11 Hz), 187.1. ^{19}F NMR: δ_F 49.1 (dd, J_{FH} = 54, 3 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2N$ ($[M + H]^+$) 222.1094; found 222.1117.

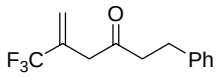
1-Phenyl-3-(trifluoromethyl)but-3-en-1-one (47)



To a mixture of pyridinium chlorochromate (38.4 g, 178 mmol) and silica gel (38.4 g) in dichloromethane (350 mL) was added 1-phenyl-3-(trifluoromethyl)but-3-en-1-ol **12h** (13.9 g, 64.4 mmol). The reaction mixture was stirred for 2 h at rt, and then diluted with Et_2O. The solid materials were removed by filtration through a short column of florisil. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give **47** (12.2 g, 88%) as colorless crystals.

IR (neat): 3062, 1689, 1414, 1358, 1323, 1169, 1115, 1005, 949, 754, 688 cm^{-1}. ^1H NMR: δ 3.85 (2H, s), 5.51 (1H, br s), 5.95 (1H, br s), 7.46–7.51 (2H, m), 7.57–7.62 (1H, m), 7.94–7.98 (2H, m). ^{13}C NMR: δ 38.7, 122.6 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 272 Hz), 128.3, 128.7, 131.8 (q, J_{CF} = 31 Hz), 133.5, 135.9, 194.8. ^{19}F NMR: δ_F 92.9 (3F, s). Anal. Calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.24. Found: C, 61.75; H, 4.39.

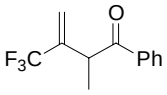
1-Phenyl-5-(trifluoromethyl)hex-5-en-3-one (48)



To a mixture of pyridinium chlorochromate (13.6 g, 63.2 mmol) and silica gel (14 g) in dichloromethane (126 mL) was added 1-phenyl-5-(trifluoromethyl)hex-5-en-3-ol **12a** (10.3 g, 42.2 mmol). The reaction mixture was stirred for 12 h at rt, and then diluted with Et_2O. The solid materials were removed by filtration through a pad of Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–Et_2O, 5:1) to give **48** (9.81 g, 96%) as a colorless liquid.

IR (neat): 3030, 2927, 1722, 1604, 1496, 1456, 1412, 1363, 1308, 1169, 1113, 950, 748, 698 cm^{-1}. ^1H NMR: δ 2.82 (2H, t, J = 7.6 Hz), 2.92 (2H, t, J = 7.6 Hz), 3.25 (2H, s), 5.45 (1H, q, J_{HF} = 1.1 Hz), 5.89 (1H, q, J_{HF} = 1.5 Hz), 7.17–7.22 (3H, m), 7.29 (2H, dd, J = 7.6, 7.6 Hz). ^{13}C NMR: δ 29.5, 43.2, 43.9, 122.7 (q, J_{CF} = 6 Hz), 123.0 (q, J_{CF} = 274 Hz), 126.2, 128.3, 128.5, 131.3 (q, J_{CF} = 31 Hz), 140.5, 204.2. ^{19}F NMR: δ_F 92.7 (br s). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.46; H, 5.41. Found: C, 64.68; H, 5.60.

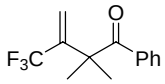
2-Methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (49)



To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-one **47** (500 mg, 2.33 mmol) in Et_2O (20 mL) was added a solution of potassium hexamethyldisilazide (0.56 M in toluene; 4.1 mL, 2.3 mmol) dropwise, and the reaction mixture was stirred for 40 min at –78 °C. Methyl trifluoromethanesulfonate (0.26 mL, 2.3 mmol) was added at that temperature, and then the mixture was warmed to rt. After stirring for 6 h, reaction was quenched with phosphate buffer (pH 7, 20 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 4:1) to give **49** (429 mg, 81%) as a colorless liquid.

IR (neat): 2987, 2943, 1687, 1273, 1219, 1169, 1115, 962, 704, 687 cm^{-1}. ^1H NMR: δ 1.42 (3H, d, J = 6.8 Hz), 4.36 (1H, q, J = 6.8 Hz), 5.52 (1H, br s), 5.87 (1H, br s), 7.45–7.49 (2H, m), 7.55–7.60 (1H, m), 7.94–7.98 (2H, m). ^{13}C NMR: δ 17.8, 40.2, 120.7 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 272 Hz), 128.4, 128.7, 133.3, 135.5, 137.9 (q, J_{CF} = 30 Hz), 198.5. ^{19}F NMR: δ_F 94.0 (br s). Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.16; H, 4.86. Found: C, 63.13; H, 5.05.

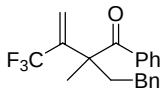
2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (50)



To a solution of 2-methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one **49** (205 mg, 0.90 mmol) in Et_2O (10 mL) was added a solution of potassium hexamethyldisilazide (0.56 M in toluene; 1.6 mL, 0.90 mmol) dropwise, and the reaction mixture was stirred for 1 h at –78 °C. Methyl trifluoromethanesulfonate (0.11 mL, 0.90 mmol) was added at that temperature, and then the mixture was warmed to rt. After stirring for 12 h, reaction was quenched with phosphate buffer (pH 7, 10 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **50** (110 mg, 51%) as a colorless liquid.

IR (neat): 2987, 1684, 1323, 1246, 1178, 1119, 1092, 972, 719, 690 cm^{-1}. ^1H NMR: δ 1.53 (6H, s), 5.60 (1H, br s), 5.93 (1H, br s), 7.35–7.40 (2H, m), 7.46–7.50 (1H, m), 7.84–7.87 (2H, m). ^{13}C NMR: δ 26.4, 49.8, 120.4 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 276 Hz), 128.1, 129.2, 132.1, 135.6, 143.5 (q, J_{CF} = 27 Hz), 200.8. ^{19}F NMR: δ_F 100.3 (br s). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.46; H, 5.41. Found: C, 64.25; H, 5.58.

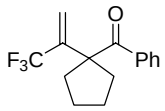
2-Methyl-1-phenyl-2-phenylmethyl-3-trifluoromethylbut-3-en-1-one (51)



To a solution of 2-methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one **49** (1.14 g, 5.0 mmol) in Et_2O (50 mL) was added a solution of potassium hexamethyldisilazide (0.50 M in toluene; 10.5 mL, 5.25 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 10 min at 0 °C. Benzyl bromide (1.19 mL, 10 mmol) was added at –78 °C, and then the mixture was allowed to warm up to rt. After stirring for 12 h, reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (50 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **51** (1.40 g, 88%) as a colorless liquid.

IR (neat): 3062, 3032, 2941, 1684, 1317, 1219, 1167, 1119, 1082, 964, 771 cm^{-1}. ^1H NMR: δ 1.43 (3H, s), 3.22 (1H, d, J = 13.7 Hz), 3.43 (1H, d, J = 13.7 Hz), 5.33 (1H, br s), 5.95 (1H, br s), 7.04 (2H, d, J = 7.4 Hz), 7.17–7.23 (3H, m), 7.37 (2H, dd, J = 8.0, 8.0 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 23.1, 42.7, 54.1, 122.5 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 126.6, 127.8, 128.1, 129.3, 131.3, 132.2, 136.3×2, 141.4 (q, J_{CF} = 28 Hz), 200.0. ^{19}F NMR: δ_F 101.6 (br s). HRMS (FAB): calcd for $C_{19}H_{18}F_3O$ ($[M+H]^+$) 319.1310; found 319.1316.

[1-(1,1,1-Trifluoroprop-2-en-2-yl)cyclopentyl](phenyl)methanone (53)



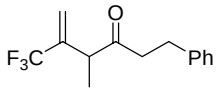
To a solution of 1-phenyl-3-(trifluoromethyl)but-3-en-1-one **47** (1.29 g, 6.0 mmol) in Et_2O (30 mL) was added a solution of potassium hexamethyldisilazide (0.50 M in toluene; 12.6 mL, 6.3 mmol) dropwise at –78 °C. The reaction mixture was stirred for 10 min at 0 °C, and was transferred to a solution of 1,4-diiodobutane (4.7 mL, 36 mmol) and hexamethylphosphoric triamide (HMPA, 10 mL) in Et_2O (30 mL) at –78 °C. The reaction mixture was allowed to be rt and stirred for 12 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1 to 5:1) to give a mixture of [1-(1,1,1-Trifluoroprop-2-en-2-yl)cyclopentyl](phenyl)methanone **53** and 2-(4-iodobutyl)-2-methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (1.82 g) as a colorless liquid.

To a solution of the mixture (1.43 g) in Et_2O (30 mL) was added a solution of potassium hexamethyldisilazide (0.50 M in toluene; 7.22 mL, 3.6 mmol) dropwise at –78 °C. The reaction mixture was stirred for 5 min at –78 °C, and allowed to be rt. After stirring for 4 h, the reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **53** as a colorless liquid.

IR (neat): 2958, 2925, 2854, 1684, 1317, 1234, 1167, 1126 cm^{-1}. ^1H NMR: δ 1.56–1.64 (2H, m), 1.67–1.76 (2H, m), 2.02 (2H, ddd, J = 13.0, 6.5, 6.5 Hz), 2.46 (2H, ddd, J = 13.0, 6.5, 6.5 Hz), 5.55 (1H, br m), 5.87 (1H, br m), 7.38 (2H, dd, J = 7.5, 7.5 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.88 (2H, d, J = 7.5 Hz). ^{13}C NMR: δ 24.3, 35.9, 60.7, 119.9 (q, J_{CF} = 6

Hz), 123.6 (q, J_{CF} = 277 Hz), 128.1, 129.5, 132.2, 135.4, 142.1 (q, J_{CF} = 27 Hz), 199.2. ^{19}F NMR: δ_F 99.9 (br s). HRMS (FAB): calcd for $C_{15}H_{16}F_3O$ ($[M+H]^+$) 269.1153; found 269.1178.

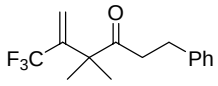
4-Methyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (54)



To a solution of 1-phenyl-5-(trifluoromethyl)hex-5-en-3-one **48** (9.81 g, 40.5 mmol) in Et_2O (200 mL) was added a solution of potassium hexamethyldisilazide (0.70 M in toluene; 59.6 mL, 41.7 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 1 h at that temperature. Methyl trifluoromethanesulfonate (9.2 mL, 81 mmol) was added, and the mixture was stirred for 15 min. After being allowed to warm up to rt, the reaction mixture was stirred for 12 h. Reaction was quenched with phosphate buffer (pH 7, 50 mL), and organic materials were extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **54** (9.74 g, 94%) as a colorless liquid.

IR (neat): 3030, 2983, 2941, 1720, 1604, 1496, 1454, 1415, 1304, 1277, 1171, 1115, 953, 748, 698 cm^{-1}. ^{1}H NMR: δ 1.25 (3H, d, J = 7.0 Hz), 2.71–2.78 (1H, m), 2.81–2.90 (3H, m), 3.37 (1H, q, J = 7.0 Hz), 5.35 (1H, s), 5.80 (1H, s), 7.15–7.20 (3H, m), 7.27 (2H, dd, J = 7.5 Hz). ^{13}C NMR: δ 16.5, 29.7, 42.6, 45.7, 120.3 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 126.1, 128.3, 128.4, 137.6 (q, J_{CF} = 30 Hz), 140.7, 207.3. ^{19}F NMR: δ_F 93.3 (br s). Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.62; H, 5.90. Found: C, 65.84; H, 6.13.

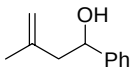
4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (55)



To a solution of 4-methyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one **54** (5.72 g, 22.3 mmol) in Et_2O (200 mL) was added a solution of potassium hexamethyldisilazide (0.70 M in toluene; 33.5 mL, 23.4 mmol) dropwise at –105 °C, and the reaction mixture was stirred for 30 min at –90 °C. Methyl trifluoromethanesulfonate (5.05 mL, 44.6 mmol) was added at –105 °C, and the mixture was stirred for 10 min at that temperature. After being allowed to warm up to rt, the mixture was stirred for 2 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **55** (4.38 g, 73%) as a colorless liquid.

IR (neat): 3028, 2983, 2941, 1716, 1454, 1325, 1176, 1126, 1099, 953 cm^{-1}. ^{1}H NMR: δ 1.31 (6H, s), 2.73 (2H, t, J = 7.6 Hz), 2.89 (2H, t, J = 7.6 Hz), 5.56 (1H, br s), 5.91 (1H, br s), 7.19 (2H, d, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.29 (2H, dd, J = 7.5, 7.5 Hz). ^{13}C NMR: δ 23.5, 30.1, 38.7, 50.4, 120.8 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 126.0, 128.3, 128.4, 141.0, 142.4 (q, J_{CF} = 28 Hz), 209.1. ^{19}F NMR: δ_F 100.3 (br s). HRMS (FAB): calcd for $C_{15}H_{18}F_3O$ ($[M+H]^+$) 271.1310; found 271.1281.

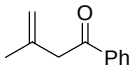
3-Methyl-1-phenylbut-3-en-1-ol (56)



A solution of 2-methylallyl chloride (3.95 mL, 40 mmol) in THF (10 mL) was added dropwise at rt to a mixture of magnesium (4.86 g, 200 mmol) in THF (40 mL) over 1 h. The reaction mixture was transferred to a solution of benzaldehyde (3.1 g, 30 mmol) in THF (30 mL) at 0 °C, and the resulted mixture was stirred for 1 h at that temperature, then for 12 h at rt. The reaction was quenched with aqueous NH_4Cl (100 mL), and organic materials were extracted with EtOAc (50 mL × 2). The combined extracts were washed with brine (50 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **56** (4.64 g, 71%) as a colorless liquid.

IR (neat): 3419, 3074, 3030, 2970, 2935, 1645, 1495, 1055, 891 cm^{-1}. ^1H NMR: δ 1.80 (3H, s), 2.15 (1H, d, J = 2.0 Hz), 2.39 (1H, d, J = 6.7 Hz), 2.45 (1H, d, J = 6.7 Hz), 4.81 (1H, ddd, J = 6.7, 6.7, 2.0 Hz), 4.86 (1H, q, J = 1.0 Hz), 4.93 (1H, t, J = 1.6 Hz), 7.28 (1H, t, J = 7.8 Hz), 7.33–7.40 (4H, m). ^{13}C NMR: δ 22.3, 48.4, 71.3, 114.1, 125.7, 127.5, 128.4, 142.4, 144.0. HRMS (FAB): calcd for $C_{11}H_{15}O$ ($[M+H]^+$) 163.1123; found 163.1101.

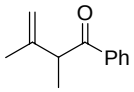
3-Methyl-1-phenylbut-3-en-1-one (57)



To a mixture of pyridinium chlorochromate (17.4 g, 80.7 mmol) and silica gel (17.4 g) in dichloromethane (150 mL) was added 3-methyl-1-phenylbut-3-en-1-ol **56** (4.37 g, 26.9 mmol). The reaction mixture was stirred for 2 h at rt, and then diluted with Et_2O. The solid materials were removed by filtration through a short column of florisil. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **57** (4.16 g, 97%) as a pale yellow liquid.

IR (neat): 3078, 2974, 2912, 1682, 1448, 1335, 1277, 1218, 1003, 893 cm^{-1}. ^1H NMR: δ 1.82 (3H, s), 3.69 (2H, s), 4.86 (1H, s), 4.99 (1H, s), 7.46 (2H, dd, J = 7.4, 7.4 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.98 (2H, d, J = 7.4 Hz). ^{13}C NMR: δ 22.8, 47.7, 114.9, 128.3, 128.5, 133.1, 136.7, 139.7, 198.1. HRMS (FAB): calcd for $C_{11}H_{13}O$ ($[M+H]^+$) 161.0966; found 161.0953.

2,3-Dimethyl-1-phenylbut-3-en-1-one (58)

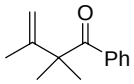


To a solution of 3-methyl-1-phenylbut-3-en-1-one **57** (1.04 g, 6.5 mmol) in Et_2O (60 mL) was added a solution of potassium hexamethyldisilazide (0.50 M in toluene; 13.0 mL, 6.5 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 1 h at that temperature. Methyl trifluoromethanesulfonate (1.46 mL, 13 mmol) was added, and the mixture was stirred for 15 min. After being allowed to warm up to rt, the reaction mixture was stirred for 1 h. The reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with Et_2O (20 mL × 2). The combined extracts were washed with brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under

reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **58** (1.13 g, quant.) as a colorless liquid.

IR (neat): 3076, 2974, 2935, 1682, 1448, 1219, 968, 771 cm^{-1}. ^1H NMR: δ 1.33 (3H, d, J = 6.8 Hz), 1.73 (3H, s), 4.12 (1H, q, J = 6.8 Hz), 4.88 (1H, s), 4.89 (1H, dq, J = 1.4, 1.4 Hz), 7.42 (2H, dd, J = 7.3, 7.3 Hz), 7.52 (1H, t, J = 7.3 Hz), 7.97 (2H, d, J = 7.3 Hz). ^{13}C NMR: δ 16.0, 20.5, 49.0, 113.5, 128.4×2, 132.8, 136.6, 145.2, 200.9. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.71; H, 8.30.

2,2,3-Trimethyl-1-phenylbut-3-en-1-one (59)



To a solution of 2,3-dimethyl-1-phenylbut-3-en-1-one **58** (1.13 g, 6.5 mmol) in Et_2O (60 mL) was added a solution of potassium hexamethyldisilazide (0.50 M in toluene; 13.0 mL, 6.5 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 1 h at that temperature. Methyl trifluoromethanesulfonate (1.46 mL, 13 mmol) was added, and the mixture was stirred for 15 min. After being allowed to warm up to rt, the reaction mixture was stirred for 12 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with Et_2O (20 mL × 2). The combined extracts were washed with brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1) to give **59** (1.07 g, 88%) as a colorless liquid.

IR (neat): 3087, 2976, 2939, 1676, 1637, 1446, 1245, 1173, 970, 893 cm^{-1}. ^1H NMR: δ 1.40 (6H, s), 1.75 (3H, s), 5.02 (1H, dq, J = 1.3, 1.3 Hz), 5.11, 7.36 (2H, dd, J = 7.9 Hz), 7.47 (1H, t, J = 7.9 Hz), 7.99 (2H, d, J = 7.9 Hz). ^{13}C NMR: δ 20.5, 26.0, 52.8, 110.7, 128.1, 129.0, 132.1, 136.7, 149.6, 204.0. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.75; H, 8.73.

Oximation of ketone

Method A

To a solution of hydroxylamine hydrochloride (347 mg, 5.0 mmol) in pyridine (5 mL) was added ketone (0.5 mmol), and the reaction mixture was heated to reflux for 1 d. After phosphate buffer (pH 7, 30 mL) was added to quench the reaction, the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with aqueous HCl (1 M; 10 mL) and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give ketone oxime **60**.

Method B

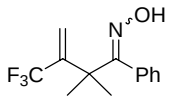
To a solution of ketone (3.0 mmol) and hydroxylamine hydrochloride (3.13 g, 45 mmol) in ethylene glycol (20 mL) and ethanol (5 mL) was added pyridine (1.2 mL, 15 mmol), and the reaction mixture was heated at 130 °C for 1 d. After phosphate buffer (pH 7, 30 mL) was added to quench the reaction, the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with water (30 mL) and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give

ketone oxime **60**.

Method C

To a solution of ketone (0.5 mmol) in ethanol (3 mL) was added hydroxylamine hydrochloride (69 mg, 1.0 mmol) and pyridine (0.12 mL, 1.5 mmol). After the reaction mixture was stirred for 12 h at rt, phosphate buffer (pH 7) was added to quench the reaction. The mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with aqueous HCl (1 M; 10 mL) and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give ketone oxime **60**.

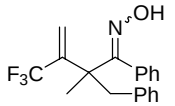
2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime (60a)



Colorless crystals. 59% (method A).

mp. 122–127 °C (dec.). IR (neat): 3257, 2983, 1323, 1176, 1149, 1117, 1097, 955, 766, 702 cm^{-1}. ^1H NMR: δ 1.38 (6H, s), 5.44 (1H, br s), 5.83 (1H, br s), 7.09–7.11 (2H, m), 7.33–7.44 (3H, m), 8.39 (1H, s). ^{13}C NMR: δ 26.2, 43.4, 120.9 (q, J_{CF} = 6 Hz), 123.9 (q, J_{CF} = 276 Hz), 127.8, 127.9, 128.3, 132.3, 142.6 (q, J_{CF} = 27 Hz), 162.6. ^{19}F NMR: δ_F 101.3 (br s). Anal. Calcd for $C_{13}H_{14}F_3NO$: C, 60.70; H, 5.49; N, 5.44. Found: C, 60.51; H, 5.69; N, 5.21.

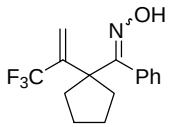
2-Methyl-1-phenyl-2-phenylmethyl-3-(trifluoromethyl)but-3-en-1-one oxime (60b)



Colorless crystals. 51% (method B).

mp. 91–93 °C. IR (neat): 3298, 3060, 3030, 2945, 1410, 1317, 1167, 1119, 1082, 958, 696 cm^{-1}. ^1H NMR: δ 1.17 (3H, s), 3.18 (1H, d, J = 14.1 Hz), 3.20 (1H, d, J = 14.1 Hz), 5.48 (1H, br s), 5.96 (1H, br s), 7.04 (2H, d, J = 7.9 Hz), 7.15 (2H, d, J = 7.3 Hz), 7.21–7.26 (3H, m), 7.34–7.37 (3H, m), 7.90 (1H, s). ^{13}C NMR: δ 22.9, 43.7, 47.5, 122.8 (q, J_{CF} = 6 Hz), 124.0 (q, J_{CF} = 277 Hz), 126.6, 127.9×2, 128.1, 128.4, 131.2, 132.5, 136.9, 142.0 (q, J_{CF} = 277 Hz), 162.3. ^{19}F NMR: δ_F 102.7 (br s). Anal. Calcd for $C_{19}H_{18}F_3NO$: C, 68.46; H, 5.44; N, 4.20. Found: C, 68.28; H, 5.49; N, 4.23.

[1-(1,1,1-Trifluoroprop-2-en-2-yl)cyclopentyl](phenyl)methanone oxime (60c)

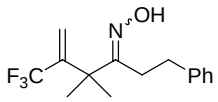


Colorless crystals. 47% (method B).

mp. 120–127 °C (dec.). IR (neat): 3263, 2972, 2881, 1410, 1319, 1161, 1111, 974, 771 cm^{-1}. ^1H NMR: δ 1.62–1.84 (6H, m), 2.11–2.19 (2H, m), 5.30 (1H, q, J_{HF} = 1.4 Hz), 5.82 (1H, br s), 7.09 (2H, d, J = 7.8 Hz), 7.32–7.41 (3H, m), 8.37

(1H, s). ^{13}C NMR: δ 22.1, 34.6, 55.3, 121.7 (q, J_{CF} = 6 Hz), 123.9 (q, J_{CF} = 277 Hz), 127.9, 128.0, 128.3, 132.4, 140.5 (q, J_{CF} = 29 Hz), 159.8. ^{19}F NMR: δ_F 100.3 (br s). Anal. Calcd for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69; N, 4.94. Found: C, 63.65; H, 5.80; N, 4.95.

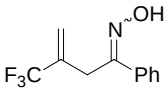
4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one oxime (60d)



Colorless crystals. 48% (method A).

mp. 108–111 °C. IR (neat): 3271, 3132, 2974, 2943, 1456, 1319, 1176, 1153, 1120, 947, 771 cm^{-1}. ^{1}H NMR: δ 1.43 (6H, s), 2.47–2.51 (2H, m), 2.87–2.91 (2H, m), 5.56 (1H, q, J_{HF} = 1.4 Hz), 5.90 (1H, s), 7.18–7.24 (3H, m), 7.29 (2H, dd, J = 7.4, 7.4 Hz), 9.03 (1H, br s). ^{13}C NMR: δ 25.4, 29.5, 32.0, 44.2, 120.7 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 277 Hz), 126.1, 128.2, 128.5, 142.1, 143.2 (q, J_{CF} = 28 Hz), 163.0. ^{19}F NMR: δ_F 100.4 (br s). Anal. Calcd for $C_{15}H_{18}F_3NO$: C, 63.15; H, 6.36; N, 4.91. Found: C, 63.36; 6.48; N, 5.00.

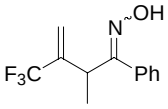
1-Phenyl-3-(trifluoromethyl)but-3-en-1-one oxime (60e)



Colorless crystals. 89% (method C).

mp. 97–98 °C. IR (neat): 3249, 3070, 2925, 1319, 1288, 1219, 1163, 1111, 968, 941, 773 cm^{-1}. ^{1}H NMR: δ 3.72 (2H, s), 5.26 (1H, br s), 5.71 (1H, br s), 7.37–7.41 (3H, m), 7.57–7.62 (2H, m) 9.44 (br s). ^{13}C NMR: δ 26.3, 118.9 (q, J_{CF} = 5 Hz), 123.3 (q, J_{CF} = 273 Hz), 125.9, 128.7, 129.8, 132.4 (q, J_{CF} = 31 Hz), 134.4, 154.6. ^{19}F NMR: δ_F 92.4 (br s). Anal. Calcd for $C_{11}H_{10}F_3NO$: C, 57.64; H, 4.40; N, 6.11. Found: C, 57.48; H, 4.54; N, 5.91.

2-Methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime (60f)

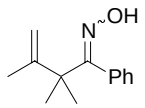


Colorless crystals. 91% (method C).

Oximes were obtained as a mixture of two isomers (major : minor = 53 : 47).

IR (neat): 3296, 2889, 1417, 1302, 1169, 1119, 949, 768, 694 cm^{-1}. ^{1}H NMR: (major) δ 1.41 (3H, d, J = 7.0 Hz), 3.67 (1H, q, J = 7.0 Hz), 5.47 (1H, br s), 5.82 (1H, br s), 7.28–7.41 (5H, m), 9.30 (1H, br s). (minor) δ 1.46 (3H, d, J = 7.2 Hz), 4.48 (1H, q, J = 7.2 Hz), 5.48 (1H, br s), 5.86 (1H, br s), 7.28–7.41 (5H, m), 9.68 (1H, br s). ^{13}C NMR: (major) δ 18.3, 39.7, 120.4 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 273 Hz), 127.8, 128.1, 128.9, 132.4, 138.1 (q, J_{CF} = 28 Hz), 158.5. (minor) 15.7, 32.8, 119.8 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 273 Hz), 127.6, 128.1, 128.9, 134.6, 139.2 (q, J_{CF} = 29 Hz), 159.0. ^{19}F NMR: (major) δ_F 94.2 (3F, br s). (minor) δ_F 94.9 (3F, br s). HRMS (FAB): calcd for $C_{12}H_{13}F_3NO$ ([M + H]$^+$) 244.0949; found 244.0962.

