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トリフリルオキシベンザインの付加環化反応：
ベンゾ縮合複素環の位置制御合成

本論文は大阪大学大学院薬学研究科博士論文である

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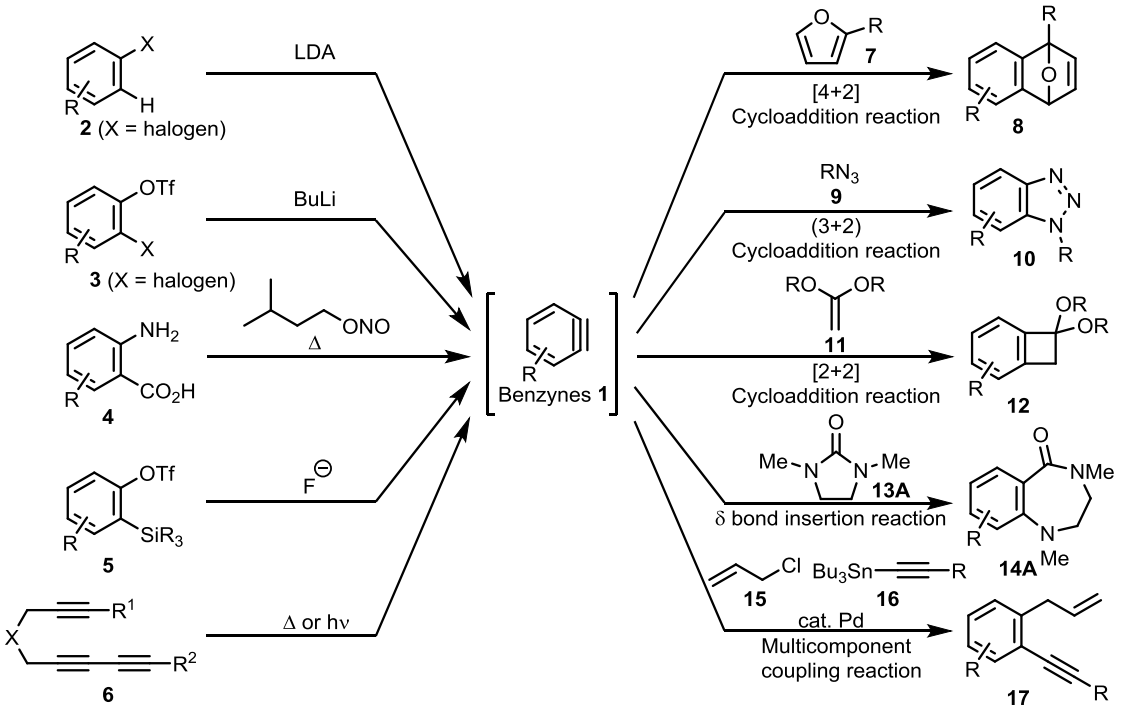
略　　号

Ac	acetyl
Alloc	allyloxycarbonyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Cbz	carbobenzoxy
CPME	cyclopentyl methyl ether
DMF	*N*,*N*-dimethyl-4-aminopyridine
DMI	1,3-dimethyl-2-imidazolidinone
Et	ethyl
HPLC	high performance liquid chromatography
IR	infrared spectroscopy
Me	methyl
Mp	melting point
MS	mass spectrometry
Ms	mathanesulfonyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	2-nitro benzenesulfonyl
Ph	phenyl
rt	room temperature
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

総　　論

ベンザイン **1** は平面 6 員環内に 2 つの二重結合と 1 つの三重結合を有する求電子的な高反応性中間体であり、古くからその発生法及び反応に関する研究が活発に行われてきた（Scheme 1）。[1] これまでに多様なベンザイン発生法が報告されているが、特に、①ハロゲン化ベンゼン **2** の 2 位の水素を強塩基により引き抜く発生法 [2a] と②2-ハロフェニルトリフラート **3** のハロゲン－リチウム交換による発生法 [2b] は、前駆体合成の簡便さの観点で優れている。また、③アントラニル酸 **4** のジアゾ化と続く熱分解による発生法 [2c] も比較的反応条件が温和であるため重宝されてきた。また、④2-シリルフェニルトリフラート **5** にフッ素アニオンを作用させるベンザイン発生法 [2d] は、反応条件が極めて温和であり、現在、最も広く利用されている。[2a] さらに最近、⑤トリイン化合物 **6** から加熱 [2e] 又は光照射 [2f] によってベンザイン環そのものを構築する手法も活発に研究されている。