2,2,3-Trimethyl-1-phenylbut-3-en-1-one oxime (60g)



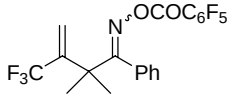
Colorless crystals. 84% (method A).

IR (neat): 3234, 3095, 3060, 2970, 2931, 1637, 1442, 1378, 1277, 1153, 947, 891 cm^{-1}. ^{1}H NMR: δ 1.24 (6H, s), 1.85 (3H, s), 4.75 (1H, s), 4.90 (1H, dq, J = 1.3, 1.3 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.32–7.38 (3H, m), 8.77 (1H, br s). ^{13}C NMR: δ 20.1, 25.6, 46.0, 112.2, 127.7×2, 128.1, 133.0, 148.2, 163.5. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.69; H, 8.56; N, 6.84.

Pentafluorobenzoylation of oxime derivatives

To a solution of oxime **60** (1.0 mmol) and pentafluorobenzoyl chloride (0.22 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.28 mL, 2 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. After the reaction was quenched with phosphate buffer (pH 7, 10 mL), organic materials were extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give 2-(trifluoromethyl)allyl ketone oxime *O*-pentafluorobenzoate **61**.

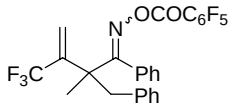
2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate (61a)



Colorless crystals. 82%.

mp. 61–64 °C. IR (neat): 2991, 1763, 1653, 1522, 1498, 1325, 1184, 1124, 1090, 995, 926, 879, 700 cm^{-1}. ^{1}H NMR: δ 1.53 (6H, s), 5.56 (1H, br s), 5.93 (1H, br s), 7.05–7.07 (2H, m), 7.37–7.38 (3H, m). ^{13}C NMR: δ 25.9, 44.5, 106.9 (m), 122.1 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 126.8, 128.0, 129.0, 131.4, 137.5 (dm, J_{CF} = 256 Hz), 141.4 (q, J_{CF} = 27 Hz), 143.2 (dm, J_{CF} = 260 Hz), 145.1 (dm, J_{CF} = 257 Hz), 156.6, 173.5. ^{19}F NMR: δ_F 1.4 (2F, m), 13.6 (1F, m), 24.5 (2F, m), 101.2 (3F, br s). Anal. Calcd for $C_{20}H_{13}F_8NO_2$: C, 53.23; H, 2.90; N, 3.10. Found: C, 53.05; H, 3.00; N, 2.86.

2-Methyl-1-phenyl-2-phenylmethyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate (61b)

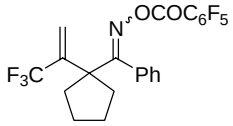


A pale yellow liquid. 76%.

IR (neat): 3032, 2943, 1761, 1653, 1496, 1327, 1188, 1126, 1002, 771 cm^{-1}. ^{1}H NMR: δ 1.24 (3H, s), 3.32 (1H, d, J =

13.8 Hz), 3.47 (1H, d, J = 13.8 Hz), 5.70 (1H, br s), 6.10 (1H, br s), 6.98 (2H, d, J = 7.9 Hz), 7.22–7.37 (8H, m). ^{13}C NMR: δ 22.4, 43.9, 48.8, 107.0 (m), 123.7 (q, J_{CF} = 277 Hz), 124.2 (q, J_{CF} = 6 Hz), 126.8×2, 128.0, 128.1, 129.1, 131.5, 131.7, 136.3, 137.6 (dm, J_{CF} = 256 Hz), 140.5 (q, J_{CF} = 26 Hz), 143.3 (dm, J_{CF} = 251 Hz), 145.3 (dm, J_{CF} = 254 Hz), 156.5, 172.7. ^{19}F NMR: δ_F 1.6 (2F, m), 13.9 (1F, m), 24.6 (2F, m), 102.2 (3F, br s). HRMS (FAB): calcd for $C_{26}H_{18}F_8NO_2$ ([M+H]$^+$) 528.1210; found 528.1206.

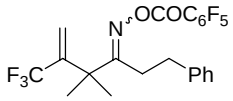
[1-(1,1,1-Trifluoroprop-2-en-2-yl)cyclopentyl](phenyl)methanone oxime *O*-pentafluorobenzoate (61c)



A pale yellow liquid. 82%.

IR (neat): 2966, 2881, 1763, 1653, 1496, 1325, 1188, 1124, 995, 700 cm^{-1}. ^{1}H NMR: δ 1.73–1.84 (2H, m), 1.84–1.95 (4H, m), 2.31–2.39 (2H, m), 5.40 (1H, q, J_{HF} = 0.9 Hz), 5.91 (1H, s), 7.02–7.06 (2H, m), 7.33–7.39 (3H, m). ^{13}C NMR: δ 22.1, 34.7, 56.4, 106.9 (m), 122.9 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 126.8, 127.9, 129.1, 131.5, 137.6 (dm, J_{CF} = 255 Hz), 139.5 (q, J_{CF} = 28 Hz), 143.2 (dm, J_{CF} = 255 Hz), 145.1 (dm, J_{CF} = 255 Hz), 156.6, 170.9. ^{19}F NMR: δ_F 1.5 (2F, m), 13.5 (1F, m), 24.4 (2F, m), 100.2 (3F, br s). HRMS (FAB): calcd for $C_{22}H_{16}F_8NO_2$ ([M+H]$^+$) 478.1053; found 478.1067.

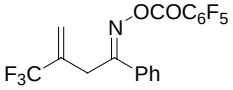
4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one oxime *O*-pentafluorobenzoate (61d)



Colorless crystals. 87%.

mp. 89–90 °C. IR (neat): 2991, 2945, 1757, 1653, 1489, 1321, 1192, 1090, 771 cm^{-1}. ^{1}H NMR: δ 1.52 (6H, s), 2.55–2.60 (2H, m), 2.83–2.87 (2H, m), 5.64 (1H, br s), 5.99 (1H, br s), 7.12 (2H, d, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.27 (2H, dd, J = 7.5, 7.5 Hz). ^{13}C NMR: δ 25.1, 30.9, 32.6, 45.2, 107.2 (m), 121.7 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 276 Hz), 126.4, 127.9, 128.6, 137.7 (dm, J_{CF} = 256 Hz), 140.5, 142.2 (q, J_{CF} = 27 Hz), 143.4 (dm, J_{CF} = 259 Hz), 145.3 (dm, J_{CF} = 255 Hz), 156.6, 172.5. ^{19}F NMR: δ_F 1.9 (2F, m), 14.1 (1F, m), 24.7 (2F, m), 100.5 (3F, br s). Anal. Calcd for $C_{22}H_{17}F_8NO_2$: C, 55.12; H, 3.57; N, 2.92. Found: C, 55.21; H, 3.71; N, 2.83.

1-Phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate (61e)

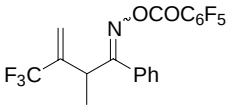


Colorless crystals. 88%.

mp. 85–86 °C. IR (neat): 1761, 1651, 1525, 1491, 1327, 1288, 1171, 1117, 1003, 895, 764 cm^{-1}. ^{1}H NMR: δ 3.80 (2H, s), 5.30 (1H, br s), 5.78 (1H, br s), 7.43–7.48 (2H, m), 7.49–7.54 (1H, m), 7.77–7.80 (2H, m). ^{13}C NMR: δ 28.7, 106.7 (m), 119.6 (q, J_{CF} = 5 Hz), 122.9 (q, J_{CF} = 272 Hz), 127.2, 128.9, 131.6, 131.9 (q, J_{CF} = 31 Hz), 132.4, 137.7 (dm, J_{CF} =

251 Hz), 143.6 (dm, J_{CF} = 260 Hz), 145.6 (dm, J_{CF} = 258 Hz), 163.1. ^{19}F NMR: δ_F 2.2 (2F, m), 15.0 (1F, m), 24.9 (2F, m), 92.2 (3F, br s). HRMS (FAB): calcd for $C_{18}H_{10}F_8NO_2$ ([M+H]$^+$) 424.0584; found 424.0584. Anal. Calcd for $C_{18}H_9F_8NO_2$: C, 51.08; H, 2.14; N, 3.31. Found: C, 50.85; H, 2.32; N, 3.12.

2-Methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate (61f)



isomer 1 (less polar).

A yellow liquid. 28%.

IR (neat): 3068, 2991, 2945, 1763, 1653, 1496, 1327, 1173, 1122, 995 cm^{-1}. ^{1}H NMR: δ 1.54 (3H, d, J = 7.0 Hz), 3.84 (1H, q, J = 7.0 Hz), 5.58 (1H, s), 5.92 (1H, s), 7.18–7.22 (2H, m), 7.38–7.42 (3H, m). ^{13}C NMR: δ 18.1, 40.3, 106.7 (m), 121.6 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 274 Hz), 127.1, 128.2, 129.8, 131.5, 137.6 (dm, J_{CF} = 256 Hz), 137.9 (q, J_{CF} = 30 Hz), 143.2 (dm, J_{CF} = 287 Hz), 145.3 (dm, J_{CF} = 258 Hz), 156.6, 169.6.

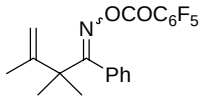
^{19}F NMR: δ_F 1.7 (2F, m), 14.0 (1F, m), 24.6 (2F, m), 93.9 (3F, br s). HRMS (FAB): calcd for $C_{19}H_{12}F_8NO_2$ ([M+H]$^+$) 438.0740; found 438.0716.

isomer 2 (polar).

A colorless liquid. 38%.

IR (neat): 3062, 2991, 2949, 1766, 1653, 1496, 1325, 1173, 1120, 995 cm^{-1}. ^{1}H NMR: δ 1.49 (3H, d, J = 7.2 Hz), 4.46 (1H, q, J = 7.2 Hz), 5.48 (1H, s), 5.91 (1H, s), 7.41 (2H, dd, J = 7.4, 7.4 Hz), 7.47 (1H, t, J = 7.4 Hz), 7.51 (2H, J = 7.4 Hz). ^{13}C NMR: δ 15.9, 35.0, 106.6–106.8 (m), 120.7 (q, J_{CF} = 6 Hz), 123.2 (q, J_{CF} = 275 Hz), 128.4×2, 130.5, 132.1, 137.3 (q, J_{CF} = 29 Hz), 137.8 (dm, J_{CF} = 256 Hz), 143.6 (dm, J_{CF} = 261 Hz), 145.4 (dm, J_{CF} = 264 Hz), 156.1, 168.6. ^{19}F NMR: δ_F 2.1 (2F, m), 14.6 (1F, m), 24.7 (2F, m), 94.7 (3F, br s). HRMS (FAB): calcd for $C_{19}H_{12}F_8NO_2$ ([M+H]$^+$) 438.0740; found 438.0759.

2,2,3-Trimethyl-1-phenylbut-3-en-1-one oxime *O*-pentafluorobenzoate (61g)



A colorless liquid. 34%.

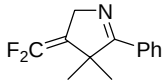
IR (neat): 2976, 2935, 1756, 1653, 1496, 1325, 1190, 995, 858, 771 cm^{-1}. ^{1}H NMR: δ 1.37 (6H, s), 1.93 (3H, s), 4.84 (1H, s), 5.01 (1H, dq, J = 1.2, 1.2 Hz), 7.03–7.06 (2H, m), 7.31–7.36 (3H, m). ^{13}C NMR: δ 20.0, 25.3, 47.4, 107.0 (m), 113.6, 126.6, 127.7, 128.7, 132.0, 137.5 (dm, J_{CF} = 256 Hz), 143.1 (dm, J_{CF} = 260 Hz), 145.1 (dm, J_{CF} = 264 Hz), 146.5, 156.7, 174.5. ^{19}F NMR: δ_F 1.4 (2F, m), 13.3 (1F, m), 24.2 (2F, m). HRMS (FAB): calcd for $C_{20}H_{17}F_5NO_2$ ([M+H]$^+$) 398.1179; found 398.1149.

第三章第二節

5-*endo* Heck-type reaction of *O*-pentafluorobenzoyl oxime 61

To a solution of triphenylphosphine (131 mg, 0.50 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.050 mmol) in *N*,*N*-dimethylacetamide (DMA; 10 mL) was added 2-(trifluoromethyl)allyl ketone oxime *O*-pentafluorobenzoate **61** (0.50 mmol) at rt. After the reaction mixture was stirred at 100 °C, phosphate buffer (pH 7, 10 mL) was added to quench the reaction, and organic materials were extracted with Et_2O (10 mL × 3). The combined organic extracts were washed with water (10 mL × 3) and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give **62**.

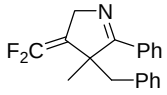
3-Difluoromethylene-3,4-dihydro-4,4-dimethyl-5-phenyl-2*H*-pyrrole (62a)



A pale yellow liquid. 60%.

IR (neat): 2978, 1765, 1466, 1267, 1223, 1132, 1047, 1014, 775, 694, 598 cm^{-1}. ^1H NMR: δ 1.52 (6H, s), 4.61 (2H, dd, J_{HF} = 3.6, 3.6 Hz), 7.37–7.42 (3H, m), 7.69–7.73 (2H, m). ^{13}C NMR: δ 24.6 (dd, J_{CF} = 3, 2 Hz), 51.6 (dd, J_{CF} = 4, 3 Hz), 57.8 (dd, J_{CF} = 3, 2 Hz), 97.5 (dd, J_{CF} = 21, 15 Hz), 127.9, 128.2, 129.7, 133.7 (dd, J_{CF} = 2, 2 Hz), 149.3 (dd, J_{CF} = 287, 282 Hz), 178.5. ^{19}F NMR: δ_F 68.5 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 3.6 Hz), 76.3 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 3.6 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2N$ ($[M+H]^+$) 222.1094; found 222.1091.

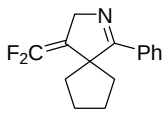
4-Benzyl-3-difluoromethylene-3,4-dihydro-4-methyl-5-phenyl-2*H*-pyrrole (62b)



A pale yellow liquid. 71%.

IR (neat): 3030, 2979, 2933, 1763, 1606, 1452, 1254, 1014, 692 cm^{-1}. ^1H NMR: δ 1.73 (3H, s), 3.07 (1H, d, J = 14.0 Hz), 3.40 (1H, dd, J = 14.0, 1.6 Hz), 3.69 (1H, ddd, J = 20.5 Hz, J_{HF} = 3.7, 3.7 Hz), 4.40 (1H, ddd, J = 20.5 Hz, J_{HF} = 2.8, 2.8 Hz), 6.91–6.95 (2H, m), 7.13–7.17 (3H, m), 7.43–7.51 (3H, m), 7.92–7.97 (2H, m). ^{13}C NMR: δ 24.3, 43.5, 57.5 (dd, J_{CF} = 5, 3 Hz), 58.2 (br m), 95.9 (dd, J_{CF} = 23, 14 Hz), 126.6, 128.1, 128.4, 128.5, 129.4, 130.2, 134.0, 137.1, 149.2 (dd, J_{CF} = 287, 284 Hz), 175.7. ^{19}F NMR: δ_F 70.3 (1F, d, J_{FF} = 62 Hz), 76.6 (1F, d, J_{FF} = 62 Hz). HRMS (FAB): calcd for $C_{19}H_{18}F_2N$ ($[M+H]^+$) 298.1407; found 298.1389.

4-Difluoromethylene-1-phenyl-2-azaspiro[4.4]non-1-ene (62c)

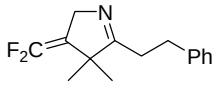


Pale yellow crystals. 65%.

mp. 78–79 °C. IR (neat): 2976, 2883, 2846, 1761, 1606, 1570, 1458, 1252, 1088, 775 cm^{-1}. ^1H NMR: δ 1.76–1.85 (2H, m), 1.85–2.03 (4H, m), 2.29 (2H, ddd, J = 13.7, 6.9, 6.9 Hz), 4.59 (2H, dd, J_{HF} = 3.2, 3.2 Hz), 7.36–7.43 (3H, m), 7.68

(2H, d, J = 8.2 Hz). ^{13}C NMR: δ 27.0, 37.5, 58.6, 60.6 (br s), 99.9 (dd, J_{CF} = 23, 14 Hz), 128.1, 128.2, 129.6, 133.8, 149.5 (dd, J_{CF} = 288, 281 Hz), 178.3. ^{19}F NMR: δ_F 70.6 (1F, d, J_{HF} = 65 Hz), 74.8 (1F, d, J_{HF} = 65 Hz). Anal. Calcd for $C_{15}H_{15}F_2N$: C, 72.86; H, 6.11; N, 5.66. Found: C, 72.78; H, 6.32; N, 5.67.

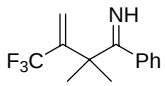
3-Difluoromethylene-3,4-dihydro-4,4-dimethyl-5-phenethyl-2*H*-pyrrole (62d)



A pale yellow liquid. 20% (NMR yield).

IR (neat): 3028, 2968, 2929, 1766, 1641, 1496, 1464, 1277, 1219, 1045 cm^{-1}. ^{1}H NMR: δ 1.25 (6H, s), 2.48–2.53 (2H, m), 3.00 (2H, t, J = 7.9 Hz), 4.45–4.47 (2H, m), 7.20–7.30 (5H, m). ^{13}C NMR: δ 23.4, 30.1, 32.4, 51.3, 57.9, 96.0 (dd, J_{CF} = 21, 15 Hz), 126.1, 128.3, 128.4, 141.7, 149.7 (dd, J_{CF} = 283, 283 Hz), 181.8. ^{19}F NMR: δ_F 68.4 (1F, dd, J_{FF} = 61 Hz, J_{HF} = 3 Hz), 76.6 (1F, d, J_{FF} = 61 Hz). HRMS (FAB): calcd for $C_{15}H_{18}F_2N$ ([M+H]$^+$) 250.1407; found 250.1397.

2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-imine (63a)



To a solution of 2,2-dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate **61a** (199 mg, 0.441 mmol) in DMA (5 mL) were added H_2O (100 μL), $Pd(PPh_3)_4$ (51 mg, 0.044 mmol), and PPh_3 (116 mg, 0.441 mmol) at rt. After the reaction mixture was stirred at 90 °C for 1 h, the reaction was quenched with phosphate buffer (pH 7, 10 mL) at 0 °C, and organic materials were extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–Et_2O, 4:1) to give **63a** (80 mg, 76%) as a pale yellow liquid.

IR (neat): 2983, 1616, 1323, 1178, 1124, 1093, 957, 895, 758, 702 cm^{-1}. ^{1}H NMR: δ 1.46 (6H, s), 5.60 (1H, q, J_{HF} = 0.9 Hz), 5.91 (1H, br s), 7.25–7.36 (5H, m), 9.62 (1H, br s). ^{13}C NMR: δ 26.7, 46.2, 120.8 (br s), 123.9 (q, J_{CF} = 277 Hz), 126.8 (br s), 128.0, 128.8, 140.3 (br s), 143.4 (q, J_{CF} = 27 Hz), 184.8. ^{19}F NMR: δ_F 101.1 (br s). HRMS (FAB): calcd for $C_{13}H_{15}F_3N$ ([M+H]$^+$) 242.1156; found 242.1141.

ORTEP structure of

2-(4-methylbenzenesulfonyl)-1-phenyl-6a-(trifluoromethyl)hexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one **25**

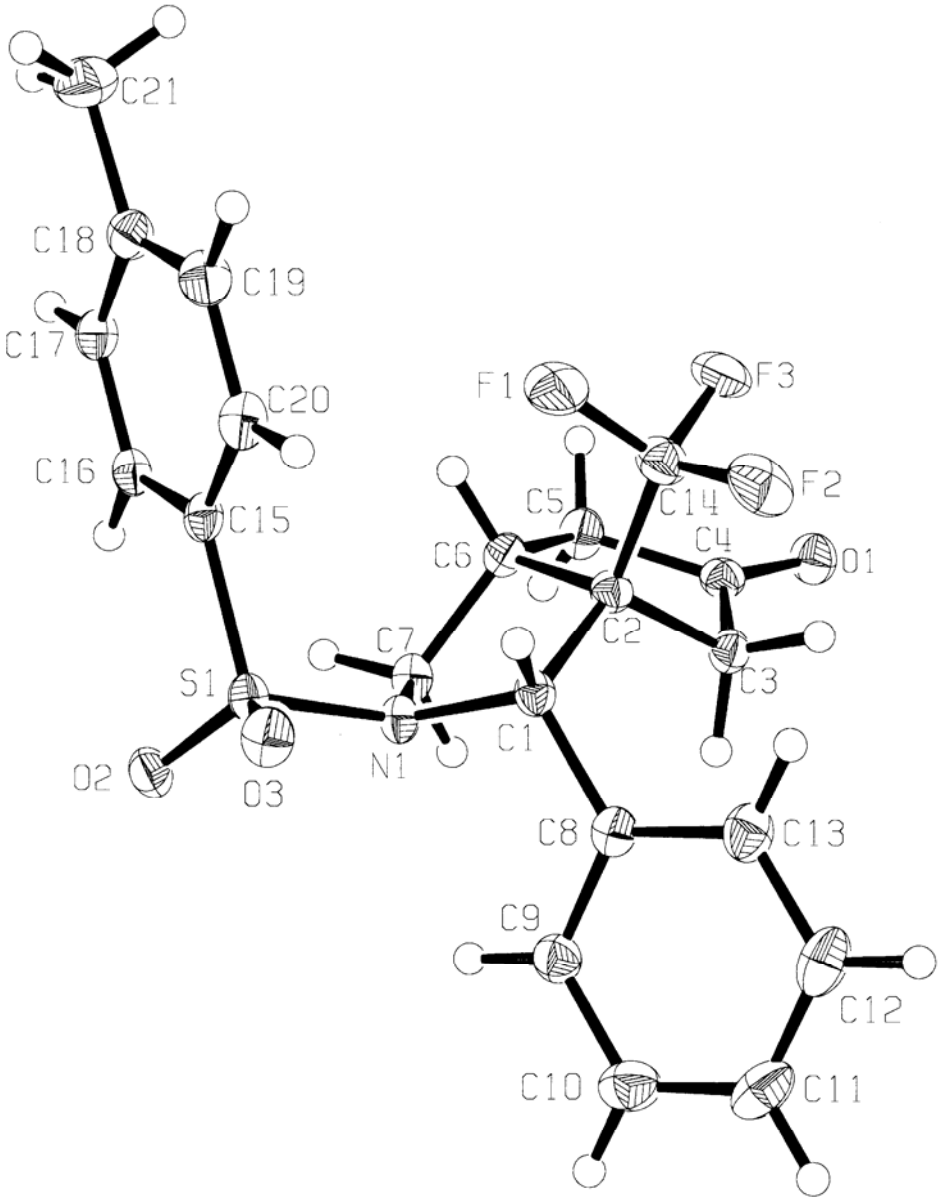


Table 1. Crystal data and structure refinement for nadano2.

Identification code	nadano2	
Empirical formula	C21 H20 F3 N O3 S	
Formula weight	423.44	
Temperature	120(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 13.365(5) Å	α= 90°.
	b = 9.396(3) Å	β= 92.7110(16)°.
	c = 15.191(5) Å	γ = 90°.
Volume	1905.5(11) $Å^3$	
Z	4	
Density (calculated)	1.476 Mg/m^3	
Absorption coefficient	0.222 mm^{-1}	
F(000)	880	
Crystal size	0.60 x 0.40 x 0.30 mm^3	
Theta range for data collection	3.00 to 27.48°.	
Index ranges	-17<=h<=17, -12<=k<=12, -19<=l<=19	
Reflections collected	20726	
Independent reflections	4351 [R(int) = 0.0196]	
Completeness to theta = 27.48°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9364 and 0.8783	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4351 / 0 / 263	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0914	
R indices (all data)	R1 = 0.0381, wR2 = 0.0939	
Largest diff. peak and hole	0.308 and -0.383 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nadano2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8628(1)	3355(1)	991(1)	18(1)
C(2)	7628(1)	2636(1)	632(1)	18(1)
C(3)	7293(1)	1296(1)	1116(1)	19(1)
C(4)	6161(1)	1341(1)	1046(1)	20(1)
C(5)	5827(1)	2887(1)	960(1)	24(1)
C(6)	6781(1)	3738(1)	794(1)	19(1)
C(7)	7218(1)	4567(1)	1586(1)	19(1)
N(1)	8291(1)	4674(1)	1421(1)	18(1)
O(1)	5611(1)	319(1)	1050(1)	26(1)
C(8)	9254(1)	2431(1)	1633(1)	20(1)
C(9)	9434(1)	2841(1)	2502(1)	24(1)
C(10)	10013(1)	1996(2)	3081(1)	31(1)
C(11)	10415(1)	731(2)	2799(1)	32(1)
C(12)	10233(1)	304(2)	1933(1)	33(1)
C(13)	9664(1)	1151(2)	1351(1)	27(1)
C(14)	7671(1)	2312(2)	-339(1)	25(1)
F(1)	7833(1)	3477(1)	-822(1)	37(1)
F(2)	8394(1)	1378(1)	-516(1)	37(1)
F(3)	6806(1)	1738(1)	-664(1)	32(1)
S(1)	8758(1)	6225(1)	1177(1)	19(1)
O(2)	8521(1)	7156(1)	1888(1)	24(1)
O(3)	9781(1)	5975(1)	979(1)	26(1)
C(15)	8110(1)	6872(1)	223(1)	18(1)
C(16)	7248(1)	7690(1)	302(1)	19(1)
C(17)	6746(1)	8207(1)	-453(1)	21(1)
C(18)	7091(1)	7918(1)	-1287(1)	23(1)
C(19)	7947(1)	7079(2)	-1347(1)	26(1)
C(20)	8457(1)	6553(1)	-605(1)	23(1)
C(21)	6563(1)	8533(2)	-2100(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for nadano2.