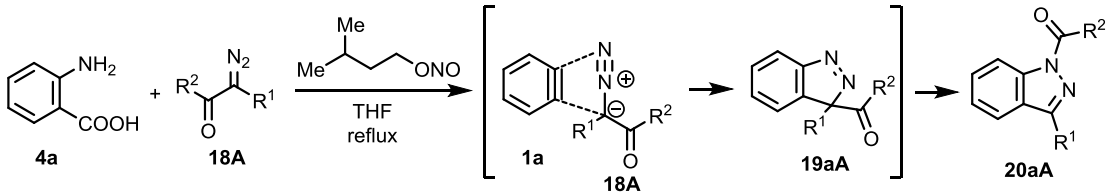
一方、**1** の反応は、フラン **7** などの 4π 電子系化合物との [4+2]付加環化反応、[3a–3c, 注 1] アジド **9** などの 1,3-双極子化合物との(3+2)付加環化反応、[11a] ケテンアセタール **11** などの 2π 電子系化合物との[2+2]付加環化反応、[3d] ジメチルイミダゾリジノン (DMI) **13A** などの求核種の σ 結合挿入反応、[8a] アリルクロライド **15** とスズ化合物 **16** のように求核性化合物と求電子性化合物を組み合わせて用いる成分連結反応 [3e] 等、多岐にわたっている。これらはいずれも、ベンゼン環の隣接位置に 2 つの σ 結合を一挙に構築しながら多様な芳香族化合物を合成する魅力的な反応である。



Scheme 1. Generation of benzynes **1** and their reactions.

注 1: 本論文においてシグマトロピー転位は、IUPAC 命名法に従い、原子数を用いて命名する場合は丸括弧 () を、π 電子数を用いて命名する場合は角括弧 [] を用いる。なお、2+2、4+2 付加環化反応については慣例的に角括弧 [] を用いる。

中でも、多くの生物活性物質を構成するベンゾ縮合芳香環化合物[4, 5]を短工程で合成する **1** と **9** のような1,3-双極子分子との (3+2)付加環化反応や **13A** のような求核性物質とのσ結合形成反応は、特に重要な位置を占める。[6-8]その中でも特に大きな割合を占める (3+2)付加環化反応を用いたベンゾ縮合複素環化合物合成法の概要を以下に述べる。 1974 年、Shechter らは、α-ケトジアゾ化合物 **18A** 存在下、アントラニル酸 **4a** と亜硝酸イソアミルを THF 中、加熱還流することによって 1-アシル-1*H*-インダゾール **20aA** が得られることを報告した（Scheme 2）。[9, 注2] この反応では、**4a** のニトロソ化反応を経て発生したベンザイン **1a** と **18A** との (3+2) 付加環化反応の後、生じたインダゾール **19aA** のアシル基が転位することによって **20aA** が生成したと考えられる。