C(1)-N(1)	1.4807(15)	C(16)-C(17)	1.3883(19)
C(1)-C(8)	1.5261(18)	C(16)-H(14)	0.9500
C(1)-C(2)	1.5714(17)	C(17)-C(18)	1.3948(19)
C(1)-H(1)	1.0000	C(17)-H(15)	0.9500
C(2)-C(14)	1.5089(18)	C(18)-C(19)	1.397(2)
C(2)-C(3)	1.5356(17)	C(18)-C(21)	1.507(2)
C(2)-C(6)	1.5621(17)	C(19)-C(20)	1.380(2)
C(3)-C(4)	1.5123(18)	C(19)-H(16)	0.9500
C(3)-H(2)	0.9900	C(20)-H(17)	0.9500
C(3)-H(3)	0.9900	C(21)-H(18)	0.9800
C(4)-O(1)	1.2096(16)	C(21)-H(19)	0.9800
C(4)-C(5)	1.5234(19)	C(21)-H(20)	0.9800
C(5)-C(6)	1.5355(17)		
C(5)-H(4)	0.9900	N(1)-C(1)-C(8)	111.31(10)
C(5)-H(5)	0.9900	N(1)-C(1)-C(2)	103.98(9)
C(6)-C(7)	1.5263(18)	C(8)-C(1)-C(2)	114.11(10)
C(6)-H(6)	1.0000	N(1)-C(1)-H(1)	109.1
C(7)-N(1)	1.4701(15)	C(8)-C(1)-H(1)	109.1
C(7)-H(7)	0.9900	C(2)-C(1)-H(1)	109.1
C(7)-H(8)	0.9900	C(14)-C(2)-C(3)	109.14(10)
N(1)-S(1)	1.6349(11)	C(14)-C(2)-C(6)	110.45(11)
C(8)-C(9)	1.3860(19)	C(3)-C(2)-C(6)	103.77(9)
C(8)-C(13)	1.3969(18)	C(14)-C(2)-C(1)	110.77(10)
C(9)-C(10)	1.392(2)	C(3)-C(2)-C(1)	116.65(10)
C(9)-H(9)	0.9500	C(6)-C(2)-C(1)	105.72(10)
C(10)-C(11)	1.381(2)	C(4)-C(3)-C(2)	104.89(10)
C(10)-H(10)	0.9500	C(4)-C(3)-H(2)	110.8
C(11)-C(12)	1.385(2)	C(2)-C(3)-H(2)	110.8
C(11)-H(11)	0.9500	C(4)-C(3)-H(3)	110.8
C(12)-C(13)	1.389(2)	C(2)-C(3)-H(3)	110.8
C(12)-H(12)	0.9500	H(2)-C(3)-H(3)	108.8
C(13)-H(13)	0.9500	O(1)-C(4)-C(3)	125.75(12)
C(14)-F(1)	1.3413(16)	O(1)-C(4)-C(5)	125.56(12)
C(14)-F(2)	1.3419(17)	C(3)-C(4)-C(5)	108.68(10)
C(14)-F(3)	1.3487(16)	C(4)-C(5)-C(6)	105.60(10)
S(1)-O(3)	1.4330(10)	C(4)-C(5)-H(4)	110.6
S(1)-O(2)	1.4359(10)	C(6)-C(5)-H(4)	110.6
S(1)-C(15)	1.7616(14)	C(4)-C(5)-H(5)	110.6
C(15)-C(20)	1.3939(18)	C(6)-C(5)-H(5)	110.6
C(15)-C(16)	1.3946(17)	H(4)-C(5)-H(5)	108.8

C(7)-C(6)-C(5)	115.21(11)	F(2)-C(14)-F(3)	106.10(11)
C(7)-C(6)-C(2)	102.07(10)	F(1)-C(14)-C(2)	112.58(11)
C(5)-C(6)-C(2)	107.11(10)	F(2)-C(14)-C(2)	112.94(11)
C(7)-C(6)-H(6)	110.7	F(3)-C(14)-C(2)	111.55(11)
C(5)-C(6)-H(6)	110.7	O(3)-S(1)-O(2)	120.31(6)
C(2)-C(6)-H(6)	110.7	O(3)-S(1)-N(1)	106.26(6)
N(1)-C(7)-C(6)	103.93(9)	O(2)-S(1)-N(1)	105.83(6)
N(1)-C(7)-H(7)	111.0	O(3)-S(1)-C(15)	108.68(6)
C(6)-C(7)-H(7)	111.0	O(2)-S(1)-C(15)	106.90(6)
N(1)-C(7)-H(8)	111.0	N(1)-S(1)-C(15)	108.38(6)
C(6)-C(7)-H(8)	111.0	C(20)-C(15)-C(16)	120.49(12)
H(7)-C(7)-H(8)	109.0	C(20)-C(15)-S(1)	119.79(10)
C(7)-N(1)-C(1)	109.71(9)	C(16)-C(15)-S(1)	119.72(9)
C(7)-N(1)-S(1)	119.04(8)	C(17)-C(16)-C(15)	119.36(11)
C(1)-N(1)-S(1)	121.25(8)	C(17)-C(16)-H(14)	120.3
C(9)-C(8)-C(13)	118.53(12)	C(15)-C(16)-H(14)	120.3
C(9)-C(8)-C(1)	121.07(11)	C(16)-C(17)-C(18)	121.01(12)
C(13)-C(8)-C(1)	120.40(12)	C(16)-C(17)-H(15)	119.5
C(8)-C(9)-C(10)	120.66(13)	C(18)-C(17)-H(15)	119.5
C(8)-C(9)-H(9)	119.7	C(17)-C(18)-C(19)	118.38(12)
C(10)-C(9)-H(9)	119.7	C(17)-C(18)-C(21)	120.51(13)
C(11)-C(10)-C(9)	120.49(14)	C(19)-C(18)-C(21)	121.09(12)
C(11)-C(10)-H(10)	119.8	C(20)-C(19)-C(18)	121.57(12)
C(9)-C(10)-H(10)	119.8	C(20)-C(19)-H(16)	119.2
C(10)-C(11)-C(12)	119.40(13)	C(18)-C(19)-H(16)	119.2
C(10)-C(11)-H(11)	120.3	C(19)-C(20)-C(15)	119.17(12)
C(12)-C(11)-H(11)	120.3	C(19)-C(20)-H(17)	120.4
C(11)-C(12)-C(13)	120.26(14)	C(15)-C(20)-H(17)	120.4
C(11)-C(12)-H(12)	119.9	C(18)-C(21)-H(18)	109.5
C(13)-C(12)-H(12)	119.9	C(18)-C(21)-H(19)	109.5
C(12)-C(13)-C(8)	120.65(14)	H(18)-C(21)-H(19)	109.5
C(12)-C(13)-H(13)	119.7	C(18)-C(21)-H(20)	109.5
C(8)-C(13)-H(13)	119.7	H(18)-C(21)-H(20)	109.5
F(1)-C(14)-F(2)	106.73(11)	H(19)-C(21)-H(20)	109.5
F(1)-C(14)-F(3)	106.48(11)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for nadano2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(1)	16(1)	17(1)	-1(1)	4(1)	0(1)
C(2)	20(1)	18(1)	16(1)	-1(1)	2(1)	-1(1)
C(3)	22(1)	17(1)	20(1)	1(1)	2(1)	0(1)
C(4)	23(1)	22(1)	16(1)	0(1)	1(1)	-2(1)
C(5)	19(1)	22(1)	33(1)	1(1)	0(1)	-1(1)
C(6)	19(1)	18(1)	21(1)	2(1)	1(1)	0(1)
C(7)	19(1)	17(1)	22(1)	0(1)	5(1)	0(1)
N(1)	19(1)	15(1)	20(1)	-1(1)	4(1)	0(1)
O(1)	26(1)	23(1)	29(1)	1(1)	2(1)	-6(1)
C(8)	16(1)	19(1)	24(1)	1(1)	3(1)	-1(1)
C(9)	21(1)	23(1)	26(1)	-1(1)	-1(1)	-1(1)
C(10)	26(1)	36(1)	30(1)	5(1)	-5(1)	-4(1)
C(11)	21(1)	33(1)	41(1)	15(1)	0(1)	1(1)
C(12)	28(1)	25(1)	46(1)	6(1)	9(1)	8(1)
C(13)	28(1)	24(1)	30(1)	-2(1)	5(1)	5(1)
C(14)	30(1)	27(1)	20(1)	-2(1)	2(1)	-3(1)
F(1)	55(1)	39(1)	18(1)	4(1)	6(1)	-12(1)
F(2)	39(1)	45(1)	27(1)	-13(1)	9(1)	5(1)
F(3)	37(1)	37(1)	21(1)	-4(1)	-5(1)	-7(1)
S(1)	18(1)	16(1)	21(1)	-1(1)	2(1)	-2(1)
O(2)	29(1)	20(1)	23(1)	-4(1)	1(1)	-2(1)
O(3)	18(1)	25(1)	34(1)	1(1)	3(1)	-2(1)
C(15)	20(1)	15(1)	21(1)	1(1)	4(1)	-3(1)
C(16)	22(1)	16(1)	20(1)	-2(1)	5(1)	-2(1)
C(17)	21(1)	18(1)	24(1)	0(1)	3(1)	-2(1)
C(18)	26(1)	21(1)	22(1)	2(1)	3(1)	-5(1)
C(19)	30(1)	26(1)	21(1)	-1(1)	10(1)	-2(1)
C(20)	23(1)	21(1)	26(1)	1(1)	10(1)	0(1)
C(21)	39(1)	39(1)	22(1)	5(1)	2(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for nadano2.

	x	y	z	U(eq)
H(1)	9040	3615	482	21
H(2)	7547	427	833	23
H(3)	7540	1313	1740	23
H(4)	5525	3213	1507	29
H(5)	5329	3001	462	29
H(6)	6672	4379	272	23
H(7)	6910	5523	1618	23
H(8)	7113	4051	2142	23
H(9)	9160	3707	2705	28
H(10)	10133	2292	3674	37
H(11)	10811	158	3195	38
H(12)	10500	-572	1736	39
H(13)	9553	857	756	33
H(14)	7006	7892	867	23
H(15)	6160	8765	-401	25
H(16)	8185	6865	-1911	31
H(17)	9037	5981	-658	28
H(18)	7036	9105	-2424	50
H(19)	6007	9136	-1927	50
H(20)	6303	7758	-2477	50

Table 6. Torsion angles [°] for nadano2.

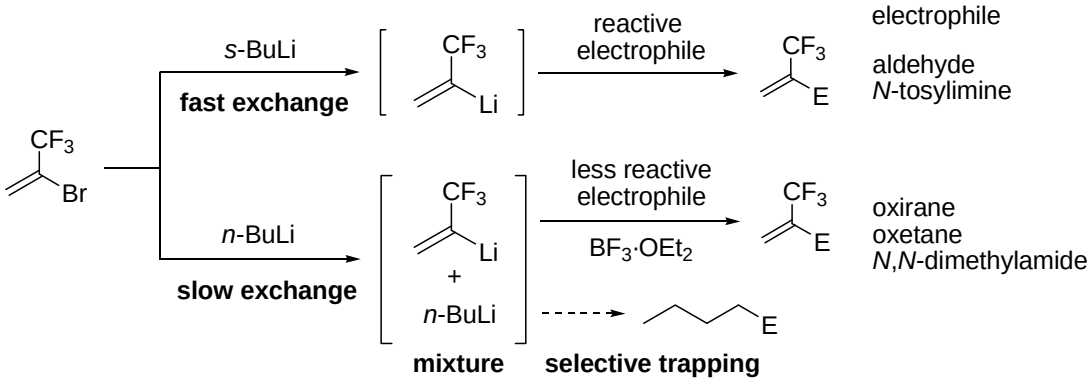
N(1)-C(1)-C(2)-C(14)	126.59(11)	C(9)-C(10)-C(11)-C(12)	-0.2(2)
C(8)-C(1)-C(2)-C(14)	-111.95(12)	C(10)-C(11)-C(12)-C(13)	0.9(2)
N(1)-C(1)-C(2)-C(3)	-107.77(11)	C(11)-C(12)-C(13)-C(8)	-1.0(2)
C(8)-C(1)-C(2)-C(3)	13.68(15)	C(9)-C(8)-C(13)-C(12)	0.6(2)
N(1)-C(1)-C(2)-C(6)	6.93(12)	C(1)-C(8)-C(13)-C(12)	-179.89(12)
C(8)-C(1)-C(2)-C(6)	128.39(11)	C(3)-C(2)-C(14)-F(1)	171.96(11)
C(14)-C(2)-C(3)-C(4)	-86.06(12)	C(6)-C(2)-C(14)-F(1)	58.49(14)
C(6)-C(2)-C(3)-C(4)	31.70(12)	C(1)-C(2)-C(14)-F(1)	-58.30(14)
C(1)-C(2)-C(3)-C(4)	147.49(10)	C(3)-C(2)-C(14)-F(2)	-67.07(14)
C(2)-C(3)-C(4)-O(1)	152.26(13)	C(6)-C(2)-C(14)-F(2)	179.46(10)
C(2)-C(3)-C(4)-C(5)	-27.16(13)	C(1)-C(2)-C(14)-F(2)	62.67(14)
O(1)-C(4)-C(5)-C(6)	-168.37(12)	C(3)-C(2)-C(14)-F(3)	52.32(14)
C(3)-C(4)-C(5)-C(6)	11.06(14)	C(6)-C(2)-C(14)-F(3)	-61.15(14)
C(4)-C(5)-C(6)-C(7)	-103.61(12)	C(1)-C(2)-C(14)-F(3)	-177.94(10)
C(4)-C(5)-C(6)-C(2)	9.15(14)	C(7)-N(1)-S(1)-O(3)	-175.02(9)
C(14)-C(2)-C(6)-C(7)	-147.07(10)	C(1)-N(1)-S(1)-O(3)	-33.01(11)
C(3)-C(2)-C(6)-C(7)	96.08(11)	C(7)-N(1)-S(1)-O(2)	56.00(10)
C(1)-C(2)-C(6)-C(7)	-27.20(12)	C(1)-N(1)-S(1)-O(2)	-161.99(9)
C(14)-C(2)-C(6)-C(5)	91.49(12)	C(7)-N(1)-S(1)-C(15)	-58.38(10)
C(3)-C(2)-C(6)-C(5)	-25.36(13)	C(1)-N(1)-S(1)-C(15)	83.63(11)
C(1)-C(2)-C(6)-C(5)	-148.64(10)	O(3)-S(1)-C(15)-C(20)	24.88(12)
C(5)-C(6)-C(7)-N(1)	153.30(10)	O(2)-S(1)-C(15)-C(20)	156.14(10)
C(2)-C(6)-C(7)-N(1)	37.63(11)	N(1)-S(1)-C(15)-C(20)	-90.19(11)
C(6)-C(7)-N(1)-C(1)	-35.59(12)	O(3)-S(1)-C(15)-C(16)	-155.64(10)
C(6)-C(7)-N(1)-S(1)	110.43(10)	O(2)-S(1)-C(15)-C(16)	-24.38(11)
C(8)-C(1)-N(1)-C(7)	-105.84(11)	N(1)-S(1)-C(15)-C(16)	89.29(11)
C(2)-C(1)-N(1)-C(7)	17.46(12)	C(20)-C(15)-C(16)-C(17)	-1.10(18)
C(8)-C(1)-N(1)-S(1)	109.02(10)	S(1)-C(15)-C(16)-C(17)	179.43(9)
C(2)-C(1)-N(1)-S(1)	-127.67(9)	C(15)-C(16)-C(17)-C(18)	0.07(18)
N(1)-C(1)-C(8)-C(9)	1.01(16)	C(16)-C(17)-C(18)-C(19)	0.86(19)
C(2)-C(1)-C(8)-C(9)	-116.30(13)	C(16)-C(17)-C(18)-C(21)	-177.59(12)
N(1)-C(1)-C(8)-C(13)	-178.52(11)	C(17)-C(18)-C(19)-C(20)	-0.8(2)
C(2)-C(1)-C(8)-C(13)	64.16(15)	C(21)-C(18)-C(19)-C(20)	177.64(13)
C(13)-C(8)-C(9)-C(10)	0.08(19)	C(18)-C(19)-C(20)-C(15)	-0.2(2)
C(1)-C(8)-C(9)-C(10)	-179.47(12)	C(16)-C(15)-C(20)-C(19)	1.17(19)
C(8)-C(9)-C(10)-C(11)	-0.2(2)	S(1)-C(15)-C(20)-C(19)	-179.36(10)

Symmetry transformations used to generate equivalent atoms

総括

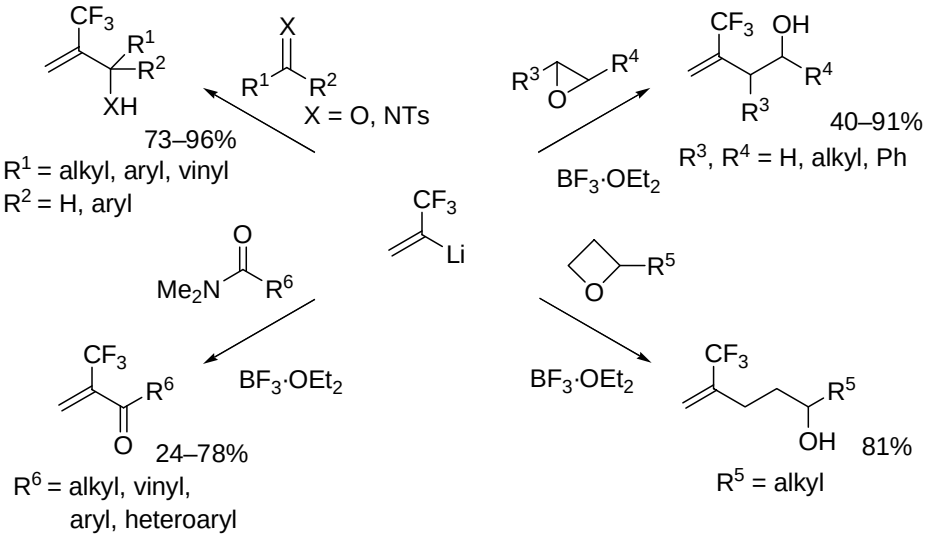
本論文は、含フッ素 C-3 ビルディングブロックとして(トリフルオロメチル)ビニルリチウムを利用した(トリフルオロメチル)ビニル化合物合成法と、生成物の種々の含フッ素化合物への変換について述べたものである。(トリフルオロメチル)ビニル基を有する化合物は様々な反応性を示し、含フッ素化合物の構築に有望な化合物群である。その合成には、イオン結合性の高い金属化合物である 1-(トリフルオロメチル)ビニルリチウムやマグネシウム化合物の利用が簡便と考えられるが、β位のフッ素原子の脱離を伴って 1,1-ジフルオロアレンへ分解し易く、これらを利用した(トリフルオロメチル)ビニル化合物の合成反応は利用するには大きな制約があった。筆者は、1-(トリフルオロメチル)ビニルリチウムの生成と挙動を詳細に検討することによって、様々な求電子剤との反応へ有効に利用する手法を見出した。さらに、得られた(トリフルオロメチル)ビニル化合物に求核的 5-*endo*-*trig* 反応、Nazarov 環化反応、Pauson－Khand 反応、5-*endo* Heck 型反応を適用し、含フッ素炭素置換基を有するヘテロ環および炭素環の合成法を開発した。

まず、第一章第一節から第三節にかけて、1-(トリフルオロメチル)ビニルリチウムを使用した合成反応について述べた。2-ブロモ-3,3,3-トリフルオロプロペンに *s*-BuLi を作用させると、－105 ℃においてもリチウム－ハロゲン交換が速やかに完結し、ビニルリチウムが生成することを明らかにした。このビニルリチウムに、活性な求電子剤として *N*-トシルイミンを作用させ、2-(トリフルオロメチル)アリルアミドを良好な収率で得た。この手法では、ビニルリチウムの分解反応を避けるため、低温下で比較的反応性の高い求電子剤を作用させる必要がある。一方、*n*-BuLi を用いるリチウム－ハロゲン交換反応の検討を行ったところ、適度な求電子性の化合物を共存させると、リチウム－ハロゲン交換反応を行いながらビニルリチウムのみを選択的に捕捉できることを見出した。これは、1-(トリフルオロメチル)ビニルリチウムと *n*-BuLi が共存しても、各々の会合度が異なるため選択的にビニルリチウムが捕捉されたためである。

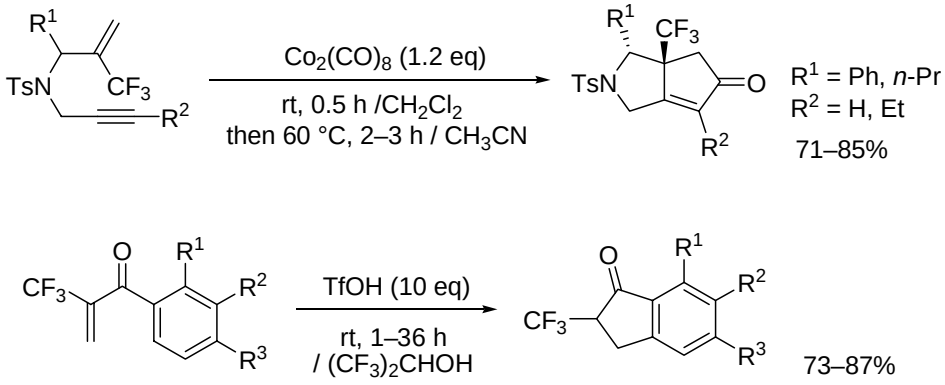


求電子剤としてオキシランやオキセタンを用いることにより(トリフルオロメチル)ビニル基を有す

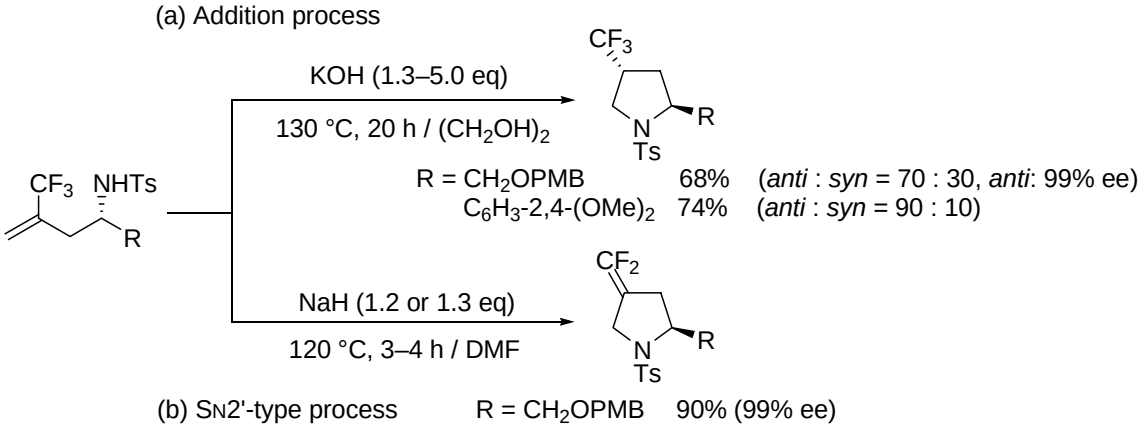
るアルコールを、また、カルボン酸 *N,N*-ジメチルアミドからはα-トリフルオロメチル-α,β-不飽和ケトンを効率良く合成することができた。このように、ブロモトリフルオロプロペンのリチウム－ハロゲン交換に *s*-BuLi もしくは *n*-BuLi を用いる上記 2 つの手法を使い分けることで、1-(トリフルオロメチル)ビニルリチウムを広範な求電子剤との反応に利用することが可能となった。



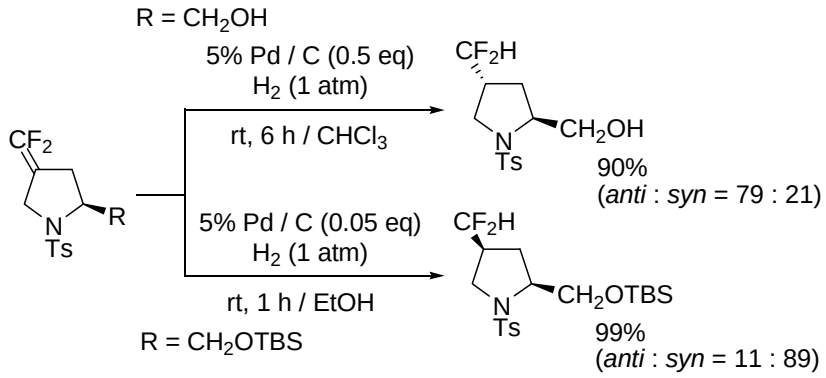
第一章第四節では、上記反応で得られた(トリフルオロメチル)ビニル化合物を用い、様々な含フッ素化合物合成へと応用した結果に関して述べた。まず、第一節において得られた 2-(トリフルオロメチル)アリルアミドをプロパルギル化して 1,6-エンインへ誘導し、Pauson－Khand 反応を適用すると、核間にトリフルオロメチル基を持つ縮環化合物を合成することができた。また、第三節において得られたα-トリフルオロメチル-α,β-不飽和ケトンを用い、Nazarov 環化を行わせるとα-(トリフルオロメチル)インダノン類が得られた。これらの反応により、従来のトリフルオロメチル化剤による方法では、合成が困難であったり、選択性が低いといった合成上の問題を抱える化合物群を、C-3 ビルディングブロックである 1-(トリフルオロメチル)ビニルリチウムから、短工程で効率良く合成する手法を提供できる。



第二章では、第一章第二節において見出した 1-(トリフルオロメチル)ビニルリチウムと光学活性オキシランの反応で得られる含フッ素光学活性アルコール誘導体を用い、求核的 5-*endo*-*trig* 環化を鍵反応とする含フッ素光学活性プロリンを合成する手法について述べた。含フッ素光学活性アルコール誘導体より得られた環化前駆体の *N*-[3-(トリフルオロメチル)ホモアリル]スルホンアミドを塩基で処理すると、プロトン性条件下では分子内付加反応が、また、非プロトン性条件下ではフッ素化物イオンの脱離を伴う S_N2'反応が進行し、それぞれトリフルオロメチル(CF_3)基およびジフルオロメチレン(CF_2=)基を有するピロリジン骨格を収率良く構築することができた。