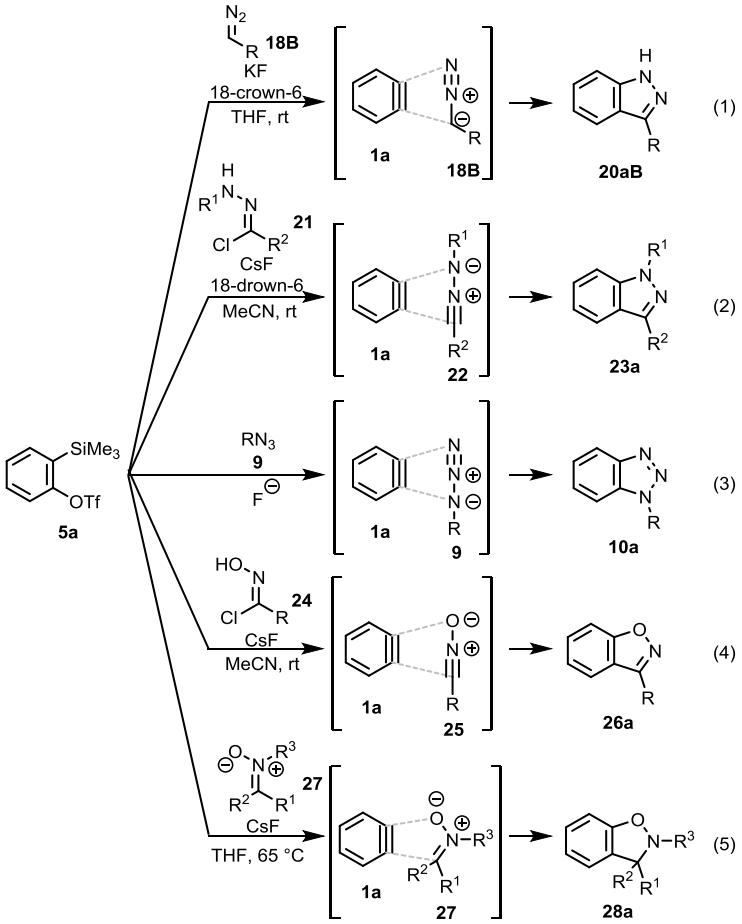


Scheme 2. (3+2) Cycloaddition reactions of benzyne **1a** with α-diazoketones **18A**.

その後 30 年以上、ベンザインの (3+2) 付加環化反応は、それほど注目を集めることがなかった。2007 年山本らは、上記 Shechter らのジアゾケトンの反応を、小林らによって開発された前駆体 **5a**[2d] を用いて、フッ素アニオンを用いる温和な反応条件下に行う手法を報告し、注目を集めた（Scheme 3-1）。[10a] すなわち、ジアゾメタン誘導体 **21** 存在下、**5a** からフッ素アニオンによってベンザイン **1a** を発生させ、(3+2) 付加環化反応を行うことで、インダゾール 1 位の窒素上に置換基を持たない 1*H*-インダゾール **20aB** が合成出来ることを報告した。また、Moses らは、イミドイルクロリド **21** から発生させたニトリルイミン **22** と **1a** の付加環化反応によるインダゾール合成法を開発した（Scheme 3-2）。[10b] すなわち、前駆体として **5a** を用いてクラウンエーテル存在下、**21** の MeCN 溶液中、CsF を加えたところ、**1a** 及び **22** の発生とその (3+2) 付加環化反応が同時に進行し、1*H*-インダゾール **23a** が得られた。一方、アジド **9** との (3+2) 付加環化反応が複数の研究グループから報告された（Scheme 3-3）。[11] 本反応を用いれば、温和な条件下、種々の置換基を持つベンゾトリアゾール **10a** を簡便に合成することができる。また Larock らは、系中で発生させたニトリルオキシド **25** やニトロン **27** との (3+2) 付加環化反応を行い、それぞれベンゾイソオキサゾール骨格 **26a**、ベンゾイソオキサゾリン骨格 **28a** を構築できることを報告した（Schemes 3-4 and 3-5）。[12, 13]

注 2: 本論文では、以下のように化合物番号を付ける。まず、ベンザイン類およびその前駆体において、個々の化合物を表記するときには **1a**, **1b** のようにアルファベットの小文字を付記する。また、求ベンザイン

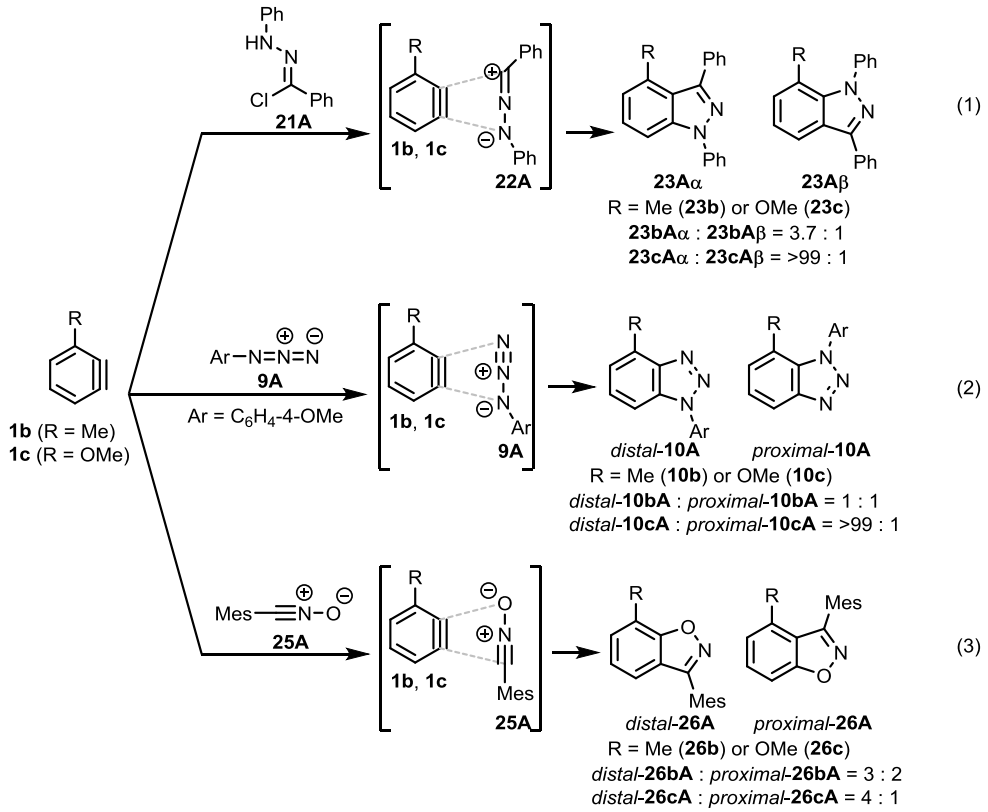
arynophile では、**18A, 18B** のようにアルファベットの大文字を付記する。ベンザインとの反応生成物は **18aA** のように表記する。



Scheme 3. (3+2) Cycloaddition reactions of benzyne **1a**, generated from **5a**, with diazo compounds **18B**, nitrileimines **22**, azides **9**, nitrile oxides **25** and nitrones **27**.

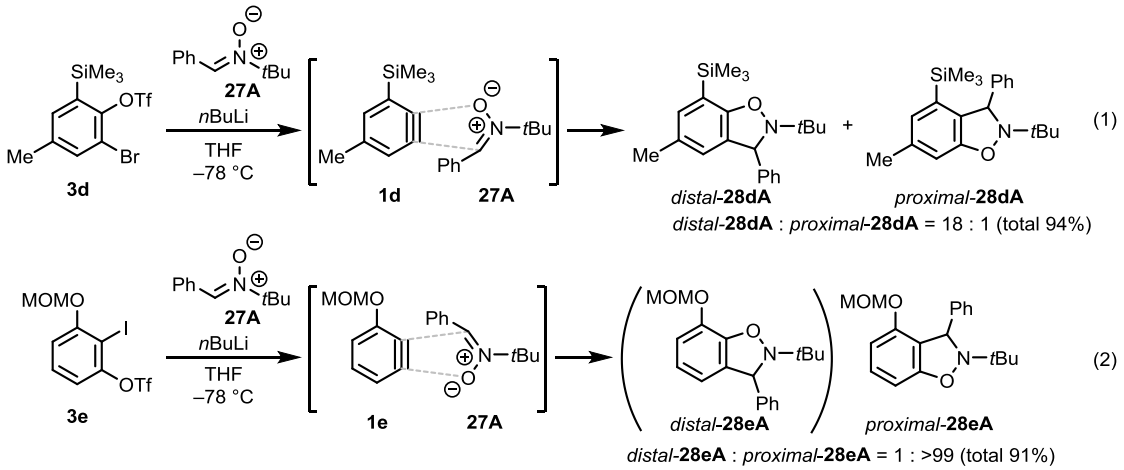
以上のように、ベンザインと 1,3-双極子分子との（3+2）付加環化反応はベンゾ縮合複素環化合物を合成する優れた反応である。しかし、非対称に置換基を有するベンザインの反応では配向選択性が問題となり、多くの場合、分離困難な位置異性体混合物を与える。[14] 例えば、3 位にメチル基が置換したベンザイン **1b** と 1,3-双極子分子 **22A**, **9A** との（3+2)付加環化反応は、2 つの位置異性体 **23bA** α、**23bA** β 及び *distal*-**10A**、*proximal*-**10A** の混合物を生成する（Scheme 4)。[10b, 11d] 一方、3 位にメトキシ基を有するベンザイン **1c** は多くの反応において高い配向選択性を発現する（Schemes 4-1 and 4-2)。[15] これは、酸素置換基の電子求引性誘起効果によりベンザイン反応に関わる 2 つの炭素上 p 軌道の電子密度に大きな差が生じるためと理解出来る。