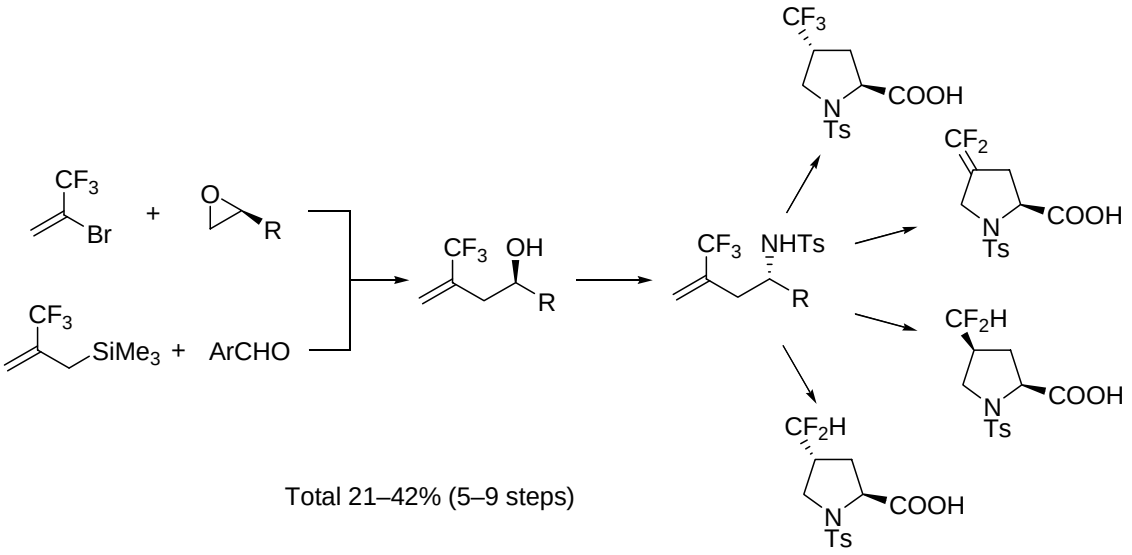


また、CF_2=基を有するピロリジン誘導体の水素化により、CF_2H 基を持つプロリンの合成を検討した。2 位の置換基を利用した面選択的水素化を試み、パラジウム触媒と 2 位のヒドロキシメチル基の相互作用を利用すると *anti* 体の CF_2H-ピロリジンを、またパラジウム触媒と 2 位のシロキシメチル基の立体反発を用いると *syn* 体の CF_2H-ピロリジンを、それぞれ優先的に得ることができた。

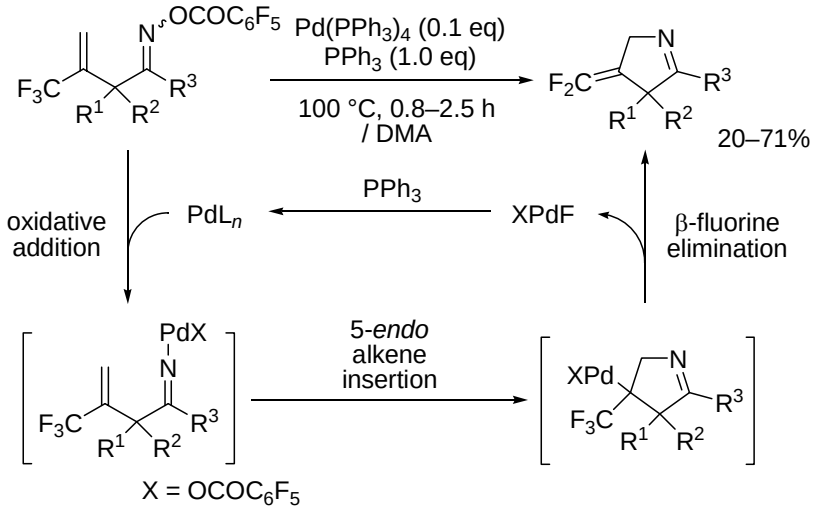


これらの含フッ素炭素置換基を有するピロリジン化合物の 2 位の 2,4-ジメトキシフェニル基あるいはヒドロキシメチル基を酸化してカルボキシ基とすることにより、CF_3 基、CF_2=基、CF_2H 基の各フ

ルオロ炭素置換基が 4 位へ導入された光学活性プロリン誘導体を合成することができた。4 位置換プロリンはペプチド化学や薬化学の分野で重要な位置を占め、中でも含フッ素炭素置換基を導入したプロリンが近年注目を集めている。本研究はこれまで報告された含フッ素炭素置換基を有するプロリン誘導体の合成とは異なり、ヒドロキシプロリン等の生体由来の原料に依存しない手法を提供する。



第三章では、(トリフルオロメチル)ビニル基を有するオキシム誘導体の 5-*endo* Heck 型反応に関して述べた。筆者は、フッ素含有原子団に特徴的な合成反応を開発する目的で、(トリフルオロメチル)ビニルリチウムとオキシランとの反応から誘導した 2-(トリフルオロメチル)アリル基を有する *O*-アシルオキシム誘導体の Heck 型環化反応を試みた。*O*-ペンタフルオロベンゾイルオキシムに対してパラジウム触媒を作用させると、環化反応が進行し、4-ジフルオロメチレン-1-ピロリンが得られた。環化後の C－Pd 結合を有する中間体から β-フッ素脱離が優先して起こり、ジフルオロメチレン基を有するピロリンが生成したことになる。環化様式は、C－Pd 結合へのアルケン挿入で一般に困難とされる 5-*endo* 型であるが、1-(トリフルオロメチル)ビニル基を用いることによってこの環化を達成することができた。さらに、β-フッ素脱離で生成した二価のパラジウムをトリフェニルホスフィンで還元することにより、本反応を触媒化することにも成功した。



以上のように筆者は、含フッ素 C-3 ビルディングブロックとして 1-(トリフルオロメチル)ビニルリチウムに着目し、種々の 1-(トリフルオロメチル)ビニル基を有する化合物を合成した。得られた(トリフルオロメチル)ビニル化合物から、光学活性プロリンをはじめ、各種含フッ素炭素置換基を有する環状化合物の選択的な合成法を確立した。また、 (トリフルオロメチル)ビニル基を用いる Heck 型の反応として、これまで極めて例の少ない 5-*endo* 形式での Heck 型環化反応を開発した。第二章のプロリン合成に用いた求核的 5-*endo*-*trig* 環化反応および第三章の 5-*endo* Heck 型反応はフッ素の特性を活用して初めて達成されたものである。

報文目録

(1) “1-(Trifluoromethyl)vinylation via Oxirane or Oxetane Ring-Opening: A Facile Synthesis of 4- or 5-Hydroxy-Functionalized 2-trifluoromethyl-1-alkenes”, Ryo Nadano, and Junji Ichikawa *Synthesis* 2006, 128–132.

(2) “5-*endo-trig* Cyclization of 1,1-Difluoro-1-alkenes: Synthesis of 3-Butyl-2-fluoro-1-tosylindole”, Junji Ichikawa, Ryo Nadano, Takashi Mori, and Yukinori Wada *Organic Syntheses* 2006, 111–120.

(3) “5-*endo* Heck-type cyclization of 2-(trifluoromethyl)allyl ketone oximes: synthesis of 4-difluoromethylene-substituted 1-pyrrolines”, Junji Ichikawa, Ryo Nadano and Naotaka Ito *Chemical Communications* 2006, 4425 – 4427.

(4) “Divergent Chemical Synthesis of Prolines Bearing Fluorinated One-Carbon Units at the 4-Position via Nucleophilic 5-*Endo-Trig* Cyclizations”, Ryo Nadano, Yu Iwai, Takashi Mori, and Junji Ichikawa *Journal of Organic Chemistry* 2006, 71, 8748 – 8754.

(5) “A Facile Synthesis of *N*-[2-(Trifluoromethyl)allyl]amides and their Transformation into Angularly Trifluoromethylated Bicyclic Cyclopentenones”, Ryo Nadano, and Junji Ichikawa *Chemistry Letters* 2007, 36, 22 – 23.

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(1)　第 28 回フッ素化学討論会　2004 年 11 月 4 日－5 日「4 位に含フッ素炭素置換基を有するプロリン類の合成」

(2)　第 29 回フッ素化学討論会　2005 年 11 月 1 日－2 日「1-(トリフルオロメチル)ビニルリチウムを用いる官能性 2-トリフルオロメチル-1-アルケンの合成」

(3)　第 86 回日本化学会春季年会　2006 年 3 月 27 日－30 日　「1-(トリフルオロメチル)ビニルリチウムを用いる官能性 2-トリフルオロメチル-1-アルケンの合成」

(4)　18th International Symposium on Fluorine Chemistry　2006 年 7 月 30 日－8 月 4 日「Heck-Type 5-*endo* Cyclizations Promoted by Fluorine Substituents」

(5)　第 30 回フッ素化学討論会　2006 年 11 月 9 日－10 日　「1-(トリフルオロメチル)ビニル基導入に基づく核間トリフルオロメチル基含有二環性シクロペンテノンの合成」

1-(Trifluoromethyl)vinylation via Oxirane or Oxetane Ring-Opening: A Facile Synthesis of 4- or 5-Hydroxy-Functionalized 2-Trifluoromethyl-1-alkenes

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Abstract: Introduction of a 1-(trifluoromethyl)vinyl group has been accomplished by the reaction of thermally unstable 1-(trifluoromethyl)vinyllithium (**1**) with strained cyclic ethers. Treatment of 2-bromo-3,3,3-trifluoropropene with butyllithium generates **1**, which in turn reacts with several oxiranes or an oxetane at –100 °C in the presence of $BF_3{\cdot}OEt_2$ to afford the corresponding 2-trifluoromethyl-1-alkenes bearing a hydroxy group on the 4- or 5-position. An enantiopure oxirane undergoes ring-opening without racemization, providing an optically active homoallylic alcohol with a 3-trifluoromethyl group.

Key words: (trifluoromethyl)vinyl group, ring-opening, oxirane, unsaturated alcohol, lithium–halogen exchange

The building block strategy has now become one of the most efficient approaches for the synthesis of fluorine-containing compounds.[1] In this respect, a 1-(trifluoromethyl)vinyl group is a versatile component due to (i) its double bond which is reactive toward nucleophiles and (ii) its allylic fluorine atoms which act as leaving groups.[2,3] Recently, we have established versatile and flexible synthetic routes to (i) 1,1-difluoro-1-alkenes via S_N2'-type reaction of a 1-(trifluoromethyl)vinylsilane[4] and (ii) fluorine-containing heterocycles via nucleophilic 6- and 5-*endo-trig* cyclizations starting from trifluoromethylvinyl compounds.[5] Due to the synthetic potential of the 1-(trifluoromethyl)vinyl system, extensive efforts have been made to exploit synthetic methods for 2-trifluoromethyl-1-alkenes.[2,6–10] Among them, 1-(trifluoromethyl)vinylmetal species are straightforward reagents to provide a variety of compounds bearing a (trifluoromethyl)vinyl moiety. 1-(Trifluoromethyl)vinyl compounds with a conjugated system can be prepared by palladium-catalyzed coupling reactions of 'relatively stable' (trifluoromethyl)vinylmetals, such as (trifluoromethylvinyl)zinc,[7] -tin,[8] and -boronic acid,[9] with appropriate unsaturated organohalides. In contrast, methods for the preparation of non-conjugated 1-(trifluoromethyl)vinyl compounds are still limited.[7c,d]

Tarrant reported that 1-(trifluoromethyl)vinyllithium (**1**), generated on treatment of 2-bromo-3,3,3-trifluoropropene (**2**) with butyllithium, reacted with aldehydes or ketones to afford 2-(trifluoromethyl)allyllic alcohols.[10] Whereas the lithium reagent was of high enough reactivity to allow the preparation of non-conjugated (trifluoromethyl)vinyl compounds, this approach had serious drawbacks: (i) bromide **2** had the potential to react with butyllithium in an S_N2' fashion; (ii) the generated lithium species **1** was highly unstable and readily underwent elimination of lithium fluoride even at –100 °C, leading to 1,1-difluoroallene, thus, the reaction required alternative addition of butyllithium and a carbonyl substrate to **2** in several aliquots,[10a] and (iii) the product alcohols were obtained only in 30–50% yields along with butyl carbinols derived from butyllithium, which suggested incomplete lithium–halogen exchange.

In view of alcohol synthesis, ring cleavage of strained cyclic ethers with nucleophiles is a versatile process. Organolithium species, such as alkyl-, alkenyl-, and alkynyllithiums, are known to effect ring-opening reactions of oxiranes and oxetanes in the presence of $BF_3{\cdot}OEt_2$.[11] In terms of this process, we discovered a curious fact that an oxirane was opened up by phenyllithium in preference to butyllithium, although normally sp^3-hybridized carbanions are more nucleophilic than sp^2-hybridized carbanions.[12] Taking account of this finding, we expected that oxiranes might react selectively with vinyllithium **1** in the lithium–halogen exchange reaction between bromide **2** and butyllithium. We report herein an efficient method for the synthesis of alcohols with a 1-(trifluoromethyl)vinyl moiety via the unstable vinyllithium **1**.

To confirm the generation of vinyllithium **1**, we re-examined the reaction of 2-bromo-3,3,3-trifluoropropene with butyllithium under different reaction conditions, and the ^{19}F NMR spectra of the reaction mixtures were measured after quenching with methanol (Scheme 1). When the reaction was carried out at –78 °C for 15 minutes, difluoroallene, generated by decomposition of **1** via elimination of lithium fluoride, and 3,3,3-trifluoropropene were obtained in 54% and 20% yields, respectively, while starting material **2** (17%) was recovered. Running the reaction at –96 °C for 15 minutes, we observed only 31% yield of 3,3,3-trifluoropropene and 11% yield of difluoroallene along with 58% of recovered **2**. These results indicated that (i) the conversion to vinyllithium **1** was not driven to completion at –78 °C and once formed was thermally unstable, and that (ii) the decomposition of **1** to difluoroallene proceeded even at –96 °C and a large amount of butyllithium remained at that temperature.

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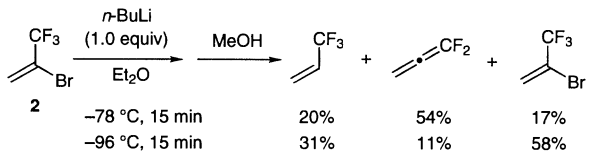
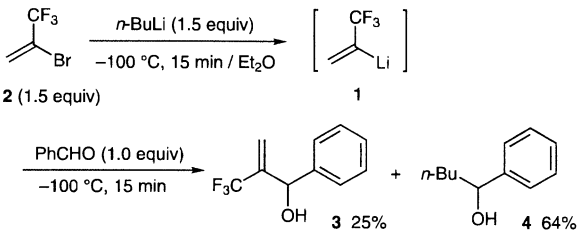


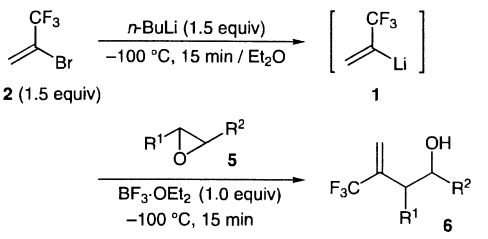
Scheme 1

Moreover, we conducted the reaction of these lithium species with an aldehyde to evaluate their composition. When a 1:1 mixture of **2** and butyllithium was kept at −100 °C for 15 minutes and then treated with benzaldehyde, alcohols **3** and **4**, the adducts of vinyllithium **1** and butyllithium, were obtained in 25% and 64% yields, respectively (Scheme 2). These data suggested that the poor yield of 1-(trifluoromethyl)vinyl carbinol was due to (i) the incomplete lithium–halogen exchange between bromide **2** and butyllithium and (ii) the thermal instability of vinyllithium **1**.



Scheme 2

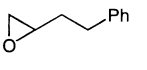
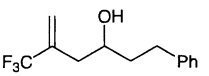
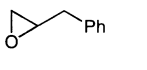
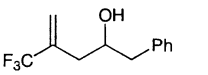
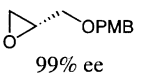
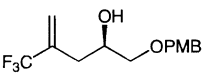
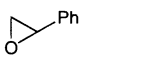
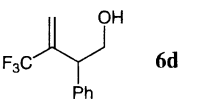
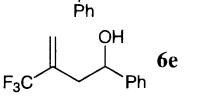
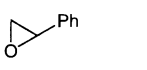
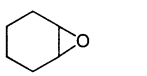
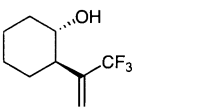
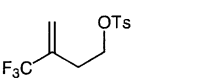
In the course of our study involving the reaction of cyclic ethers, we had encountered unusual reactivity: an oxirane underwent BF_3-promoted ring-opening preferentially with phenyllithium even in the presence of buthyllithium.[12] This fact prompted us to apply the process to selective trapping of the in-situ generated vinyllithium **1**, leading to homoallylic alcohols with a trifluoromethyl group. We examined the reaction of several oxiranes with **1** in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$ to obtain 3-(trifluoromethyl)homoallyllic alcohols **6** selectively as expected (Scheme 3).[13,14] The results are summarized in Table 1.



Scheme 3

The reaction was conducted following the procedure outlined here: butyllithium was added to a diethyl ether solution of bromide **2** and $BF_3{\cdot}OEt_2$ at −100 °C; after being stirred at −100 °C for 15 minutes, the mixture was treated with an oxirane in diethyl ether. Monoalkyl-substituted oxiranes readily underwent ring-opening with vinyllithium **1** to afford the corresponding homoallylic alcohols **6a–c** in high yield (Table 1, entries 1–3). An optically active glycidyl ether was transformed to partially protected diol **6c** in 99% ee, where no racemization was observed (Table 1, entry 3). Styrene oxide was subjected to nucleophilic attack on the more hindered carbon as well as the methylene carbon, which resulted in a mixture of regioisomers. Under the same reaction conditions as above, a mixture of 2-phenyl-3-butenol (**6d**) and 1-phenyl-3-butenol (**6e**) was obtained in 48% yield with a **6d/6e** ratio of 38:62. Screening the reaction conditions revealed that the isomer ratio ranged from 1:4 to 2:1 depending on alkyllithium and the addition order of the reagents. Addition of *tert*-butyllithium instead of butyllithium in the order: **2**, *tert*-butyllithium, $BF_3{\cdot}OEt_2$, and styrene oxide improved the ratio of **6d/6e** to 19:81 (Table 1, entry 4). When the reagents were added in the following order: **2**, $BF_3{\cdot}OEt_2$, styrene oxide, and butyllithium, **6d** was predominantly obtained in the ratio of 67:33 (Table 1, entry 5). The low yields starting from styrene oxide were probably due to its high reactivity, which gave rise to non-selective addition of butyllithium as well as **1**. A 2,3-disubstituted oxirane,

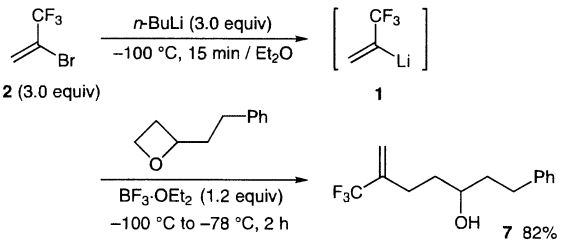
Table 1 Synthesis of 3-(Trifluoromethyl)homoallylic Alcohols **6**

Entry	Electrophile **5**	Product **6**	Yield (%)[a]
1			**6a** (91)
2			**6b** (89)
3[b]	 99% ee		**6c** (81) 99% ee
4[c]		 **6d**  **6e**	**6d+6e** (31) [19:81][d]
5[e]			**6d+6e** (49) [67:33][d]
6			**6f** (40) (49)[f]
7			**6g** (34)

[a] Isolated yield.
[b] PMB: *p*-methoxybenzyl.
[c] *t*-BuLi was used instead of *n*-BuLi (see text).
[d] Determined by ^1H NMR spectroscopy.
[e] *n*-BuLi was added after the addition of **5** (see text).
[f] Yield deduced from ^{19}F NMR spectrum relative to internal standard $(CF_3)_2CTol_2$.

cyclohexene oxide provided the corresponding cyclohexanol **6f** in modest yield (Table 1, entry 6), whereas 2,2-disubstituted oxirane, 2,2-dibenzyloxirane gave no ring-opening products. Due to its volatility, the product derived from ethylene oxide was isolated as the corresponding tosylate **6g** by subsequent treatment of the reaction mixture with tosyl chloride and pyridine (Table 1, entry 7).

To expand the scope of this method, we tried another strained cyclic ether, an oxetane in the reaction with vinyllithium **1**. The reaction with 2-phenethyloxetane gave 1-phenyl-6-(trifluormethyl)hept-6-en-3-ol (**7**) in 30% yield along with recovered starting oxetane under the same reaction conditions as above. A longer reaction time and three equivalents of the lithium species improved the yield of **7** up to 82% (Scheme 4).



Scheme 4

We have succeeded in efficiently trapping highly unstable 1-(trifluoromethyl)vinyllithium (**1**), generated in situ via lithium–halogen exchange of 2-bromo-3,3,3-trifluoropropene (**2**), in the vinyl-selective ring-opening of strained cyclic ethers. Vinyllithium **1** reacted with oxiranes and an oxetane in the presence of $BF_3{\cdot}OEt_2$ to afford 4- and 5-hydroxy functionalized 2-trifluoromethyl-1-alkenes **6** and **7**, respectively. Since oxiranes and oxetanes are readily available, this method provides an easy access to a wide range of alkyl alcohols bearing a 1-(trifluoromethyl)vinyl unit.

^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz), and ^{19}F NMR (470 MHz) spectra were recorded in $CDCl_3$ on a Bruker Avance-500 spectrometer. ^{1}H NMR chemical shifts are given in ppm downfield from TMS. ^{13}C NMR chemical shifts are given in ppm downfield from TMS, relative to $CDCl_3$ (δ = 77.0). ^{19}F NMR chemical shifts are given in ppm downfield from C_6F_6. IR spectra were recorded on a Horiba FT-300S spectrometer. Elemental analyses were performed with a YANAKO MT-6 CHN Corder apparatus. Mass spectra were taken with a JEOL MS-700M spectrometer.

All reactions were carried out under argon. Et_2O was purchased in an anhydrous form from Kanto Chemical Co., Inc. and stored over 4 Å molecular sieves. Column chromatography and preparative thin-layer chromatography were performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 and Wako Pure Chemical Industries, Ltd., B5-F), respectively.

The ee of **2d** was determined by HPLC using an AD-H Daicel column (*i*-PrOH–hexane, 1:50).

Ethylene oxide, styrene oxide, and cyclohexene oxide were commercially available. 2-Benzyloxirane,[15] 2-phenethyloxirane,[16] (*S*)-*p*-methoxybenzyl glycidyl ether,[17] and 2-phenethyloxetane[18] were prepared according to the literature.

Oxirane Ring-Opening with 1-(Trifluoromethyl)vinyllithium; General Procedure

To a soln of 2-bromo-3,3,3-trifluoropropene (0.47 mL, 4.5 mmol) and $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) in Et_2O (15 mL) was added dropwise a soln of *n*-BuLi (2.67 M in hexane; 1.69 mL, 4.5 mmol) in Et_2O (2 mL) at −100 °C. After the mixture was stirred for 15 min, a soln of an oxirane (3.0 mmol) in Et_2O (2 mL) was added dropwise. The mixture was stirred for 15 min, and then allowed to warm to r.t. The reaction mixture was quenched with phosphate buffer (pH 7, 30 mL) and organic materials were extracted with EtOAc (2 × 15 mL). The combined extracts were washed with H_2O (2 × 10 mL), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give a 3-(trifluoromethyl)homoallylic alcohol.

1-Phenyl-5-(trifluoromethyl)hex-5-en-3-ol (6a)

Colorless liquid; yield: 91%.

IR (neat): 3384, 3027, 2929, 1604, 1496, 1454, 1344, 1165, 1117, 947, 748 cm^{-1}.

^{1}H NMR: δ = 1.70 (1 H, d, J = 4.2 Hz), 1.76–1.88 (2 H, m), 2.32 (1 H, ddd, J = 15.0, 8.4, 0.9 Hz), 2.44 (1 H, ddd, J = 15.0, 4.2, 0.9 Hz), 2.70 (1 H, ddd, J = 13.8, 9.6, 6.7 Hz), 2.83 (1 H, ddd, J = 13.8, 9.8, 5.8 Hz), 3.85 (1 H, ddddd, J = 8.4, 8.4, 4.2, 4.2, 4.2 Hz), 5.46 (1 H, q, J_{HF} = 1.2 Hz), 5.79 (1 H, q, J_{HF} = 1.5 Hz), 7.18–7.21 (3 H, m), 7.27–7.31 (2 H, m).

^{13}C NMR: δ = 32.0, 38.2, 38.8, 68.7, 121.0 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 126.0, 128.4, 128.5, 135.0 (q, J_{CF} = 30 Hz), 141.6.

^{19}F NMR: δ = 93.5 (br s).

Anal. Calcd for $C_{13}H_{15}F_3O$: C, 63.93; H, 6.19. Found: C, 64.19; H, 6.40.

1-Phenyl-4-(trifluoromethyl)pent-4-en-2-ol (6b)

Colorless liquid; yield: 89%.

IR (neat): 3426, 3030, 2924, 1496, 1455, 1418, 1164, 1111, 1080, 946 cm^{-1}.

^{1}H NMR: δ = 1.71 (1 H, d, J = 4.3 Hz), 2.34 (1 H, ddd, J = 15.1, 8.6, 0.8 Hz), 2.43 (1 H, ddd, J = 15.1, 4.3, 0.8 Hz), 2.66 (1 H, dd, J = 13.6, 8.6 Hz), 2.83 (1 H, dd, J = 13.6, 4.3 Hz), 4.00 (1 H, ddddd, J = 8.6, 8.6, 4.3, 4.3, 4.3 Hz), 5.52 (1 H, q, J_{HF} = 1.3 Hz), 5.81 (1 H, q, J_{HF} = 1.4 Hz), 7.20 (2 H, d, J = 7.3 Hz), 7.22 (1 H, t, J = 7.3 Hz), 7.30 (2 H, dd, J = 7.3, 7.3 Hz).