しかし、Brown らは、**1c** とニトリルオキシド **25A** との (3+2) 付加環化反応は、配向選択性が低いことを報告している（Scheme 4-3)。[12a] この結果は、配向基の電子的な相互作用と、置換基どうしの立体相互作用が相反し、配向選択性が低下したと考えられる。



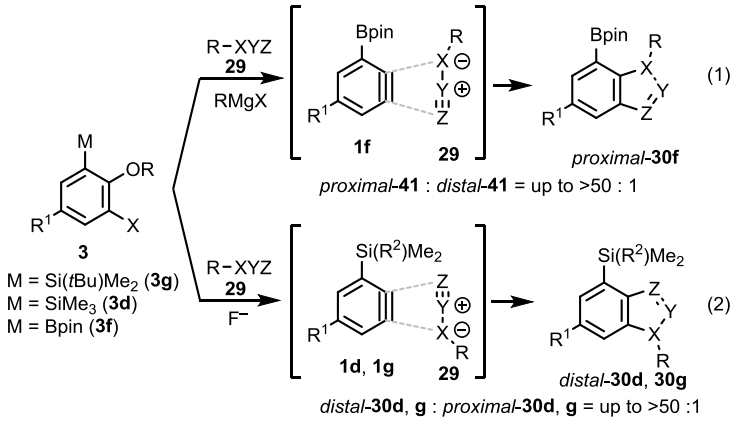
Scheme 4. Reactions of 3-methyl-benzyne **1b** or 3-methoxy-benzyne **1c** with 1,3-dipoles **22A**, **9A** and **25A**.

非対称ベンザインの(3+2) 付加環化反応の位置選択性発現機構に関して新たな知見を与えた研究として、鈴木らは、3 位にケイ素官能基を導入したシリルベンザイン **1d** を前駆体 **3d** から発生させ、ニトロン **27A** と反応させる手法を報告した（Scheme 5-1）。[16a] この反応ではケイ素官能基とニトロンの sp^2 炭素上の置換基が離れた *distal*-**28dA** を選択的に与えた。一方、3-(メトキシメチルオキシ) ベンザイン **1e** を用いると配向性が逆転することから (Scheme 5-2)、シリルベンザインを用いた場合の配向性は、シリル基の電子供与性誘起効果によるものであると理解できる。



Scheme 5. (3+2) Cycloaddition reactions of 3-silylbenzyne **1d** or 3-(methoxymethoxy)benzyne **1e** with nitrone **27A**.