^{13}C NMR: δ = 37.3, 43.6, 70.0, 120.8 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 126.7, 128.6, 129.4, 135.0 (q, J_{CF} = 30 Hz), 137.8.

^{19}F NMR: δ = 93.6 (br s).

Anal. Calcd for $C_{12}H_{13}F_3O$: C, 62.60; H, 5.69. Found: C, 62.52; H, 5.86.

(*R*)-1-(4-Methoxybenzyloxy)-4-(trifluoromethyl)pent-4-en-2-ol (6c)

Colorless liquid; yield: 81%.

IR (neat): 3446, 2908, 2864, 1612, 1513, 1246, 1165, 1109, 1034, 947, 820 cm^{-1}.

^{1}H NMR: δ = 2.32–2.34 (2 H, m), 2.56 (1 H, br s), 3.35 (1 H, dd, J = 9.5, 6.8 Hz), 3.50 (1 H, dd, J = 9.5, 3.3 Hz), 3.80 (3 H, s), 3.97–4.02 (1 H, m), 4.46 (1 H, d, J = 11.5 Hz), 4.49 (1 H, d, J = 11.5 Hz), 5.49 (1 H, q, J_{HF} = 1.2 Hz), 5.77 (1 H, q, J_{HF} = 1.3 Hz), 6.89 (2 H, d, J = 8.7 Hz), 7.25 (2 H, d, J = 8.7 Hz).

^{13}C NMR: δ = 33.6, 55.2, 68.1, 73.0, 73.2, 113.8, 120.6 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 274 Hz), 129.4, 129.7, 134.5 (q, J_{CF} = 30 Hz), 159.3.

^{19}F NMR: δ = 93.2 (br s).

Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.93; H, 5.90. Found: C, 57.91; H, 5.95.

***trans*-2-[1-(Trifluoromethyl)vinyl]cyclohexanol (6f)**
Colorless liquid; yield: 40%.

IR (neat): 3404, 2933, 2860, 1450, 1346, 1296, 1163, 1113, 1063, 937 cm^{-1}.

^1H NMR: δ = 1.22–1.34 (4 H, m), 1.69–1.72 (1 H, m), 1.78–1.82 (1 H, m), 1.92–1.94 (1 H, m), 2.02 (1 H, br s), 2.07–2.10 (1 H, m), 2.11–2.16 (1 H, m), 3.58 (1 H, ddd, J = 10.2, 10.2, 4.3 Hz), 5.49 (1 H, s), 5.85 (1 H, q, J_{HF} = 1.3 Hz).

^{13}C NMR: δ = 24.7, 25.7, 33.0, 34.9, 47.1, 72.6, 118.5 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 274 Hz), 140.8 (q, J_{CF} = 29 Hz).

^{19}F NMR: δ = 94.0 (br s).

HRMS (FAB): *m/z* calcd for $C_9H_{14}F_3O$ [M + H]$^+$: 195.0997; found: 195.0977.

2-Phenyl-3-(trifluoromethyl)but-3-en-1-ol (6d)
To a soln of 2-bromo-3,3,3-trifluoropropene (1.24 mL, 12 mmol) and styrene oxide (0.91 mL, 8.0 mmol) in Et_2O (40 mL) were added dropwise $BF_3{\cdot}OEt_2$ (1.52 mL, 12 mmol) and then a soln of *n*-BuLi (2.71 M in hexane; 4.43 mL, 12 mmol) in Et_2O (4 mL) at –100 °C. The reaction mixture was stirred for 15 min and then allowed to warm to r.t. The reaction was quenched with phosphate buffer (pH 7, 40 mL) and organic materials were extracted with EtOAc (3 × 30 mL). The combined extracts were washed with H_2O (30 mL), brine (30 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **6d** (564 mg, 33%) as a colorless liquid.

IR (neat): 3377, 3031, 2933, 2887, 1495, 1454, 1414, 1309, 1167, 1117, 1059, 949 cm^{-1}.

^1H NMR: δ = 1.57 (1 H, br s), 3.78 (1 H, dd, J = 6.8, 6.8 Hz), 3.93–4.01 (2 H, m), 5.85 (1 H, q, J_{HF} = 1.1 Hz), 5.96 (1 H, q, J_{HF} = 1.4 Hz), 7.26–7.30 (3 H, m), 7.34–7.37 (2 H, m).

^{13}C NMR: δ = 47.4, 65.0, 119.7 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 275 Hz), 127.5, 128.1, 128.8, 138.2, 138.6 (q, J_{CF} = 28 Hz).

^{19}F NMR: δ = 94.2 (br s).

HRMS (FAB): *m/z* calcd for $C_{11}H_{12}F_3O$ [M + H]$^+$: 217.0840; found: 217.0857.

1-Phenyl-3-(trifluoromethyl)but-3-en-1-ol (6e)
To a soln of 2-bromo-3,3,3-trifluoropropene (0.51 mL, 4.9 mmol) in Et_2O (15 mL) was added dropwise *t*-BuLi (1.47 M in pentane; 3.1 mL, 4.5 mmol) at –100 °C. After the reaction mixture was stirred for 30 min, a soln of $BF_3{\cdot}OEt_2$ (0.57 mL, 4.5 mmol) in Et_2O (3 mL) was added. After stirring for 5 min, a soln of styrene oxide (360 mg, 3.0 mmol) in Et_2O (3 mL) was added. The reaction mixture was stirred for 15 min and then allowed to warm to r.t. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and organic materials were extracted with EtOAc (3 × 20 mL). The combined extracts were washed with H_2O (20 mL), brine (20 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 10:1) to give **6e** (166 mg, 26%) as a colorless liquid.

IR (neat): 3388, 3064, 3033, 2927, 1346, 1165, 1111, 1045, 947, 756, 698 cm^{-1}.

^1H NMR: δ = 2.26 (1 H, br s), 2.55 (1 H, dd, J = 15.1, 4.9 Hz), 2.62 (1 H, ddd, J = 15.1, 8.7, 1.0 Hz), 4.84 (1 H, m), 5.38 (1 H, q, J_{HF} = 1.2 Hz), 5.74 (1 H, q, J_{HF} = 1.4 Hz), 7.27–7.34 (5 H, m).

^{13}C NMR: δ = 39.6, 71.9, 121.3 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 125.8, 127.9, 128.5, 134.6 (q, J_{CF} = 30 Hz), 143.2.

^{19}F NMR: δ = 93.6 (br s).

HRMS (FAB): *m/z* calcd for $C_{11}H_{11}F_3ONa$ [M + Na]$^+$: 239.0660; found: 239.0654.

3-(Trifluoromethyl)but-3-enyl 4-Methylbenzenesulfonate (6g)
After the ring-opening reaction of ethylene oxide (5 mmol) with 1-(trifluoromethyl)vinyllithium, solvents were partially evaporated to ca. 25% of the original volume. Pyridine (5 mL) and TsCl (0.95 g, 5.0 mmol) were added to the residue. After the mixture was stirred at r.t. overnight, the reaction was quenched with aq HCl (1 M; 30 mL). Organic materials were extracted with EtOAc (3 × 20 mL). The combined extracts were washed with H_2O (10 mL), brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **6g** (498 mg, 34%) as a colorless liquid.

IR (neat): 2970, 2929, 1599, 1358, 1171, 1117, 978, 908 cm^{-1}.

^1H NMR: δ = 2.45 (3 H, s), 2.57 (2 H, t, J = 6.6 Hz), 4.17 (2 H, t, J = 6.6 Hz), 5.42 (1 H, q, J_{HF} = 1.3 Hz), 5.76 (1 H, br s), 7.36 (2 H, d, J = 8.4 Hz), 7.78 (2 H, d, J = 8.4 Hz).

^{13}C NMR: δ = 21.5, 29.1, 67.1, 121.1 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 274 Hz), 127.8, 129.9, 132.6, 133.0 (q, J_{CF} = 30 Hz), 145.1.

^{19}F NMR: δ = 93.1 (br s).

Anal. Calcd for $C_{12}H_{13}F_3O_3S$: C, 48.97; H, 4.45. Found: C, 49.17; H, 4.68.

1-Phenyl-6-(trifluoromethyl)hept-6-en-3-ol (7)
To a soln of 2-bromo-3,3,3-trifluoropropene (0.31 mL, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) in Et_2O (5 mL) was added dropwise a soln of *n*-BuLi (2.67 M in hexane; 1.1 mL, 3.0 mmol) in Et_2O (2 mL) at –100 °C. After the mixture was stirred for 15 min, a soln of 2-phenethyloxetane (158 mg, 0.97 mmol) in Et_2O (2 mL) was added dropwise. The mixture was stirred for 15 min and warmed to –78 °C over 2 h. After the mixture was allowed to warm to r.t., the reaction was quenched with phosphate buffer (pH 7, 15 mL). Organic materials were extracted with EtOAc (3 × 15 mL). The combined extracts were washed with H_2O (15 mL), brine (15 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give **7** (206 mg, 82%) as a colorless liquid.

IR (neat): 3354, 3028, 2927, 2862, 1496, 1454, 1323, 1165, 1113, 939 cm^{-1}.

^1H NMR: δ = 1.48 (1 H, br s), 1.61–1.83 (4 H, m), 2.25 (1 H, ddd, J = 15.7, 10.5, 5.9 Hz), 2.41 (1 H, ddd, J = 15.7, 10.7, 5.0 Hz), 2.69 (1 H, ddd, J = 13.7, 9.3, 6.9 Hz), 2.80 (1 H, ddd, J = 13.7, 9.4, 6.1 Hz), 3.66 (1 H, dddd, J = 8.2, 8.2, 4.1, 4.1 Hz), 5.31 (1 H, q, J_{HF} = 1.4 Hz), 5.66 (1 H, q, J_{HF} = 1.3 Hz), 7.18–7.21 (3 H, m), 7.26–7.31 (2 H, m).

^{13}C NMR: δ = 25.7, 32.0, 35.2, 39.1, 70.5, 117.7 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 274 Hz), 125.9, 128.4, 128.5, 138.2 (q, J_{CF} = 29 Hz), 141.7.

^{19}F NMR: δ = 93.3 (br s).

Anal. Calcd for $C_{14}H_{17}F_3O$: C, 65.10; H, 6.63. Found: C, 65.08; H, 6.86.

Acknowledgment

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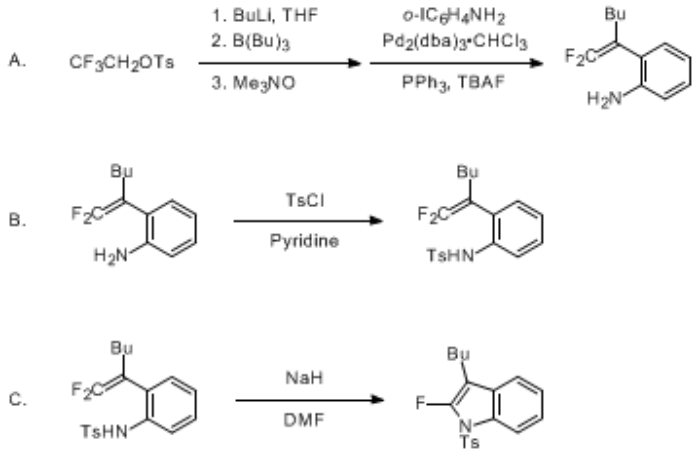
5-*endo-trig* CYCLIZATION OF 1,1-DIFLUORO-1-ALKENES: SYNTHESIS OF 3-BUTYL-2-FLUORO-1-TOSYLINDOLE

[1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-]



Submitted by Junji Ichikawa, Ryo Nadano, Takashi Mori, and Yukinori Wada[1].
Checked by Sigrid Holle and Alois Fürstner.

1. Procedure

A. *o-(1,1-Difluorohex-1-en-2-yl)aniline*. A 1-L, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirbar, two pressure-equalizing dropping funnels, and a reflux condenser fitted with an argon stopcock inlet. The system is flame-dried and flushed with argon. The flask is charged with anhydrous tetrahydrofuran (200 mL) (Note 1) and 2,2,2-trifluoroethyl *p*-toluenesulfonate (15.3 g, 60 mmol) (Note 2), and the solution is cooled to −78 °C in a dry ice–acetone bath. Butyllithium (76.8 mL, 1.64 M in hexane, 126 mmol) (Note 3) is added via one of the dropping funnels over 10 min (Note 4) and the resulting mixture is stirred for an additional 20 min. Then tributylborane (66.0 mL, 1.0 M in THF, 66 mmol) (Note 5) is added via the other dropping funnel at −78 °C over 3 min. After being stirred for 1 h, the reaction mixture is warmed to room temperature and stirred for an additional 3 h to generate 2,2-difluorovinylborane. This solution of 2,2-difluorovinylborane is cooled in an ice bath prior to addition of trimethylamine oxide (10.9 g, 145 mmol) (Note 6). The reaction mixture is stirred at 0 °C for 2 h, and then allowed to warm to room temperature. Triphenylphosphine (PPh_3, 2.52 g, 9.60 mmol) (Note 7) and tris(dibenzylideneacetone)dipalladium-chloroform (1/1) ($Pd_2(dba)_3{\cdot}CHCl_3$, 2.48 g, 2.40 mmol) (Note 8) are added in this order, and the mixture is stirred for 15 min. To the mixture are added *o*-iodoaniline (9.20 g, 42.0 mmol) (Note 9) and tetrabutylammonium fluoride (168 mL, 1.0 M in tetrahydrofuran, 168 mmol) (Note 10). After being stirred at room temperature for 15 min, the resulting mixture is heated in a 60 °C oil bath for 13 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 12). Then the reaction mixture is cooled to ambient temperature, and phosphate buffer (200 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (AcOEt, 3 × 200 mL), the combined extracts are washed successively with water (3 × 200 mL) and brine (200 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the palladium catalyst and ammonium salt are removed by short column chromatography on silica gel (Note 15). The eluent is concentrated under reduced pressure (Note 14) to give the crude product as a brown oil. This oil is distilled twice under reduced pressure (74–77 °C/1.2–1.4 mmHg) to give *o*-(1,1-difluorohex-1-en-2-yl)aniline (5.63 g, 63%) (Note 16) as a pale yellow liquid that was pure enough (90–95%) for use in the next step.

B. *o'-(1,1-Difluorohex-1-en-2-yl)-p-toluenesulfonanilide*. A 100-mL, two-necked, round-bottomed flask containing *o*-(1,1-difluorohex-1-en-2-yl)aniline (4.94 g, 23.4 mmol) is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a stopcock inlet connected to the argon line. Pyridine (50 mL) (Note 17) is introduced and the solution is cooled to 0 °C. *p*-Toluenesulfonyl chloride (TsCl, 6.69 g, 35.1 mmol) (Note 18) is added, and the mixture is stirred at room temperature for 15 h. Water (5 mL) is added and the reaction mixture is stirred for 0.5

h. Water (50 mL) and ether (100 mL) are added to the mixture before 2 M aqueous HCl solution (400 mL) is introduced. Organic materials are extracted with ether (4 × 100 mL). The combined organic extracts are washed successively with water (100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through filter paper and removal of the solvent under reduced pressure (Note 14), a brown liquid (8.77 g) (Note 19) is obtained. This is used in the next step without further purification.

C. *3-Butyl-2-fluoro-1-tosylindole*. A 300-mL, two-necked, round-bottomed flask is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a reflux condenser connected to the argon line. The system is flame-dried and flushed with argon. The flask is charged with anhydrous *N,N*-dimethylformamide (50 mL) (Note 1) and crude *o*'-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide (8.77 g) (Note 19). Sodium hydride (0.65 g, 27 mmol) (Note 20) is added in portions to the solution at 0 °C. After the reaction mixture is stirred at 0 °C for 30 min, the flask is placed in an 80 °C oil bath. The mixture is stirred at this temperature for 7 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 21). The reaction mixture is cooled to ambient temperature, and phosphate buffer (100 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (3 × 150 mL), and the combined extracts are washed with water (4 × 100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the resulting brown residue is purified by column chromatography on silica gel (Note 22). The eluent containing the product is concentrated under reduced pressure (Note 14) to provide pure 3-butyl-2-fluoro-1-tosylindole as a yellow liquid (6.43 g, 80% over two steps) (Note 23).

2. Notes

1. Anhydrous tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) (organic synthesis grade) were purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers used anhydrous THF dried by distillation over Mg-anthracene, and DMF (Fluka) that was dried by storing over molecular sieves (3 Å) and subsequent distillation under reduced pressure.

2. Trifluoroethyl *p*-toluenesulfonate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased this compound from Lancaster.

3. Butyllithium (ca. 1.6 M solution in hexane, organic synthesis grade) was purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers purchased BuLi (1.64 M in hexanes) from Fischer Science.

4. The submitters introduced the butyllithium via syringe, adding the solution along the wall of the reaction flask that was cooled by a dry ice–acetone bath.

5. Tributylborane (1.0 M solution in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc. and used as supplied.

6. Anhydrous trimethylamine oxide was prepared by sublimation of trimethylamine oxide dihydrate under reduced pressure (150 °C, 2.0 mmHg). Trimethylamine oxide dihydrate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. The checkers used anhydrous trimethylamine oxide purchased from Aldrich.

7. Triphenylphosphine (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and recrystallized from methanol prior to use. The checkers used triphenylphosphine (Aldrich) recrystallized from acetone prior to use.

8. The palladium catalyst was prepared from palladium(II) diacetate and dibenzylideneacetone according to the literature method.[2]

9. *o*-Iodoaniline (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers used the commercial sample purchased from Acros as received.

10. Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased the solution of this reagent from Aldrich.

11. Silica gel TLC plates ($60F_{254}$) were purchased from Merck Ltd. Japan, and visualized with 3% aqueous $KMnO_4$.

12. The R_f value of iodoaniline was 0.30 (ethyl acetate:hexane (1:5)); the product possessed an $R_f = 0.42$ in this solvent system. The submitters reported that the reaction was complete after only 6 h.

13. Phosphate buffer (pH 7, 1 L) was prepared by dissolving KH_2PO_4 9.1 g and $Na_2HPO_4.12H_2O$ (47.7 g) in distilled water.

14. Rotary evaporation was conducted at 100 mmHg in a 40 °C water bath.

15. Short column chromatography was performed by using a 3.5-cm × 40-cm column packed with 250 mL of silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with 500 mL of

ethyl acetate:hexane (1:5). The checkers used silica gel purchased from E. Merck, Darmstadt (230–400 mesh).

16. *o*-(1,1-Difluorohex-1-en-2-yl)aniline has the following physical properties: R_f = 0.42 (ethyl acetate:hexane (1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84–0.89 (m, 3 H), 1.30–1.35 (m, 4 H), 2.24–2.32 (m, 2 H), 3.59 (br. s, 2 H), 6.70–6.77 (m, 2 H), 6.99 (dd, 1 H, *J* = 1.6, 7.6 Hz), 7.11 (ddd, 1 H, *J* = 1.6, 7.5, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 22.3, 27.7, 29.8 (dd, *J* = 2, 3 Hz), 89.0 (dd, *J* = 17, 22 Hz), 115.6, 118.4, 119.1 (dd, *J* = 1, 4 Hz), 128.9, 130.4 (dd, *J* = 2, 3 Hz), 144.2 (dd, *J* = 1, 3 Hz), 152.8 (dd, *J* = 287, 288 Hz); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ: −89.2 (d, 1 F, *J* = 43 Hz), −93.2 (d, 1 F, *J* = 43 Hz); IR (KAP) 3475, 3385, 2958, 2930, 2862, 1737, 1617, 1496, 1232 cm^{-1}; MS (70 eV) *m/z* (rel intensity) 211 (M^+; 80), 168 (98), 148 (100); Anal. Calcd for $C_{12}H_{15}NF_2$: C, 68.23; H, 7.16; N, 6.63. Found: C, 66.95; H, 7.86; N, 5.78.

17. Pyridine (JIS special grade) was purchased from Kokusan Chemical Works, Ltd. and used as supplied. The checkers used pyridine (E. Merck, Darmstadt) distilled over KOH prior to use.

18. *p*-Toluenesulfonyl chloride (Extra Pure grade) was purchased from Kanto Chemical Co., Inc. and recrystallized from toluene prior to use. The checkers used tosyl chloride as received from Aldrich.

19. An analytically pure sample of the toluenesulfonanilide can be isolated by column chromatography on silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:5) and the eluent was concentrated with a rotary evaporator (Note 14) to give *o*'-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide as a white powder. The product exhibits the following physical properties: R_f = 0.31 (ethyl acetate:hexane (1:5)) (Note 11); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.79 (t, 3 H, *J* = 7.1 Hz), 1.05–1.23 (m, 4 H), 1.98 (br. s, 2 H), 2.35 (s, 3 H), 6.52 (s, 1 H), 6.98–7.06 (m, 2 H), 7.19–7.27 (m, 3 H), 7.60 (d, 1 H, *J* = 7.9 Hz), 7.68 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 21.5, 22.2, 28.0, 29.4, 88.0 (dd, *J* = 16, 23 Hz), 119.7, 124.1 (d, *J* = 4 Hz), 124.3, 127.2, 129.1, 129.7, 130.6, 135.0, 136.4, 144.1, 153.0 (dd, *J* = 288, 291 Hz); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ: −86.9 (d, 1 F, *J* = 39 Hz), −90.3 (d, 1 F, *J* = 41 Hz); IR (KAP) 3274, 2958, 1742, 1494, 1401, 1339, 1247, 1167, 1092, 920, 666 cm^{-1}; MS (70 eV) *m/z* (rel intensity) 365 (M^+; 0.5), 210 (100), 148 (62); HRMS calcd for $C_{19}H_{21}NO_2F_2SNa$ 388.11533 (M^+ + Na); found 388.11525.

20. The checkers used pure NaH by removing the mineral oil from the commercial sample (Aldrich) with pentane (three washings). The submitters used sodium hydride (NaH) in mineral oil (1.06 g, 60% dispersion in mineral oil, 27 mmol, organic synthesis grade) purchased from Kanto Chemical Co., Inc. without further purification.

21. The product possessed an R_f = 0.39 (ethyl acetate:hexane (1:5)).

22. Column chromatography was performed by using a 3-cm × 50-cm column packed with 300 mL of silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:10). After collection of 200 mL of eluent, 50 mL-fractions were collected. The $KMnO_4$-active product was eluted in the fractions 6–11 (Note 11). The checkers used silica purchased from E. Merck, Darmstadt (230–400 mesh).

23. 3-Butyl-2-fluoro-1-tosylindole exhibits the following physical properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (t, 3 H, *J* = 7.3 Hz), 1.16–1.25 (m, 2 H), 1.48–1.56 (m, 2 H), 2.33 (s, 3 H), 2.51 (dt, 2 H, *J* = 0.8, 7.4 Hz), 7.19 (d, 2 H, *J* = 8.0 Hz), 7.23 (ddd, 1 H, *J* = 1.1, 7.6, 7.6 Hz), 7.25–7.29 (m, 1 H), 7.33 (d, 1 H, *J* = 7.1 Hz), 7.71 (d, 2 H, *J* = 8.3 Hz), 8.07 (d, 1 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 21.3 (d, *J* = 2 Hz), 21.6, 22.1, 30.5 (d, *J* = 2 Hz), 99.7 (d, *J* = 11 Hz), 114.4, 118.9 (d, *J* = 7 Hz), 123.9, 124.0 (d, *J* = 4 Hz), 126.8, 128.1 (d, *J* = 6 Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, *J* = 277 Hz); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ: −132.8; IR (KAP) 2957, 2931, 2861, 1659, 1453, 1393, 1190, 1179, 746, 689, 663 cm^{-1}; MS (70 eV) *m/z* (rel intensity) 345 (M^+; 91), 190 (100), 148 (71); HRMS calcd for $C_{19}H_{20}NO_2FSNa$ 368.10910 (M^+ + Na); found 368.10906; Anal. Calcd for $C_{19}H_{20}NO_2FS$: C, 66.06; H, 5.84; N, 4.05. Found: C, 65.97; H, 5.90; N, 4.10.

Waste Disposal Information

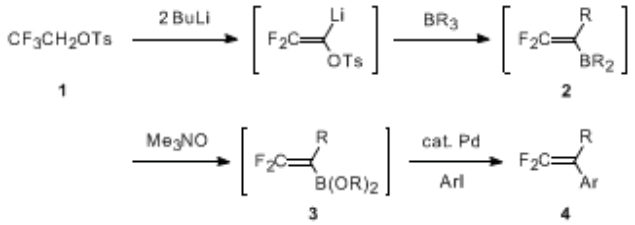
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Synthetic methods for the preparation of 2-fluoroindoles have been limited to difluorination of indole derivatives followed by elimination[3a,b] and electrophilic fluorination of stannylindoles.[3c] The procedures described herein illustrate an efficient construction of 2-fluoroindoles via intramolecular substitution of the vinylic fluorine in

β,β-difluorostyrenes bearing an *ortho*-amido substituent.[4] This reaction can be classified as a 5-*endo*-*trig* ring closure, a disfavored process according to Baldwin's rules.[5-8] While having only rarely been observed in synthetic chemistry,[6] the nucleophilic 5-*endo*-*trig* cyclization was successfully achieved by taking advantage of the unique properties of fluorine: (i) the highly polarized difluorovinylidene double bond (^{13}C NMR: ca. 150 ppm and 90 ppm for CF_2=C) aids initial ring formation by electrostatic attraction between the CF_2 carbon and the internal nucleophile, and (ii) the successive elimination of the fluoride ion suppresses the reverse ring opening, thus functioning as a "lock".[4]

Difluorostyrene derivatives **4** including *o*-(2,2-difluorovinyl)anilines are easily prepared by using a one-pot sequence as outlined below.[9a,c] The sequence comprises the following two processes starting from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**): (i) a boron-mediated alkylation via 1,2-migration, leading to 2,2-difluorovinylboranes **2** and (ii) subsequent palladium-catalyzed coupling reaction with aryl iodides via 2,2-difluorovinylboronates **3**, which affords difluorostyrenes **4** in good yield. The substituent R at the vinylic position of **4** is derived from a trialkylborane (BR_3), which is readily generated by hydroboration of the corresponding alkene. The selective oxidation of boron–alkyl bonds with trimethylamine oxide prevents the coupling reaction of B-alkyl groups in **2**.

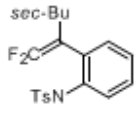
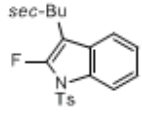
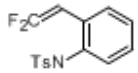
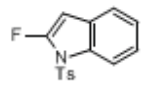
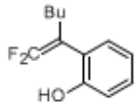
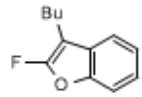
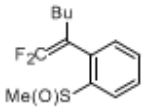
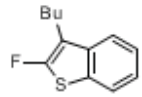
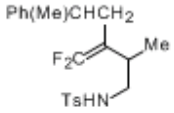
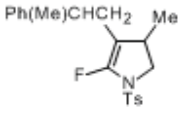
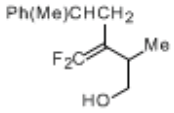
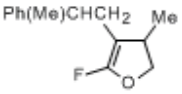
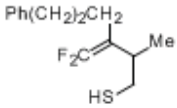
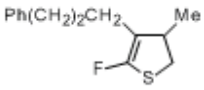


Another vinyl-selective coupling reaction of **2** with aryl iodides is accomplished via the transmetalation to 2,2-difluorovinylcopper species by adding cuprous iodide.[4a,9b,c] β,β-Difluorostyrenes **4** (R = H) without a vinylic substituent can also be prepared via 2,2-difluorovinylzirconocene from **1**.[10]

After tosylation of *o*-(2,2-difluorovinyl)anilines, treatment of the obtained sulfonanilides with 1.1 equiv of NaH in DMF promotes the normally "disfavored" 5-*endo*-*trig* cyclization to afford the corresponding 2-fluoroindoles in high yield. High-dilution conditions are not required in this ring closure.

This methodology for constructing five-membered rings is widely applicable to the cyclization of (i) β,β-difluorostyrene derivatives and (ii) 1,1-difluoro-1-butene derivatives bearing a nucleophilic nitrogen, oxygen, or sulfur atom at the *ortho* or the homoallylic position, respectively. Under similar conditions, these substrates undergo cyclization to afford ring-fluorinated heterocycles such as pyrrolines, furans, and thiophenes in high yield as shown in the Table. Five-membered carbocycles bearing a fluorine on the ring can also be obtained by this method.[4a,11] Moreover, six-membered ring-fluorinated heterocyclic and carbocyclic compounds can be provided in line with the "intramolecular substitution" concept.[11b,12]

Table. Nucleophilic 5-*endo*-*trig*-Cyclization of 1,1-Difluoro-1-alkenes

Substrate	Product	Conditions[a]	Yield
		80 °C, 5 h	81%
		70 °C, 23 h	73%
		60 °C, 2 h	80%
		reflux, 3 h[b]	82%
		90 °C, 4 d	80%
		90 °C, 7 h	67%
		90 °C, 4 h	76%

a. NaH (1.1–1.2 equiv), DMF. b. (i) $(CF_3CO)_2O$ (3 equiv), NEt_3(3 equiv), CH_2Cl_2, 0 °C, 0.5 h. (ii) K_2CO_3 (6 equiv), MeOH, 0 °C–rt, 1 h then reflux.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

o-(1,1-Difluorohex-1-en-2-yl)aniline:
Benzenamine, 2-[1-(difluoromethylene)pentyl]-; (134810-59-6)

o'-(1,1-Difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide:
Benzenesulfonamide, *N*-[2-[1-(difluoromethylene)pentyl]phenyl]-4-methyl-; (195734-33-9)

3-Butyl-2-fluoro-1-tosylindole:
1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-; (195734-36-2)

2,2,2-Trifluoroethyl *p*-toluenesulfonate:
Ethanol, 2,2,2-trifluoro-, 4-methylbenzenesulfonate; (433-06-7)

Trimethylamine oxide:
Methanamine, *N,N*-dimethyl-, *N*-oxide; (1184-78-7)

Tetrabutylammonium fluoride:
1-Butanaminium, *N,N,N*-tributyl-, fluoride; (429-41-4)

o-Iodoaniline:
Benzenamine, 2-iodo-; (615-43-0)

Triphenylphosphine:
Phosphine, triphenyl-; (603-35-0)

Tris(dibenzylideneacetone)dipalladium(0)–chloroform (1/1):
Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-, compound with trichloromethane (1:1); (52522-40-4)

5-*endo* Heck-type cyclization of 2-(trifluoromethyl)allyl ketone oximes: synthesis of 4-difluoromethylene-substituted 1-pyrrolines

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DOI: 10.1039/b610690k

2-(Trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes undergo a palladium-catalyzed 5-*endo* mode of alkene insertion *via* oxidative addition of the N–O bond, followed by β-fluorine elimination to produce 4-difluoromethylene-1-pyrrolines.

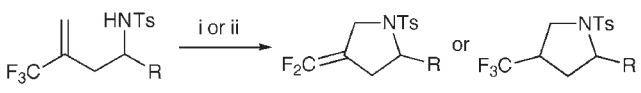
Pyrrolidine derivatives with fluorinated one-carbon units (CF_3, CF_2H, CF_2= and CFH_2) have attracted much interest as mimics of naturally occurring five-membered heterocycles in medicinal and agricultural chemistry.[1] Nevertheless, their synthetic methods are limited and remain to be developed. Recently, we have reported a facile access to pyrrolidines with a difluoromethylene or trifluoromethyl group *via* S_N2'-type or addition reactions of *N*-[3-(trifluoromethyl)homoallyl]sulfonamides (Scheme 1).[2] This route was successfully accomplished by nucleophilic 5-*endo-trig* cyclization, although it has been considered an unfavorable process because of severe distortions required in the reaction geometry, according to Baldwin's rules.[3]

Employing imine nitrogen anions with an N–C double bond instead of amide nitrogen anions with an N–C single bond might provide pyrrolines, which present a possibly more challenging 5-*endo-trig* ring closure with an extra limitation in the bond rotation. This fact first prompted us to examine the nucleophilic cyclization of 3-trifluoromethyl-2,2-dimethyl-1-phenylbut-3-en-1-imine. Deprotonation of the NH moiety with NaH followed by heating at 90 °C gave only a small amount of 4-difluoromethyl-3*H*-pyrrole with accompanying double bond isomerization.[4] This result indicates that nucleophilic attack (S_N2'-type reaction) of an imine nitrogen anion on the (trifluoromethyl)vinyl group was not sufficiently favorable to give rise to the 5-*endo-trig* cyclization.

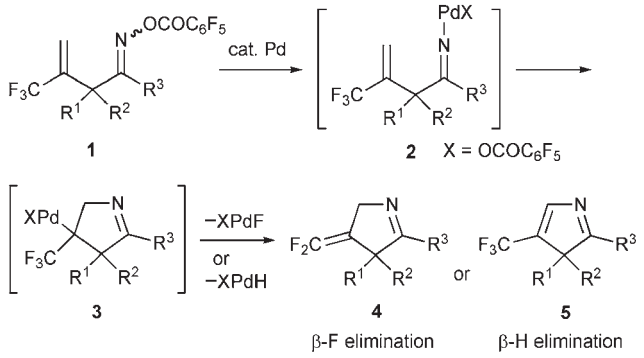
Our attention was next directed toward the cyclization promoted by a palladium catalyst, because C–N bond formation *via* an amino-Heck reaction of ketone oximes provides a powerful tool for the construction of nitrogen heterocycles.[5] In general, the intramolecular Heck reaction prefers *exo*-mode cyclization. Whereas 5-*endo* cyclization is far less likely to occur with few exceptions,[6–8] we have recently succeeded in palladium-catalyzed C–N bond formation in a 5-*endo-trig* fashion.[9] The reaction started from 1,1-difluoroallyl ketone *O*-pentafluorobenzoyloximes to afford the corresponding 5-fluoro-3*H*-pyrroles, where an electrostatic attraction between the difluorovinyl group and the N–Pd species presumably facilitated geometrically unfavorable cyclization. The Heck reactions of (trifluoromethyl)vinyl compounds with aryl halides so far reported resulted in selective arylation at the position β to the trifluoromethyl group,[10] which implies that the alkene insertion proceeded regioselectively. On the basis of these considerations, we expected that the geometrically disfavored 5-*endo* cyclization could be achieved with a palladium catalyst in 2-(trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes (Scheme 2).

In the Heck reaction of alkenes bearing a heteroatom substituent, the competition of β-hydrogen elimination and β-heteroatom elimination is another issue of intense interest.[11] The previously reported intermolecular Heck reactions of (trifluoromethyl)vinyl compounds involved only β-hydrogen elimination to yield trifluoromethylated products.[10] Furthermore, a theoretical study by B3LYP level calculations suggested that elimination of a β-hydrogen is kinetically favored over that of a β-fluorine, whereas the β-H elimination product is thermodynamically less stable than the pre-eliminated species with a β-F to metal dative bond and the β-F elimination product.[11a] Our interest in such β-eliminations also led us to investigate the geometrically disfavored 5-*endo* Heck-type cyclization of N–Pd species bearing a (trifluoromethyl)vinyl moiety.

For the preparation of substrates, 2-(trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes, we employed two methods: (i) ring opening of oxiranes with 1-(trifluoromethyl)vinyllithium[12] and (ii) addition of 2-(trifluoromethyl)allylsilane to aldehydes,[13] both of which were followed by oxidation to provide 2-(trifluoromethyl)allyl ketones. The ketones thus obtained were



Scheme 1 Nucleophilic 5-*endo-trig* cyclization of amide nitrogen anions. *Reagents and conditions*: (i) NaH (1.3 eq), 120 °C, 2–4 h, DMF; (ii) KOH (5.0 eq), 130 °C, 10–20 h, $(CH_2OH)_2$.



Scheme 2 5-*endo* Heck-type cyclization of aminopalladium species.

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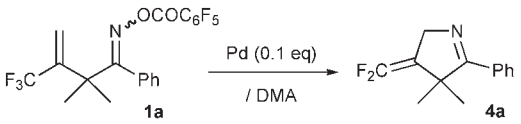
Table 1 Effect of additive and conditions on the Heck-type cyclization of **1a** (R^1 = R^2 = Me, R^3 = Ph)



Entry	Pd	Additive (eq)	Conditions	Yd./%
1	$Pd(PPh_3)_4$	Et_3N (5.0)	100 °C, 11 h	31
2	$Pd(PPh_3)_4$	$(CH_3)_2CHONa$ (2.0)	100 °C, 3 h	19
3	$Pd(PPh_3)_4$	PPh_3 (1.0)	100 °C, 1 h	60
4	$Pd(PPh_3)_4$	PPh_3 (1.0)	120 °C, 0.7 h	50
5	$Pd(OAc)_2$	PPh_3 (1.0)	100 °C, 1 h	8

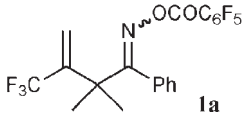
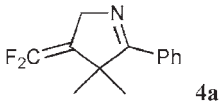
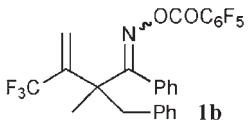
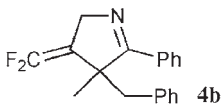
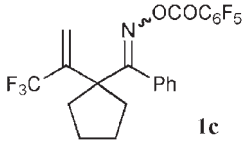
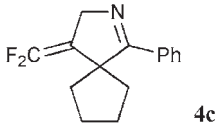
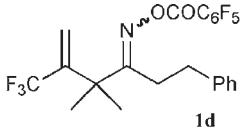
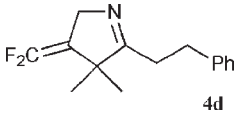
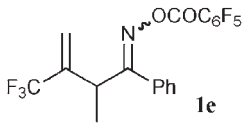
alkylated at the α-position, and then transformed into the desired *O*-pentafluorobenzoyloximes *via* oximation and subsequent pentafluorobenzoylation.

When *O*-pentafluorobenzoyloxime **1a** was treated with triethylamine and a catalytic amount of $Pd(PPh_3)_4$ in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 11 h, cyclized product **4a** with a difluoromethylene group was obtained in 31% yield (Table 1, entry 1) without accompanying ring-trifluoromethylated pyrrole **5**. This result indicates that the geometrically disfavored 5-*endo* cyclization was effected with a palladium catalyst, and that β-fluorine elimination was strongly preferred to β-hydrogen elimination in this 5-*endo* Heck-type cyclization, in contrast to the intermolecular examples so far reported in the literature.[10] The Pd(II) species generated by β-fluorine elimination should be reduced back to Pd(0) undergoing oxidative addition of the *O*-pentafluorobenzoyloxime moiety, which completes a catalytic cycle. Thus, we added sodium isopropoxide[14] or triphenylphosphine[15] for reduction, the latter improving the yield of **4a** to 60% (Table 1, entry 3).† After screening of reaction conditions, we found that the reaction performed with $Pd(PPh_3)_4$ and PPh_3 in DMA at 100 °C gave the best result.

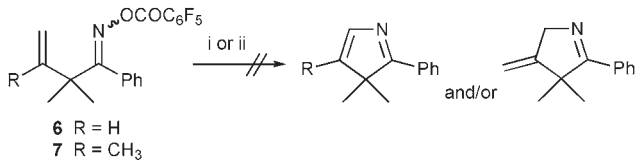
We tried other substrates **1** to synthesize difluoromethylene-substituted pyrrolines **4** under the reaction conditions above. The results are summarized in Table 2. Substrate **1b** bearing a benzyl group at the position α to the oxime group yielded the corresponding pyrroline **4b** in 71% yield (entry 2). The cyclization of substrate **1c** with a cyclopentane ring successfully afforded the spiro-type product **4c** (entry 3). The reaction of dialkyl ketone oxime **1d** proceeded, albeit in low yield (entry 4). When the reaction of α-monoalkylated substrate **1e** (R^2 = H) was examined to evaluate the effect of α-substituents, a mixture of many CF_3-containing compounds without cyclized products was obtained (entry 5). *gem*-Dialkyl substituents in **1** were required to promote the 5-*endo* Heck-type reaction, presumably because (i) an acidic proton at the α position of the oxime as well as the trifluoromethylvinyl moiety prevented the cyclization by protonation of aminopalladium intermediate **2** and/or (ii) the *gem*-dialkyl effect facilitated the unfavorable ring construction.[16]

To elucidate the role of the trifluoromethyl group, we examined the reaction of substrates **6** and **7** bearing a hydrogen atom or a methyl group instead of the trifluoromethyl substituent on the alkene moiety (Scheme 3). When **6** and **7** were subjected to reaction conditions similar to those described above, no cyclized products were observed. These results clearly show that the trifluoromethyl group plays a crucial role in the 5-*endo* Heck-type cyclization, where the trifluoromethyl substituent seems to

Table 2 Synthesis of 4-difluoromethylene-1-pyrrolines **4**[a]

Entry	Substrate	Product	Conditions	Yd./%
1	 **1a**	 **4a**	100 °C, 1 h	60
2	 **1b**	 **4b**	100 °C, 0.8 h	71
3	 **1c**	 **4c**	100 °C, 2.5 h	65
4	 **1d**	 **4d**	100 °C, 0.5 h	20[b]
5	 **1e**	—	80 °C, 2 h	—

[a] All the reactions were performed with $Pd(PPh_3)_4$ (0.1 eq) and PPh_3 (1.0 eq) in DMA. [b] Yield deduced from ^{19}F NMR spectrum relative to internal standard $(CF_3)_2C(C_6H_4$-*p*-$CH_3)_2$.



Scheme 3 Effect of vinylic substituents on the 5-*endo* Heck-type cyclization. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (0.1 eq), PPh_3 (1.0 eq), 140 °C, 2 h, DMF (for **6**), 100 °C, 1 h, DMA (for **7**); (ii) $Pd(PPh_3)_4$ (0.1 eq), PPh_3 (1.0 eq), Et_3N (2.0 eq), 140 °C, 1 h, DMF (for **6**).

contribute to the activation of the vinylic terminal carbon in **1** and the stabilization of the cyclized palladium intermediate **3**.

In summary, we have accomplished the Heck-type cyclization of 2-trifluoromethyl-1-alkenes bearing an *O*-acyloxime moiety, which represents a rare example of 5-*endo* mode alkene insertion into transition metal species. While there were two possible pathways, namely β-fluorine and β-hydrogen elimination after ring formation, the former elimination exclusively took place to construct an *exo*-difluoromethylene unit. This catalytic process provides facile access to 4-difluoromethylene-1-pyrrolines.

We are grateful to Central Glass Co., Ltd. for financial support. We also thank Tosoh F-Tech, Inc. for a generous gift of 2-bromo-3,3,3-trifluoropropene.

Notes and references

† Representative procedure: To a solution of triphenylphosphine (145 mg, 0.55 mmol) and tetrakis(triphenylphosphine)palladium (64 mg, 0.055 mmol) in DMA (20 mL) was added 2,2-dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate **1a** (247 mg, 0.547 mmol). After the reaction mixture was stirred at 100 °C for 1 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was extracted with ether three times. The combined organic extracts were washed with water three times and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography on silica gel (hexane–AcOEt 4 : 1) to give pyrroline **4a** (72 mg, 60%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (6H, s), 4.61 (2H, dd, J_{HF} = 3.6, 3.6 Hz), 7.37–7.42 (3H, m) and 7.69–7.73 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6 (dd, J_{CF} = 3, 2 Hz), 51.6 (dd, J_{CF} = 4, 3 Hz), 57.8 (dd, J_{CF} = 3, 2 Hz), 97.5 (dd, J_{CF} = 21, 15 Hz), 127.9, 128.2, 129.7, 133.7 (dd, J_{CF} = 2, 2 Hz), 149.3 (dd, J_{CF} = 287, 282 Hz) and 178.5. ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) δ 68.5 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 4 Hz) and 76.3 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 4 Hz). IR (neat) ν 2978, 1765, 1466, 1267, 1223, 1132, 1047, 1014, 775, 694 and 598 cm^{-1}. HRMS (FAB) calcd for $C_{13}H_{14}F_2N$ ($[M + H]^+$) 222.1094, found 222.1091.

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JOC*Article*

Divergent Chemical Synthesis of Prolines Bearing Fluorinated One-Carbon Units at the 4-Position via Nucleophilic 5-*Endo-Trig* Cyclizations

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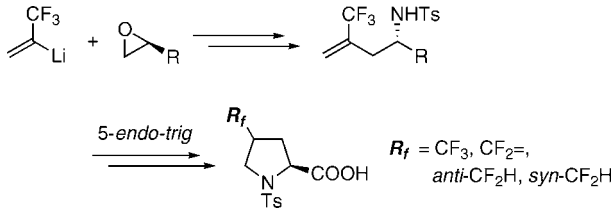

N-[3-(Trifluoromethyl)homoallyl]sulfonamides, prepared via ring opening of (*S*)-glycidyl ethers or 2-aryloxiranes with 1-(trifluoromethyl)vinyllithium, underwent intramolecular addition or S_N2'-type reaction in the normally disfavored 5-*endo-trig* fashion, leading to 2-substituted 4-(trifluoromethyl)- or 4-(difluoromethylene)pyrrolidines. Both α- and *β*-face-selective hydrogenation of the 4-difluoromethylene group afforded *syn*- and *anti*-4-(difluoromethyl)pyrrolidines, respectively. These sequences, followed by the oxidation of a 2-hydroxymethyl or 2-aryl group, successfully provided prolines with a trifluoromethyl, difluoromethylene, or difluoromethyl group at the 4-position, including optically active prolines.

Introduction

Proline is a unique amino acid with a rigid ring structure, which leads to its special role as a bending template in peptide chains.[1] Its secondary amine moiety with conformational constraint has allowed development of proline-based bioactive compounds,[2] ligands,[3] and organocatalysts.[4] 4-Substituted prolines, in particular, have found extensive use in this context,[5] well exemplified by (i) Spirapril[6] and Fosinopril,[7] angiotensin-converting enzyme (ACE) inhibitors, (ii) conformationally stabilized collagen triple helices,[8] and (iii) 4-hydroxyproline-based asymmetric organocatalysts.[9]

In the field of pharmaceuticals, agrochemicals, materials, and catalysts, introduction of fluorocarbon substituents has come into wide use as one of the most efficient methods for the modification of biological activity as well as physical and chemical properties.[10] Among fluorocarbon substituents, fluorinated one-carbon units are quite attractive:[11] (i) the incorpora-

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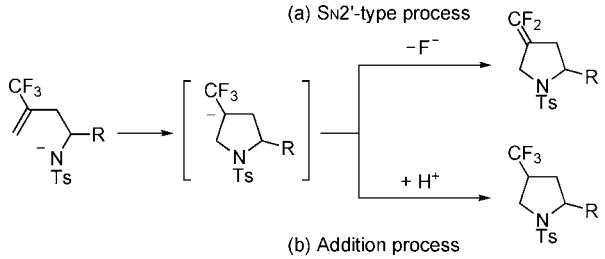
SCHEME 1. Nucleophilic 5-*Endo-Trig* Cyclizations of (3-CF_3-homoallyl)sulfonamides

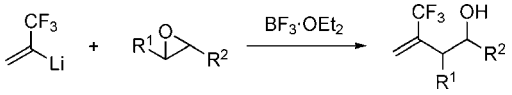


tion of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density,[12] (ii) a difluoromethyl (CF_2H) group has hydrogen bond donor ability without nucleophilicity and with high lipophilicity,[13] which makes it a special mimic of a hydroxy group,[14] and (iii) a difluoromethylene (CF_2═) group acts as a reactive site toward nucleophiles[15] and a potential isostere of carbonyl groups.[16]

Thus, prolines with such fluorinated substituents at the 4-position have importance in the design of molecules and, hence, immense potential. Recently, Goodman and Qing independently reported synthetic methods for 4-fluorocarbon-substituted prolines, with both methods starting from natural amino acids such as L-hydroxyproline and L-serine.[17,18] Their chemical synthesis based on non-natural starting materials is now a highly desirable goal.

In our recent studies, we have accomplished the construction of a pyrrolidine ring via nucleophilic 5-*endo-trig* cyclization of 2-trifluoromethyl-1-alkenes with a nitrogen functionality (Scheme 1).[19] *N*-[3-(Trifluoromethyl)homoallyl]sulfonamides underwent intramolecular S_N2'-type reaction under aprotic conditions to afford 4-difluoromethylene-substituted pyrrolidines (Scheme 1a), while protic conditions allowed nucleophilic addition, providing 4-trifluoromethyl-substituted pyrrolidines (Scheme 1b). This type of 5-*endo-trig* cyclization has been considered to be a geometrically disfavored process according to Baldwin's rules.[20] Such unique reactivity of 2-trifluoromethyl-1-alkenes is presumably due to the highly electrophilic double bond and the stabilized α-CF_3 carbanion intermediate, both of which are caused by the strong electron-withdrawing ability of the CF_3 group. Thus, both 4-difluoromethylene- and 4-trifluoromethyl-substituted pyrrolidines were selectively derived from the same sulfonamide precursor, depending on reaction in the presence or absence of a proton source.

SCHEME 2. Synthesis of 3-CF_3-Homoallyl Alcohols



We have also recently developed a synthetic method for 3-(trifluoromethyl)homoallyl alcohols via ring opening of substituted oxiranes with 1-(trifluoromethyl)vinyllithium in the presence of $BF_3{\cdot}OEt_2$, which allowed the synthesis of optically active homoallyl alcohols (Scheme 2).[21] The combination of the two processes, the oxirane ring opening and the 5-*endo-trig* cyclization, followed by introduction of a carboxy group at the 2-position, could provide 4-substituted proline derivatives in short steps, as outlined in Figure 1. The introduction of the carboxy group would be attained by oxidation of a hydroxymethyl or an aryl group, derived from the 2-substituent on the oxirane ring. The chirality of a commercially available, optically active glycidyl ether could be preserved in the sequence. A difluoromethylene substituent would be transformed to a difluoromethyl group by hydrogenation, where face-selective reactions could afford *anti*- or *syn*-4-(difluoromethyl)proline derivatives. On the basis of these considerations, we investigated synthetic methods for prolines bearing a fluorinated one-carbon unit at the 4-position.

We report a short chemical synthesis of proline derivatives bearing a fluorinated one-carbon unit, such as a trifluoromethyl, difluoromethylene, or difluoromethyl group, at the 4-position via (i) oxirane ring opening with 1-(trifluoromethyl)vinyllithium and (ii) nucleophilic 5-*endo-trig* cyclization of *N*-[3-(trifluoromethyl)homoallyl]sulfonamides.

Results and Discussion

Preparation of Tosylamide Cyclization Precursors 6. When (*S*)-glycidyl 4-(methoxy)benzyl (PMB) ether **(*S*)-2a** (99% ee)[22] was treated with 1-(trifluoromethyl)vinyllithium, generated in situ from bromotrifluoropropene **1** in the presence of $BF_3{\cdot}OEt_2$ at −100 °C, the corresponding partially protected diol **(*R*)-4a** was obtained in 82% yield with 99% ee (Scheme 3).[21] In this process, no racemization was observed. A similar ring opening of styrene oxide **2b** gave homoallylic alcohol **4b** in moderate yield. Homoallylic alcohols **4** were also prepared by the reaction of 2-(trifluoromethyl)allylsilane **3** with aldehydes.[23] Thus, homoallylic alcohol **4c** bearing a 2,4-dimethoxyphenyl group was obtained in 63% yield.[24]

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(20) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.

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(24) For enantioselective allylation of carbonyl compounds with allylic silanes, see: (a) Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615. (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556 and references therein. (c) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593 and references therein.