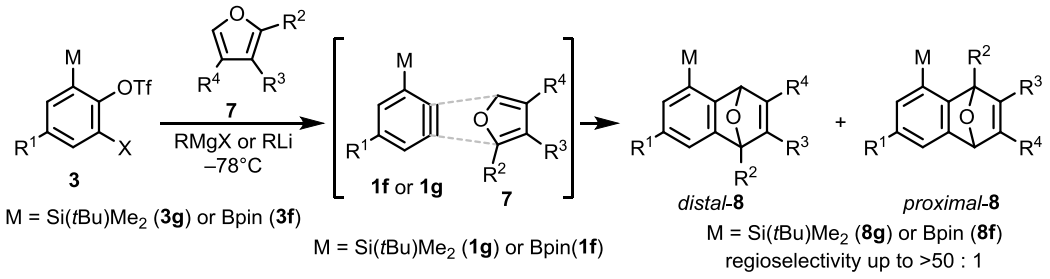
一方、井川、赤井らは、ボリル又はシリルベンザイン **1f**, **1d**, **1g** と多様な 1,3-双極子分子 **29** との (3+2) 付加環化反応における配向制御法を開発した（Scheme 6）。[17] すなわち、アジド、ジアゾ化合物、ニトリルオキシド、ニトロンのいずれの場合においても、(3+2) 付加環化反応は高配向選択的に進行した。また、ケイ素置換ベンザイン **1d**, **1g** とホウ素置換ベンザイン **1f** の付加環化反応における配向選択性は相補的な関係にあり、これら 2 種のベンザインを使い分けることによって両方の位置異性体の作り分けが可能になった。[注 3] また、その他のグループによっても、ホウ素やハロゲン置換基による(3+2)付加環化反応の配向制御法が報告されているが、その詳細は本論第一章で述べる。



Scheme 6. (3+2) Cycloaddition reactions of 3-silylbenzynes **1d**, **1g** or 3-borylbenzynes **1f** with 1,3-dipoles **29**.

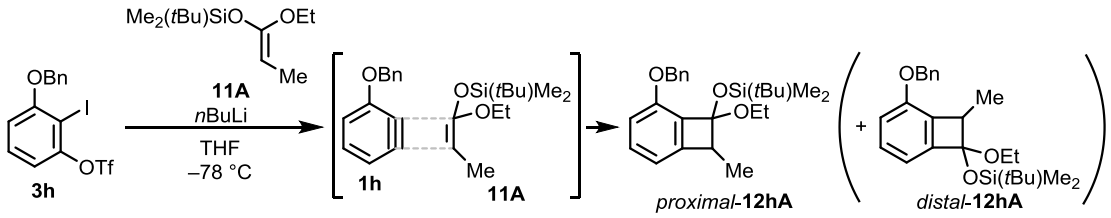
注 3: ホウ素やケイ素配向基によって、(3+2)付加環化反応以外のベンザイン反応も、配向制御が達成さ

れている。井川、赤井らは、3 位にケイ素官能基やホウ素官能基を有するベンザイン **1g**、**1f** を用いるフラン **7** との位置選択的 Diels–Alder 反応を開発した（Scheme 7）。[16b, 18a] これら反応では、基本的に置換基同士が離れた *distal* 環化体を選択的に生成した。



Scheme 7. Diels–Alder reactions of 3-silylbenzynes **1g** or 3-borylbenzynes **1f** with furans **7**.

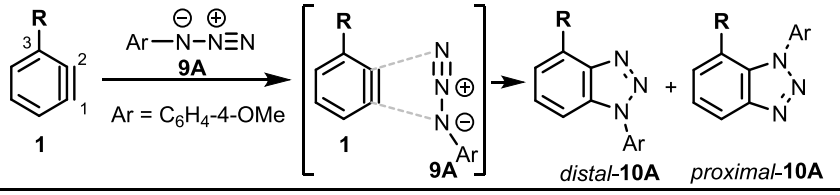
一方、鈴木らはベンザインとシリルエノールエーテルとの反応により、ベンゾシクロブテンを合成出来ることを報告した。[3d] 特に、アルコキシベンザイン **1h** は酸素官能基どうしが隣接する *proximal*-**12hA** を選択的に与えた(Scheme 8)。



Scheme 8. [2+2] Cycloaddition reaction of 3-alkoxy benzyne **1h** and silyl enol ether **11A**.