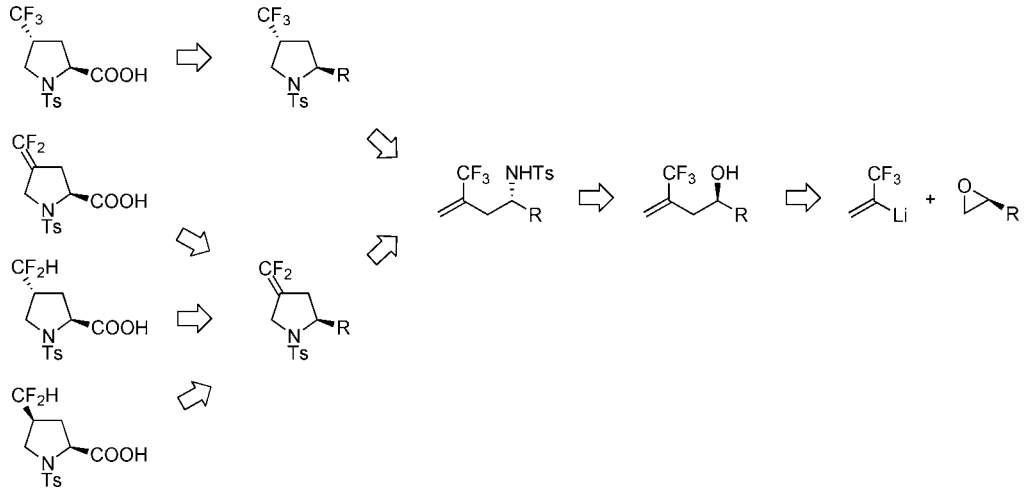
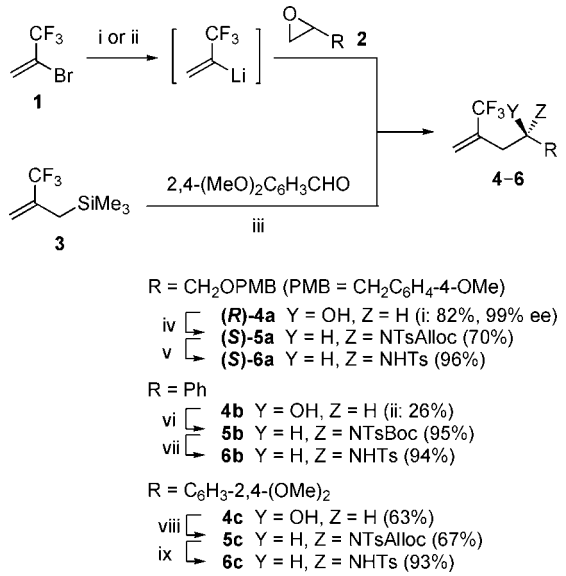


FIGURE 1. Synthetic strategy for 4-CF_3, CF_2═, or CF_2H-substituted prolines.

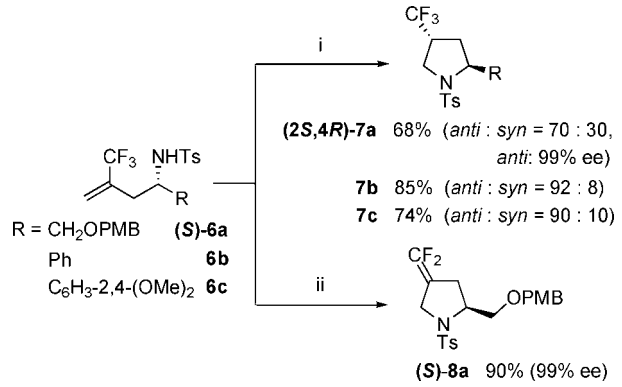
SCHEME 3. Preparation of Tosylamides 6[a]



[a] Reagents and conditions: (i) $BF_3{\cdot}OEt_2$ (1.0 equiv), *n*-BuLi (1.0 equiv), −100 °C, 15 min, Et_2O; then **2a** (R = CH_2OPMB, 0.67 equiv), −100 °C, 15 min; (ii) *t*-BuLi (1.0 equiv), −100 °C, 0.5 h, Et_2O; then, $BF_3{\cdot}OEt_2$ (1.0 equiv), 5 min; then, **2b** (R = Ph, 0.67 equiv), 15 min; (iii) 2,4-dimethoxybenzaldehyde (1.2 equiv), *n*-Bu_4NF (TBAF, 0.1 equiv), rt, 24 h, THF; (iv) CH_2═$CHCH_2OCONHTs$ (HNTsAlloc, 1.2 equiv), EtOCON═NCO_2Et (DEAD, 1.5 equiv), PPh_3 (1.5 equiv), 0 °C, 7 d, toluene;[26] (v) piperidine (3.0 equiv), $Pd(PPh_3)_4$ (2 mol %), rt, 1.5 h, MeCN; (vi) HNTsBoc (1.5 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), 0 °C, 10 h, THF; (vii) TFA (10 equiv), rt, 10 h, CH_2Cl_2; (viii) HNTsAlloc (1.5 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), rt, 10 h, THF; (ix) piperidine (4.0 equiv), $Pd(PPh_3)_4$ (2 mol %), rt, 10 h, MeCN.

The desired precursor sulfonamides were furnished as follows: Homoallylic alcohols **4a**−**c** were converted to the corresponding Alloc-protected tosylamides **5a** and **5c** or Boc-protected tosylamide **5b** by the Mitsunobu reaction.[25] Deprotection of the allyloxycarbonyl (Alloc) or *tert*-butoxycarbonyl (Boc) group was effected with piperidine and a palladium catalyst or trifluoroacetic acid to give tosylamides **6a**−**c** in excellent yield, respectively.

SCHEME 4. 5-*Endo-Trig* Cyclization of Tosylamides 6[a]



[a] Reagents and conditions: (i) KOH (5.0 equiv for **6a**,**b** or 1.3 equiv for **6c**), 130 °C, 20 h, $(CH_2OH)_2$; (ii) NaH (1.2 equiv), 120 °C, 4 h, DMF.

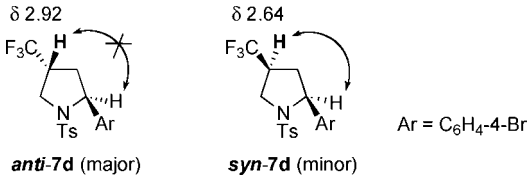
5-*Endo-Trig* Cyclization of Tosylamides 6. The cyclization of tosylamides **6a**−**c** obtained above was attempted by heating at 130 °C with an excess amount of KOH in ethylene glycol.[19] Nucleophilic addition proceeded in a 5-*endo-trig* fashion under protic conditions to afford pyrrolidines bearing a trifluoromethyl group at the 4-position with 2,4-*anti* stereoselectivity.[27] The results are summarized in Scheme 4.

Tosylamide **(*S*)-6a** cyclized to give pyrrolidine **(2*S*,4*R*)-7a** in 68% yield as a mixture of 2,4-*anti*/*syn* diastereomers (*anti*/

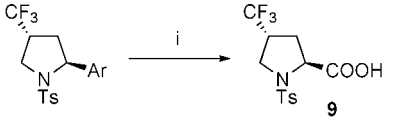
(25) Mitsunobu, O. *Synthesis* **1981**, 1.

(26) In the Mitsunobu reaction of **4a**, the yield of **5a** was improved by using toluene instead of THF as a solvent with a decrease in the amount of elimination product, a diene.

(27) The 2,4-*anti*/*syn* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on 2-(4-bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (**7d**) as a representative example. A cross peak between the 2- and 4-protons was not observed in the major product, but in the minor product. As for the 4-proton of the pyrrolidine ring, the signal of the *anti*-isomer was observed at lower field (δ 2.92) than that of the *syn*-isomer (δ 2.64), with this spectral criterion confirming similar stereochemistry for **7a**−**c**.



SCHEME 5. Synthesis of 4-(Trifluoromethyl)proline 9[a]



Ar = Ph **7b** (*anti* : *syn* = 92 : 8) 45% (*anti* : *syn* = 92 : 8)
C_6H_3-2,4-$(OMe)_2$ **7c** (*anti* : *syn* = 90 : 10) 72% (*anti* : *syn* = 90 : 10)

[a] Reagents and conditions: (i) $RuCl_3 \cdot nH_2O$ (2 mol %), $NaIO_4$ (11 equiv), rt, 4 d (for **7b**) or 6 h (for **7c**), $H_2O-CCl_4-CH_3CN$ (1.5:1:1).

syn = 70:30, *anti*: 99% ee) without racemization. Since phenyl-substituted tosylamide **6b** (R = Ph) exhibited better *anti* selectivity (*anti*/*syn* = 92:8) than that of alkyl-substituted precursor **6a**, we tried the cyclization of tosylamide **6c** bearing a 2,4-dimethoxyphenyl group, which could be more readily oxidized to a carboxy group. 4-(Trifluoromethyl)pyrrolidine **7c** was obtained in 74% yield with high diastereoselectivity (*anti*/*syn* = 90:10) in the 5-*endo*-*trig* cyclization of **6c**.

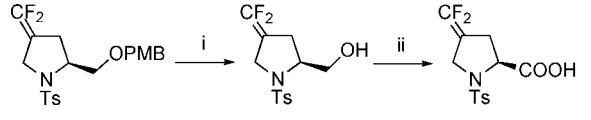
We also examined the S_N2'-type 5-*endo*-*trig* cyclization of tosylamide **6** under aprotic, basic conditions.[19] On treatment of tosylamide **(*S*)-6a** with 1.2 equiv of NaH at 120 °C in DMF, the corresponding pyrrolidine **(*S*)-8a** bearing a difluoromethylene group at the 4-position was obtained in 90% yield without racemization (Scheme 4). Thus, both trifluoromethylated and difluoromethylenated pyrrolidines **7** and **8** have been successfully constructed via addition reaction or S_N2'-type reaction, starting from a common precursor **6**.

Synthesis of 4-Trifluoromethyl-Substituted Proline 9. For the synthesis of prolines, the substituent at the 2-position should be oxidized to a carboxy group. Oxidation of the phenyl group in **7b** was examined with RuO_4, generated in situ from $NaIO_4$ and a catalytic amount of $RuCl_3$.[28] The reaction proceeded slowly to afford 4-trifluoromethyl-*N*-tosylproline **9** in 45% yield (Scheme 5). The 2,4-dimethoxyphenyl group in **7c** was oxidized with RuO_4 to improve the yield of the desired proline **9** up to 72%. This sequence provides the desired proline in only five steps from an oxirane with high 2,4-*anti* selectivity, which allows the synthesis of optically active 4-(trifluoromethyl)prolines.

Synthesis of 4-Difluoromethylene-Substituted Proline 11. The synthesis of (*S*)-4-difluoromethylene-*N*-tosylproline **(*S*)-11** was successfully effected via a two-step procedure: (i) deprotection of the PMB group in **(*S*)-8a** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and (ii) conversion of the hydroxymethyl group to a carboxy group by TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-catalyzed oxidation with $NaClO_2$,[29,30] both of which proceeded in excellent yield, albeit at a slow rate (Scheme 6). The optical purity of proline **(*S*)-11** was 99% ee, which shows that no racemization occurred during this sequence from the starting (*R*)-glycidol.[31]

Synthesis of 4-Difluoromethyl-Substituted Proline 15. We then turned our attention to prolines bearing a 4-difluoromethyl group. Goodman and Qing reported hydrogenation of endocyclic double bonds in 4-(trifluoromethyl)pyrrolines and exocyclic

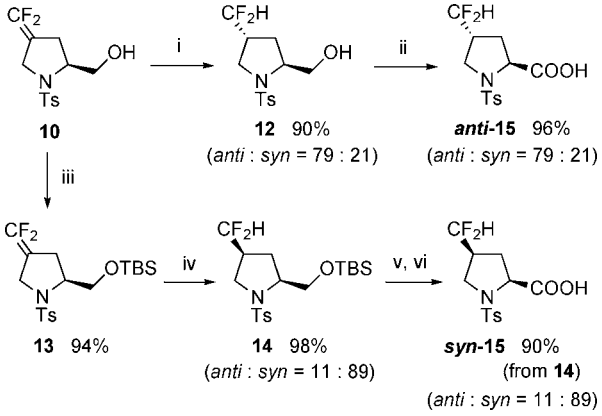
SCHEME 6. Synthesis of 4-(Difluoromethylene)proline 11[a]



(*S*)-8a **(*S*)-10** 91% (99% ee) **(*S*)-11** 93% (99% ee)

[a] Reagents and conditions: (i) DDQ (1.3 equiv), rt, 2 d, CH_2Cl_2-MeOH (10:1); (ii) TEMPO (5 mol %), $NaClO_2$ (1.3 equiv), rt, 7 d, MeCN−pH 7 phosphate buffer (1.3:1).

SCHEME 7. Synthesis of 4-(Difluoromethyl)prolines 15[a]



10 **12** 90% (*anti* : *syn* = 79 : 21) ***anti*-15** 96% (*anti* : *syn* = 79 : 21)
13 94% **14** 98% (*anti* : *syn* = 11 : 89) ***syn*-15** 90% (from **14**) (*anti* : *syn* = 11 : 89)

[a] Reagents and conditions: (i) H_2 (1 atm), Pd/C (5%, 0.5 equiv), rt, 6 h, $CHCl_3$; (ii) TEMPO (5 mol %), NaBr (0.5 equiv), trichloroisocyanuric acid (5.0 equiv), $NaHCO_3$ (10 equiv), rt, 3 h, acetone−H_2O (4:1); (iii) TBSCl (1.5 equiv), TEA (2.0 equiv), DMAP (0.3 equiv), rt, 12 h, CH_2Cl_2; (iv) H_2 (1 atm), Pd/C (5%, 5 mol %), rt, 1 h, EtOH; (v) TBAF (1.2 equiv), rt, 1 h, THF; (vi) TEMPO (2 mol %), NaBr (0.2 equiv), trichloroisocyanuric acid (2.0 equiv), $NaHCO_3$ (6.0 equiv), rt, 3 h, acetone−H_2O (4:1).

double bonds in 4-(alkylidene)pyrrolidines, leading to the stereoselective formation of 4-substituted prolines.[17,18] On the basis of these observations, we pursued face-selective hydrogenation of the difluoromethylene group, exocyclic double bond in prolinol **10**.[32]

Hydrogenation of **10** was conducted in the presence of a palladium catalyst. Whereas the reaction in methanol afforded a 1:1 mixture of *anti*- and *syn*-4-(difluoromethyl)prolinols **12**, good *anti* selectivity (*anti*/*syn* = 79:21) was observed in a haloalkane solvent, such as dichloromethane and chloroform (Scheme 7). On the other hand, high *syn* selectivity (*anti*/*syn* = 11:89) was attained by protection of the hydroxy group in **10** as bulky TBS ether **13** prior to reduction, which gave *syn*-4-(difluoromethyl)pyrrolidine **14** as a major product.[33] Each face-selectivity can be explained by (i) chelation of the hydroxy group in **10** on the palladium surface (leading to the *anti* product) and (ii) a steric effect of the bulky silyl group of **13** (leading to the *syn* product). The desired *anti*-4-difluoromethyl-*N*-tosylproline ***anti*-15** was obtained by oxidation of ***anti*-12** with trichloroisocyanuric acid and a catalytic amount of TEMPO[29] in excellent yield. A similar oxidation procedure was also

(28) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(29) TEMPO-catalyzed oxidation using trichloroisocyanuric acid: (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999. TEMPO-catalyzed oxidation using $NaClO_2$: (c) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(30) Attempted TEMPO-catalyzed oxidation of **10** with trichloroisocyanuric acid was not successful due to affecting the difluromethylene moiety.

(31) Removal of the tosyl group on the nitrogen was achieved by photoinduced reduction of the benzyl ester derived from **11** in the presence of 1,5-dimethoxynaphthalene and ascorbic acid. Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.

(32) Although the reduction of a 4-(difluoromethylene)proline derivative was reported to give a single diastereomer in ref 18a, the reported ^1H and ^{13}C NMR data proved to be those of a diastereomer mixture. See also: Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2005**, *70*, 3826 and references therein.

applied to prolinol ***syn*-12**, derived from **14** by deprotection of the silyl group, to afford ***syn*-15**.

Conclusion

We have accomplished a divergent, chemical synthesis of *N*-protected prolines bearing a fluorocarbon moiety, such as a trifluoromethyl, difluoromethylene, or difluoromethyl group, at the 4-position from common tosylamide precursors. The combination of (i) oxirane ring opening with (trifluoromethyl)vinyllithium and (ii) 5-*endo*-*trig* cyclization of *N*-(homoallyl)-sulfonamides has proven to be highly efficient to construct prolines bearing a trifluoromethyl or a difluoromethylene group, depending on protic or aprotic reaction media in (ii). Face-selective hydrogenation of the 4-difluoromethylene group in prolinol was achieved with or without protection of the 2-hydroxy group to afford *anti*- or *syn*-(difluoromethyl)proline derivatives. The results described herein provide a convenient access to prolines bearing fluorinated one-carbon units at the 4-position, which could find wide application in the design of new organocatalysts and the synthesis of the new fluorine-containing peptides.

Experimental Section

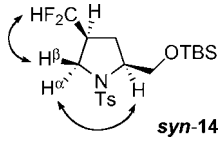
rel*-(2*R*,4*S*)-2-(2,4-Dimethoxyphenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (7c).** To a solution of **6c** (88 mg, 0.21 mmol) in ethylene glycol (3 mL) was added KOH powder (15 mg, 0.27 mmol) at rt. After the reaction mixture was stirred at 130 °C for 20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL × 3) and brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 4:1) to give **7c** (65 mg, 74%, *anti*/*syn* = 90:10) as a colorless liquid. IR (neat): 3001, 2958, 2839, 1614, 1589, 1506, 1340, 1161, 1034 cm^{-1}. ^1H NMR: (anti*-7c**) δ 1.89−2.01 (2H, m), 2.44 (3H, s), 2.84−2.95 (1H, m), 3.42 (1H, dd, J = 9.8, 9.8 Hz), 3.75 (3H, s), 3.80 (3H, s), 3.84 (1H, dd, J = 9.8, 9.8 Hz), 5.11 (1H, d, J = 8.0 Hz), 6.40 (1H, s), 6.45 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz); (***syn*-7c**) δ 2.08 (2H, m), 2.41 (3H, s), 2.46 (1H, m), 3.55 (1H, dd, J = 9.9, 9.9 Hz), 3.62 (3H, s), 3.80 (3H, s), 3.95 (1H, dd, J = 9.9, 9.9 Hz), 4.86 (1H, dd, J = 7.6, 7.6 Hz), 6.28 (1H, s), 6.44 (1H, J = 8.4 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.1 Hz). ^{13}C NMR: (***anti*-7c**) δ 21.5, 33.3, 41.0 (q, J_{CF} = 29 Hz), 47.8, 55.1, 55.3, 58.7, 98.6, 103.5, 121.8, 126.2 (q, J_{CF} = 256 Hz), 127.4, 127.8, 129.6, 134.4, 143.6, 156.6, 160.5. ^{19}F NMR: (***anti*-7c**) δ_F 91.3 (d, J_{FH} = 8 Hz); (***syn*-7c**) δ_F 91.4 (d, J_{FH} = 8 Hz). HRMS (FAB): calcd for $C_{20}H_{23}F_3NO_4S$ ([M + H]$^+$) 430.1300, found 430.1284.

(*S*)-4-Difluoromethylene-2-[(4-methoxybenzyloxy)methyl]-1-[(4-methylbenzene)sulfonyl]pyrrolidine [(*S*)-8a]. To a solution of **(*S*)-6a** (1.28 g, 2.89 mmol) in DMF (30 mL) was added NaH (55% dispersion in mineral oil; 151 mg, 3.47 mmol) at 0 °C. After being stirred for 10 min, the mixture was heated at 120 °C for 4 h. The reaction was quenched with phosphate buffer (pH 7, 40 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with water (30 mL × 4) and brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 2:1) to give **(*S*)-8a** (1.10 g, 90%) as a colorless liquid. $[\alpha]^{25}_D$ = −13.1 (*c* 1.0, $CHCl_3$). IR (neat): 2931, 2860, 1782, 1512, 1348, 1248, 1163, 1093, 1036, 816 cm^{-1}. ^1H NMR: δ 2.12−2.21 (1H, m), 2.41 (3H, s), 2.47 (1H, br d, J = 15.5 Hz), 3.38 (1H, dd, J = 9.4, 8.1 Hz), 3.63 (1H, dd, J = 9.4, 4.0 Hz), 3.79 (3H, s), 3.95 (1H, br d, J = 14.0 Hz), 3.99 (1H, br d, J = 14.0 Hz), 3.99−4.03 (1H, m), 4.43 (2H, s), 6.87 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.4, 27.8, 46.9 (d, J_{CF} = 4 Hz), 55.1, 59.2, 71.6, 72.9, 85.6 (dd, J_{CF} = 25, 23 Hz), 113.7, 127.2, 129.1, 129.7, 129.9, 134.8, 143.8, 149.9 (dd, J_{CF} = 284, 284 Hz), 159.2. ^{19}F NMR: δ_F 71.3 (1F, d, J_{FF} = 55 Hz), 74.2 (1F, d, J_{FF} = 55 Hz). HRMS (FAB): calcd for $C_{21}H_{24}F_2NO_4S$ ([M + H]$^+$) 424.1394, found 424.1390. HPLC (*i*-PrOH−hexane, 1:30): retention time 20.4 min major peak, 22.7 min minor peak.

rel*-(2*R*,4*S*)-1-(4-Methylbenzenesulfonyl)-4-(trifluoromethyl)-proline (9).** To a suspension of $NaIO_4$ (457 mg, 2.14 mmol) in CH_3CN (1 mL) and H_2O (1.5 mL) were added a solution of **7c** (84 mg, 0.19 mmol) in CCl_4 (1.0 mL) and then $RuCl_3 \cdot H_2O$ (0.8 mg, 4 μmol) at rt. The reaction mixture was stirred for 6 h at rt, and then water was added to quench the reaction. Organic materials were extracted with Et_2O (15 mL × 3). The combined extracts were washed with aqueous NaOH (1 M, 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **9** (47 mg, 72%, *anti*/*syn* = 90:10) was obtained as a colorless crystal. IR (neat): 3238, 2956, 2926, 1732, 1400, 1350, 1271, 1161, 1128, 1039 cm^{-1}. ^1H NMR: (anti*-9**) δ 2.13 (1H, ddd, J = 13.4, 9.2, 9.2 Hz), 2.34 (1H, ddd, J = 13.4, 8.0, 2.7 Hz), 2.46 (3H, s), 3.15 (1H, ddddq, J_{HF} = 8.0 Hz, J = 9.2, 8.0, 8.0, 8.0 Hz), 3.37 (1H, dd, J = 9.9, 8.0 Hz), 3.78 (1H, dd, J = 9.9, 8.0 Hz), 4.41 (1H, dd, J = 9.2, 2.7 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.76 (2H, d, J = 8.4 Hz), 8.04 (1H, br s); (***syn*-9**) δ 2.27 (1H, ddd, J = 13.5, 8.9, 7.4 Hz), 2.46 (3H, s), 2.51 (1H, ddd, J = 13.5, 8.2, 8.2 Hz), 2.62−2.76 (1H, m), 3.45 (1H, dd, J = 11.4, 10.4 Hz), 3.77 (1H, dd, J = 11.4, 8.6 Hz), 4.47 (1H, dd, J = 8.2, 7.4 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 8.04 (1H, br s). ^{13}C NMR: (***anti*-9**) δ 21.6, 30.0, 41.6 (q, J_{CF} = 30 Hz), 47.1, 59.9, 125.7 (q, J_{CF} = 276 Hz), 127.5, 130.0, 133.8, 144.5, 175.8. ^{19}F NMR: (***anti*-9**) δ_F 90.9 (d, J_{FH} = 8 Hz); (***syn*-9**) δ_F 91.5 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.38; H, 4.25; N, 3.89.

(*S*)-4-Difluoromethylene-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine [(*S*)-10]. To a solution of **(*S*)-8a** (141 mg, 0.333 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (0.15 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 98 mg, 0.43 mmol) at rt. After being stirred for 2 d, the reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 2:1) to give **(*S*)-10** (92 mg, 91%) as a pale yellow liquid. $[\alpha]^{25}_D$ = +45.5 (*c* 1.0, $CHCl_3$). IR (neat): 3529, 2954, 2924, 2854, 1782, 1344, 1271, 1161 cm^{-1}. ^1H NMR: δ 2.23−2.31 (1H, m), 2.39 (1H, br d, J = 14.5 Hz), 2.45 (3H, s), 2.52 (1H, br s), 3.65 (1H, dd, J = 11.5, 5.8 Hz), 3.70 (1H, dd, J = 11.5, 4.7 Hz), 3.79−3.86 (1H, m), 3.96 (1H, br d, J = 14.1 Hz), 4.08 (1H, br d, J = 14.1 Hz), 7.35 (2H, d, J = 7.9 Hz), 7.73 (2H, d, J = 7.9 Hz). ^{13}C NMR: δ 21.5, 27.5, 47.5 (d, J_{CF} = 3 Hz), 61.8, 64.4, 84.9 (dd, J_{CF} = 23, 23 Hz), 127.5, 130.0, 133.7, 144.3, 149.9 (dd, J_{CF} = 283, 283 Hz). ^{19}F NMR: δ_F 71.7 (1F, ddd, J_{FF} = 54 Hz, J_{FH} = 3, 3 Hz), 74.4 (1F, dd, J_{FF} = 54 Hz, J_{FH} = 1 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_3S$ ([M + H]$^+$) 304.0820, found 304.0828. The ee value was determined to be 99% by HPLC

(33) The 2,4-*anti*/*syn* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on TBS protected prolinol **14** as a representative example. Cross peaks between the 2-proton and the 5α-proton and between the 5β-proton and the difluoromethyl proton were observed as shown below.



***syn*-14**

(*i*-PrOH−hexane, 1:10, retention time 12.9 min major peak, 10.9 min minor peak).

(*S*)-4-Difluoromethylene-1-(4-methylbenzenesulfonyl)proline [(*S*)-11]. To a solution of **(*S*)-10** (144 mg, 0.475 mmol) in CH_3CN (4.8 mL) and phosphate buffer (pH 7, 3.6 mL) were added 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3.7 mg, 24 μmol) and $NaClO_2$ (80%; 70 mg, 0.62 mmol). The reaction mixture was stirred for 7 d at rt. After aqueous HCl (1 M, 2 mL) was added to the mixture, organic materials were extracted with Et_2O (10 mL × 4). The combined extracts were washed with aqueous Na_2CO_3 (10%, 10 mL × 2), and then the combined aqueous layer was acidified with concd aqueous HCl (2 mL). Organic materials were extracted by Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **(*S*)-11** (141 mg, 93%) was obtained as a colorless liquid. $[\alpha]^{25}_D = -13.7$ (*c* 1.0, $CHCl_3$). IR (neat): 3228, 2927, 2879, 1783, 1724, 1350, 1275, 1161, 1095, 1063, 771 cm^{-1}. ^1H NMR: δ 2.45 (3H, s), 2.70−2.75 (2H, m), 4.04−4.12 (2H, m), 4.53 (1H, ddd, $J = 8.4$, 4.1, 1.6 Hz), 7.35 (2H, d, $J = 8.1$ Hz), 7.62 (1H, br s), 7.75 (2H, d, $J = 8.1$ Hz). ^{13}C NMR: δ 21.5, 29.6, 46.5 (d, $J_{CF} = 3$ Hz), 60.2, 84.6 (dd, $J_{CF} = 25$, 25 Hz), 127.4, 130.0, 134.5, 144.4, 150.1 (dd, $J_{CF} = 286$, 286 Hz), 175.6. ^{19}F NMR: δ_F 73.1 (1F, d, $J_{FF} = 52$ Hz), 75.5 (1F, d, $J_{FF} = 52$ Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_4S$ ($[M + H]^+$) 318.0613, found 318.0601. The ee value was determined to be 99% by HPLC (*i*-PrOH−hexane, 1:10, retention time 12.0 min major peak, 9.1 min minor peak).

Benzyl 4-(Difluoromethylene)pyrrolidine-2-carboxylate (16). After a solution of benzyl 4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxylate (37 mg, 90 μmol), 1,5-dimethoxynaphthalene (8.8 mg, 47 μmol), and ascorbic acid (49 mg, 280 μmol) in H_2O (1.1 mL) and EtOH (19 mL) was degassed with argon, the solution was irradiated with high-pressure Hg lamp at rt for 2 h through a Pyrex tube. Aqueous HCl (1 M, 1 mL) was added, and the solvent was removed under reduced pressure. Aqueous HCl (1 M, 5 mL) was added to the residue, and the aqueous solution was washed with Et_2O (5 mL). After the aqueous layer was brought to alkaline pH with concd aqueous Na_2CO_3 (5 mL), organic materials were extracted by Et_2O (5 mL × 3). The combined extracts were washed with brine (5 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **16** (8.0 mg, 35%) was obtained as a colorless liquid. IR (neat): 3035, 2925, 2856, 1783, 1743, 1265, 1219, 1186, 771 cm^{-1}. ^1H NMR: δ 1.92 (1H, br s), 2.58−2.64 (1H, m), 2.78−2.85 (1H, m), 3.56 (1H, br d, $J = 13.7$ Hz), 3.74 (1H, br d, $J = 13.7$ Hz), 3.93 (1H, dd, $J = 7.6$, 6.0 Hz), 5.18 (2H, s), 7.32−7.41 (5H, m). ^{13}C NMR: δ 30.3, 45.5, 60.3, 67.0, 88.0, 128.2, 128.5, 128.7, 135.4, 149.7 (dd, J_{CF} =128, 128 Hz), 173.3. ^{19}F NMR: δ_F 71.7 (1F, dq, $J_{FF} =$ 59 Hz, $J_{FH} = 3$ Hz), 72.9 (1F, dq, $J_{FF} = 59$ Hz, $J_{FH} = 3$ Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_2$ ($[M + H]^+$) 254.0993, found 254.0985.

***rel*-(2*R*,4*S*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*anti*-12).** To a solution of **10** (19.2 mg, 63 μmol) in $CHCl_3$ (5 mL) was added Pd/C (5%, 67 mg, 32 μmol). The mixture was stirred under H_2 (1 atm) at rt for 6 h. The mixture was filtered through a pad of Celite. Removal of the solvent under reduced pressure gave **12** (90% NMR yield, *anti*/*syn* = 79:21) as a pale yellow liquid. IR (neat): 3521, 2952, 2881, 1597, 1398, 1336, 1155, 1087, 1024, 665 cm^{-1}. ^1H NMR: δ 1.67 (1H, ddd, $J = 12.9$, 8.8, 8.8 Hz), 1.95−2.00 (1H, m), 2.46 (3H, s), 2.71 (1H, br s), 2.71−2.84 (1H, m), 3.16 (1H, dd, $J = 10.1$, 8.2 Hz), 3.61−3.73 (3H, m), 3.80 (1H, dd, $J = 10.9$, 2.9 Hz), 5.38 (1H, ddd, $J_{HF} = 56.1$, 56.1 Hz, $J = 4.8$ Hz), 7.37 (2H, d, $J = 8.0$ Hz), 7.74 (2H, d, $J = 8.0$ Hz). ^{13}C NMR: δ 21.4, 28.5, 41.0 (t, $J_{CF} =$ 8 Hz), 48.5 (t, $J_{CF} = 4$ Hz), 61.0, 65.2, 116.1 (t, $J_{CF} = 240$ Hz), 127.6, 129.9, 133.3, 144.2. ^{19}F NMR: δ_F 40.5 (1F, ddd, $J_{FF} = 285$ Hz, $J_{FH} = 56$, 14 Hz), 41.4 (1F, ddd, $J_{FF} = 285$ Hz, $J_{FH} = 56$, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ($[M + H]^+$) 306.0977, found 306.0966.

***rel*-(2*R*,4*S*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)proline (*anti*-15).** To a solution of **12** (19.8 mg, 65 μmol, *anti*/*syn* = 79:21) in acetone (2 mL) were added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (3.6 mg, 35 μmol), TEMPO (0.56 mg, 3.6 μmol), and trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with H_2O (5 mL). Organic materials were extracted with Et_2O (5 mL × 3). The combined extracts were washed with aqueous NaOH (1 M, 5 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **15** (19.8 mg, 96%, *anti*/*syn* = 79:21) was obtained as colorless crystals. IR (neat): 3534, 2954, 2924, 2852, 1732, 1340, 1159, 1090, 1034 cm^{-1}. ^1H NMR: δ 1.98 (1H, ddd, $J = 13.3$, 9.5, 9.2 Hz), 2.30 (1H, ddd, $J = 13.3$, 6.8, 2.8 Hz), 2.46 (3H, s), 2.81−2.93 (1H, m), 3.29 (1H, dd, $J = 10.0$, 8.2 Hz), 3.69 (1H, dd, $J = 10.0$, 8.0 Hz), 4.38 (1H, dd, $J = 9.2$, 2.8 Hz), 5.60 (1H, td, $J_{HF} = 55.3$ Hz, $J =$ 4.4 Hz), 7.37 (2H, d, $J = 8.5$ Hz), 7.76 (2H, d, $J = 8.5$ Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.2 (t, $J_{CF} = 3$ Hz), 41.7 (t, $J_{CF} =$ 22 Hz), 47.4 (t, $J_{CF} = 5$ Hz), 60.2, 115.8 (t, $J_{CF} = 241$ Hz), 127.7, 130.2, 134.3, 144.6, 176.2. ^{19}F NMR: δ_F 40.2 (1F, ddd, $J_{FF} = 287$ Hz, $J_{FH} = 55$, 13 Hz), 41.0 (1F, ddd, $J_{FF} = 287$ Hz, $J_{FH} = 55$, 11 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_4S$ ($[M + H]^+$) 320.0768, found 320.0742.

2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (13). To a solution of **10** (81 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) were added *t*-$BuMe_2SiCl$ (61 mg, 0.41 mmol), NEt_3 (54 mg, 0.54 mmol), and 4-dimethylaminopyridine (DMAP, 10 mg, 0.08 mmol) at rt. The reaction mixture was stirred at rt for 3 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 10:1) to give **13** (105 mg, 94%) as a colorless liquid. IR (neat): 2954, 2929, 2858, 1782, 1350, 1271, 1163, 1093, 837, 777, 665 cm^{-1}. ^1H NMR: δ 0.04 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 2.14−2.22 (1H, m), 2.44 (3H, s), 2.49 (1H, br d, $J = 15.3$ Hz), 3.56 (1H, dd, $J = 10.1$, 7.1 Hz), 3.75 (1H, dd, $J = 10.1$, 3.6 Hz), 3.92−3.98 (2H, m), 4.01 (1H, br d, $J = 13.8$ Hz), 7.32 (2H, d, $J = 8.2$ Hz), 7.72 (2H, d, $J = 8.2$ Hz). ^{13}C NMR: δ −5.6, −5.6, 18.1, 21.5, 25.7, 27.4, 47.2 (d, $J_{CF} = 4$ Hz), 61.1, 65.5, 86.1 (dd, $J_{CF} = 26$, 22 Hz), 127.3, 129.8, 135.1, 143.8, 149.9 (dd, $J_{CF} = 284$, 284 Hz). ^{19}F NMR: δ_F 70.7 (1F, ddddd, $J_{FF} =$ 57 Hz, $J_{FH} = 3$, 3, 3, 3 Hz), 73.6 (1F, dd, $J_{FF} = 56$ Hz, $J_{FH} =$ 2 Hz). HRMS (FAB): calcd for $C_{19}H_{30}F_2NO_3SSi$ ($[M + H]^+$) 418.1684, found 418.1683.

rel*-(2*R*,4*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (14).** To a solution of **13** (75 mg, 0.18 mmol) in EtOH (3 mL) was added Pd/C (5%, 19 mg, 9.0 μmol). The mixture was stirred under H_2 (1 atm) at rt for 1 h. The mixture was filtered through a pad of Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 5:1) to give **14** (73 mg, 98%, *anti*/*syn* = 11:89) as a colorless liquid. IR (neat): 2954, 2929, 2858, 1348, 1254, 1161, 1090, 1036, 835 cm^{-1}. ^1H NMR: (syn*-14**) δ 0.08 (6H, s), 0.89 (9H, s), 1.92 (1H, ddd, $J =$ 13.4, 8.6, 6.1 Hz), 2.00 (1H, ddd, $J = 13.4$, 8.0, 8.0 Hz), 2.02−2.12 (1H, m), 2.44 (3H, s), 3.30 (1H, dd, $J = 11.7$, 8.6 Hz), 3.56 (1H, dd, $J = 11.7$, 7.5 Hz), 3.72−3.79 (2H, m), 3.84 (1H, dd, $J =$ 9.9, 3.0 Hz), 5.69 (1H, ddd, $J_{HF} = 56.3$, 56.3 Hz, $J = 5.6$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 7.72 (2H, d, $J = 8.4$ Hz); (***anti*-14**) δ 0.08 (6H, s), 0.89 (9H, s), 2.02−2.12 (2H, m), 2.44 (3H, s), 2.78−2.89 (1H, m), 3.11 (1H, dd, $J = 9.7$, 8.6 Hz), 3.66 (1H, dd, $J =$ 9.7, 6.5 Hz), 3.72−3.79 (3H, m), 5.43 (1H, ddd, $J_{HF} = 57.8$, 57.8 Hz, $J = 5.2$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 7.72 (2H, d, $J = 8.4$ Hz). ^{13}C NMR: (***syn*-14**) δ −5.5, −5.4, 18.2, 21.5, 25.8, 28.4 (dd, $J_{CF} = 5$, 3 Hz), 41.8 (t, $J_{CF} = 22$ Hz), 49.0 (dd, $J_{CF} = 7$, 4 Hz), 60.8, 65.8, 116.5 (t, $J_{CF} = 241$ Hz), 127.4, 129.9, 134.8, 143.8. ^{19}F

NMR: (***syn*-14**) δ_F 41.8 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.9 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{19}H_{32}F_2NO_3SSi$ ([M + H]$^+$) 420.1840, found 420.1853.

***rel*-(2*R*,4*R*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*syn*-12).** To a solution of **14** (86 mg, 0.20 mmol, *anti*/*syn* = 11:89) in THF (3 mL) was added TBAF (1 M in THF; 0.25 mL, 0.25 mmol) at rt. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 10:1) to give **12** (56 mg, 90%, *anti*/*syn* = 11:89) as a colorless liquid. IR (neat): 3521, 2954, 2885, 1597, 1338, 1219, 1157, 1089, 1026, 771 cm^{-1}. ^{1}H NMR: δ 1.75−1.86 (1H, m), 1.93−2.12 (2H, m), 2.46 (3H, s), 2.89 (1H, br s), 3.39 (1H, dd, J = 11.8, 8.6 Hz), 3.58 (1H, dd, J = 11.8, 7.8 Hz), 3.61−3.73 (2H, m), 3.87 (1H, br d, J = 10.5 Hz), 5.69 (1H, ddd, J_{HF} = 56.2, 56.2 Hz, J = 5.4 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.5, 28.7, 41.0 (t, J_{CF} = 22 Hz), 49.2 (t, J_{CF} = 4 Hz), 61.8, 64.8, 116.2 (t, J_{CF} = 240 Hz), 127.5, 130.1, 133.6, 144.3. ^{19}F NMR: δ_F 41.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ([M + H]$^+$) 306.0975, found 306.0978.

***rel*-(2*R*,4*R*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)-proline (*syn*-15).** To a solution of **12** (54 mg, 0.18 mmol, *anti*/*syn* = 11:89) in acetone (2 mL) was added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (4 mg, 0.03 mmol), and TEMPO (0.56 mg, 3.6 μmol) and then trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with water (5 mL). Organic materials were extracted with Et_2O (5 mL × 3), and the combined extracts were washed with aqueous NaOH (1 M, 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **15** (57 mg, 100%, *anti*/*syn* = 11:89) was obtained as a colorless crystal. IR (neat): 3546, 3220, 2964, 1733, 1340, 1219, 1161, 1035 cm^{-1}. ^{1}H NMR: δ 2.19 (1H, ddd, J = 13.5, 6.4, 6.1 Hz), 2.35 (1H, ddd, J = 13.5, 9.0, 8.8 Hz), 2.41−2.50 (1H, m), 2.46 (3H, s), 3.47 (1H, dd, J = 11.1, 6.5 Hz), 3.54 (1H, dd, J = 11.1, 7.6 Hz), 4.32 (1H, dd, J = 9.0, 6.1 Hz), 5.79 (1H, ddd, J_{HF} = 56.1, 56.1 Hz, J = 6.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.4 (t, J_{CF} = 3 Hz), 42.3 (t, J_{CF} = 22 Hz), 48.3 (t, J_{CF} = 4 Hz), 60.0, 116.1 (t, J_{CF} = 240 Hz), 127.9, 130.3, 133.9, 144.8, 176.3. ^{19}F NMR: δ_F 40.9 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 11 Hz), 42.3 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 13 Hz). Anal. Calcd for $C_{13}H_{15}F_2NO_4S$: C, 48.90; H, 4.73; N, 4.39. Found: C, 48.99; H, 4.85; N, 4.12.

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Supporting Information Available: Experimental procedures and spectroscopic data of compounds ***(R)*-4a**, **4b**, **4c**, ***(S)*-5a**, **5b**, **5c**, ***(S)*-6a**, **6b**, **6c**, **(2*R*,4*S*)-7a**, **7b**, and **7d**; copies of ^{1}H spectra of compounds **4c**, ***(S)*-5a**, **5c**, ***(S)*-6a**, **(2*R*,4*S*)-7a**, **7c**, ***(S)*-8a**, ***(S)*-10**, ***(S)*-11**, ***anti*-12**, ***syn*-12**, **13**, **14**, ***anti*-15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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A Facile Synthesis of *N*-[2-(Trifluoromethyl)allyl]amides and Their Transformation into Angularly Trifluoromethylated Bicyclic Cyclopentenones

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On treatment with *sec*-BuLi at −105 °C, 2-bromo-3,3,3-trifluoropropene undergoes rapid lithium–halogen exchange to generate thermally unstable 1-(trifluoromethyl)vinyllithium, which reacts with *N*-tosylimines to afford *N*-[2-(trifluoromethyl)allyl]amides in high yield. Propargylation of the amides, followed by the Pauson–Khand reaction, readily provides pyrrolidine ring-fused cyclopentenones with an angular trifluoromethyl group.

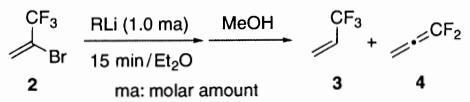
2-Trifluoromethyl-1-alkenes [1-(trifluoromethyl)vinyl compounds] constitute a versatile class of building blocks[1] for the selective introduction of fluorine-containing carbon substituents into bioactive molecules and molecular devices.[2,3] This is due to their electron-withdrawing CF_3 groups, reactive double bonds toward nucleophiles, and allylic fluorine atoms as potential leaving groups. Along this line, we have recently developed flexible synthetic routes to: (i) 1,1-difluoro-1-alkenes via an S$_N$2′-type reaction;[4] (ii) fluorocarbon-substituted heterocycles via intramolecular nucleophilic reactions;[5] and (iii) 5-trifluoromethyl-2-cyclopentenones via a regioselective Nazarov cyclization.[6] Despite the synthetic potential of the 1-(trifluoromethyl)vinyl moiety, its introduction as a C3 unit remains a difficult task, because of the thermal instability of the corresponding reactive metal species, such as a vinyllithium reagent.[7–9]

In our previous paper, we reported the efficient synthesis of [1-(trifluoromethyl)vinyl]-substituted alcohols by the ring opening of cyclic ethers with 3,3,3-trifluoroprop-1-en-2-yllithium (**1**).[8] On treatment of 2-bromo-3,3,3-trifluoroprop-1-ene (**2**) with an equimolar amount of *n*-BuLi at −100 °C, slow lithium–halogen exchange gave rise to a mixture of vinyllithium **1** and *n*-BuLi. We succeeded, however, in the selective trapping of **1** with appropriate electrophiles, such as oxiranes and oxetanes, in the presence of BF_3·OEt_2 by taking advantage of the subtle difference between reactivities of the two lithium species.[10]

On the other hand, 1-(trifluoromethyl)vinylation of highly reactive electrophiles has remained problematic. The vinylation of aldehydes suffers from nonselective addition of both **1** and *n*-BuLi to give a poor yield of the desired allyl alcohols.[7,11] Herein, we report an efficient generation of (trifluoromethyl)vinyllithium **1** to trap with reactive electrophiles, aldehydes and imines, and its application to the construction of angularly trifluoromethylated bicyclic systems, which has been a desirable goal.

We first reexamined the generation of vinyllithium **1** from bromotrifluoropropene **2** by treatment with several alkyllithiums for 15 min. After quenching with methanol, the product distributions were observed by ^{19}F NMR, as shown in Table 1. When the reaction was carried out with *n*-BuLi at −78 °C, the decomposition of vinyllithium **1** occurred to give 1,1-difluoroallene (**4**) in 54% yield, via elimination of lithium fluoride (Entry 1). When carrying out the reaction at −105 °C, we observed only a 14% yield of 3,3,3-trifluoroprop-1-ene (**3**), along with a 76% recovery of **2** (Entry 3). These results indicate that incomplete conversion is inevitable in the reaction with *n*-BuLi, due to the slow exchange rate and the thermal instability of **1**. In contrast, the lithium–halogen exchange reaction with *sec*-BuLi proceeded rapidly even at −105 °C to consume 90% of **2**, which generated **1** in at least 60% yield along with 26% of difluoroallene **4** (Entry 4).

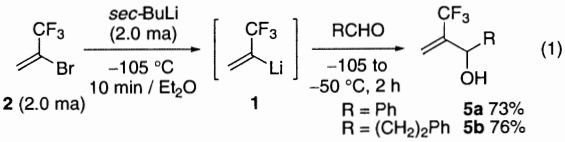
Table 1. Preparation of 1-(trifluoromethyl)vinyllithium **1**



2 ma: molar amount **3** **4**

Entry	R	temp./°C	**3**	**4**	recovery of **2**
1	*n*-Bu	−78	20%	54%	17%
2		−96	31%	11%	58%
3		−105	14%	1%	76%
4	*sec*-Bu	−105	60%	26%	10%
5	*tert*-Bu	−105	50%	35%	5%

We then attempted the reaction of aromatic and aliphatic aldehydes with vinyllithium **1**, generated in situ from 2.0 molar amounts of vinyl bromide **2** and *sec*-BuLi, in consideration of the partial decomposition of **1**. The desired 2-(trifluoromethyl)allyl alcohols **5a** and **5b** were obtained in 73 and 76% yield, respectively (eq 1). Thus, the more rapid lithium–halogen exchange allowed the reaction with reactive electrophiles.

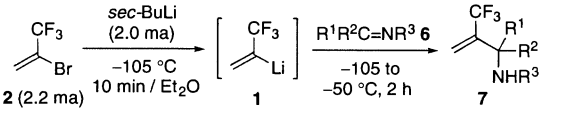


2 (2.0 ma) **1** R = Ph **5a** 73%; R = $(CH_2)_2$Ph **5b** 76% (1)

Allylamines have been used as useful components for the synthesis of *N*-heterocycles. For the construction of potential trifluoromethylated heterocycles, we pursued the reaction of vinyllithium **1** with imines to prepare 2-(trifluoromethyl)allylamines.[3] Although *N*-benzylimine **6a** was not reactive towards **1**, BF_3·OEt_2 promoted the reaction to afford the desired amine **7a** in 81% yield (Table 2, Entry 1). When *N*-benzoyl- and *N*-tosylimine **6b** and **6c** were employed as the reactive electrophiles, the corresponding *N*-allylamides **7b** and **7c** were obtained in excellent yield (Entries 2 and 3).[12]

We further examined (trifluoromethyl)vinylation of several other *N*-tosylimines **6d–6g** in view of their availability, ease of handling, and the synthetic applicability of the products. All *N*-tosylimines **6c–6g** examined provided the corresponding *N*-[2-(trifluoromethyl)allyl]sulfonamides **7c–7g** in good to excellent yield, as summarized in Table 2. Butanimine **6e** gave **7e** in good yield, even though it had acidic protons α to the imino group (Entry 5). Whereas 1,1-diphenylmethanimine **6g** showed

Table 2. Synthesis of [(trifluoromethyl)allyl]sulfonamides **7**



Entry	R^1	R^2	R^3	7	Yield/%
1[a]	H	Ph	$CH_2C_6H_5$	**7a**	81
2	H	Ph	COC_6H_5	**7b**	97
3[b]	H	Ph	Ts	**7c**	90
4[b]	H	PhCH=CH	Ts	**7d**	89
5	H	*n*-Pr	Ts	**7e**	77
6	H	*t*-Bu	Ts	**7f**	96
7	Ph	Ph	Ts	**7g**	76 (91)[c]

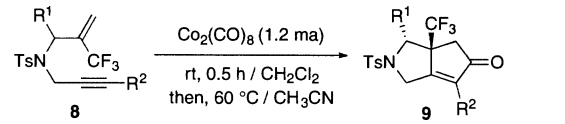
[a]BF_3·OEt_2 (1.5 ma) was added. [b]Solution of **6** was added dropwise over 20 min. [c]Vinyl bromide **2** (3.5 ma) and *sec*-BuLi (3.2 ma) were used.

modest reactivity, employing an excess amount of **1**, generated from **2** (3.5 ma) and *sec*-BuLi (3.2 ma), improved the yield to 91% (Entry 7).

Having accomplished the synthesis of 2-(trifluoromethyl)-allylamides **7**, we turned our attention to the construction of fused-ring systems involving an angular trifluoromethyl group,[2,13] whose framework might be constructed by an intramolecular Pauson–Khand reaction.[14,15] Introduction of an angular trifluoromethyl group can be an attractive tool for the analog synthesis of steroids and alkaloids, and remains a challenging task. Furthermore, very few examples of 1,6-enynes bearing a electron-withdrawing group at the C-2 vinylic carbon have been reported in the Pauson–Khand reaction.[16] These facts prompted us to investigate the Pauson–Khand reaction of *N*-propargyl-*N*-[2-(trifluoromethyl)allyl]amides **8**, readily prepared by propargylation (with a propargyl bromide and NaH in DMF at rt) of the above-obtained amides **7** in 84–92% yield.

Enyne **8a** was treated with dicobalt octacarbonyl to generate the cobalt–yne complex. Heating the complex at 60 °C in acetonitrile promoted the desired Pauson–Khand reaction of a CF_3-substituted terminal alkene, to afford the pyrrolidine ring-fused cyclopentenone **9a** bearing an angular trifluoromethyl group in 81% yield with high diastereoselectivity (*anti*:*syn* = 94:6) (Table 3, Entry 1).[17,18] Substrates **8b** and **8c** with an internal alkyne moiety or an alkyl group at the allylic position also readily underwent the cyclization to give trifluoromethylated pyrrolidines **9b** and **9c** in 85 and 71% yield, respectively (Entries 2 and 3).

Table 3. Synthesis of 3a-CF_3-cyclopenta[*c*]pyrroles **9**



Entry	R^1	R^2	Time/h	9	Yield/%	*anti*:*syn*[a]
1	Ph	H	3	**9a**	81	94:6[b]
2	Ph	Et	2	**9b**	85	83:17[c]
3	*n*-Pr	H	3	**9c**	71	86:14[c]

[a]Determined by ^{19}F NMR. [b]See Ref. 17. [c]Configuration was determined in analogy with **9a** by comparing ^1H and ^{19}F NMR data of each isomer.

The sequence of (i) (trifluoromethyl)vinylation of imines, followed by (ii) propargylation and (iii) the cobalt-mediated intramolecular Pauson–Khand reaction, successfully provides a facile entry to the fused *N*-heterocycles bearing an angular trifluoromethyl group.

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10 *n*-BuLi seemed less reactive than vinyllithium **1** under the reaction conditions, presumably due to aggregation. See, *Organolithiums: Selectivity for Synthesis*, ed. by J. Clayden, Elsevier, Oxford, **2002**.
11 When a 1:1 mixture of **2** and *n*-BuLi was kept at −100 °C for 15 min and then treated with benzaldehyde, two alcohols, derived from vinyllithium **1** and *n*-BuLi, were obtained in 25 and 64% yield, respectively.
12 To a solution of **2** (0.13 mL, 1.24 mmol) in Et_2O (10 mL) was added *sec*-butyllithium (1.07 M in cyclohexane, 1.05 mL, 1.13 mmol) in Et_2O (5 mL) at −105 °C under Ar. After stirring for 10 min, **6c** (146 mg, 0.56 mmol) in Et_2O (10 mL) was added over 20 min. The reaction mixture was allowed to warm to −50 °C over 2 h, and the reaction was quenched with phosphate buffer (pH 7, 10 mL). Organic materials were extracted with EtOAc three times, and the combined extracts were washed with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane–EtOAc, 10:1) to give **7c** (180 mg, 90%) as colorless crystals.
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