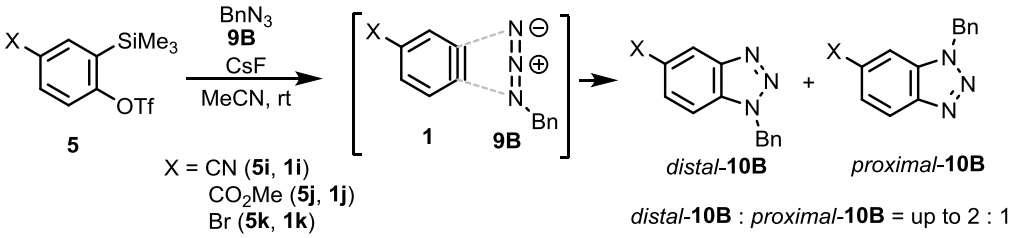
上述した 3 位に置換基を有するベンザインとアジドとの (3+2)付加環化反応において、代表的な置換基が示す配向選択性を Table 1 にまとめた。メチル基を有する場合、50:50 の位置異性体混合物を与える (entry 1)。一方、メトキシ基を有する場合、完全な配向選択性を示すものの (entry 2)、ベンザイン反応後に生成物のメトキシ基を炭素官能基などの他の置換基へと変換することは必ずしも容易ではない。ケイ素 (entry 3)やホウ素官能基 (entry 4)の場合は、高い配向制御が達成され、特にホウ素官能基は *proximal* 体を高選択的に与えた。また、生成物上のケイ素やホウ素は遷移金属触媒を用いるカップリング反応によって、多種類の元素置換基へ変換可能である。そのため、残された課題は、*distal* 体を選択的に与え、且つ変換可能な新たな配向基の開発である。

Table 1. The regioselectivity of (3+2)cycloaddition reactions between 3-substituted benzynes **1** and azide **9A**.



entry	1		10A			
		R		R	*distal* : *proximal*	further transformation of R
1[11d]	**1b**	Me	**10bA**	Me	50 : 50	not easy
2[11d]	**1c**	OMe	**10cA**	OMe	>98 : 2	partly
3[17]	**1d**	$SiMe_3$	**10dA**	$SiMe_3$	85 : 15	partly
4[17]	**1f**	Bpin	**10fA**	Bpin	2 : >98	excellent

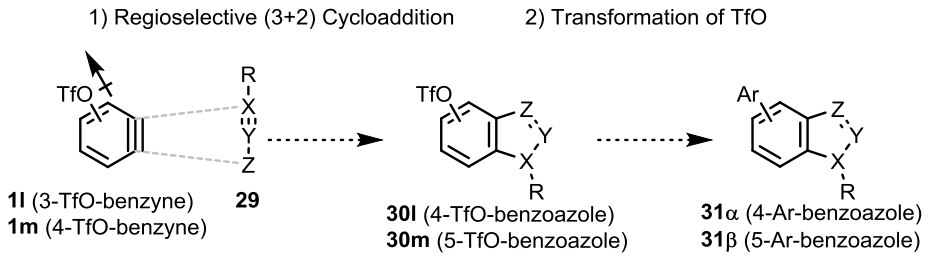
また、三重結合からさらに離れた 4 位の置換基による反応位置制御が複数のグループによって試みられているが、[19] 位置選択性は極めて低い (Scheme 9 にその一例を示す [19h])。



Scheme 9. The regioselectivity of the (3+2) cycloaddition reactions between 4-substituted benzynes **1** and the azide **9B**.

このような背景下、著者はアルコキシ基よりさらに強力な電子求引性を有し、且つ金属触媒反応で変換可能なトリフリルオキシ (TfO) 基を用いてベンザインの反応位置制御を行え

ば、上述の問題を解決出来ると考えた（Scheme 10）。さらに、TfO 基は三重結合の隣接位だけでなく、遠隔位からの反応位置制御も可能になると予想した。TfO 基は多様な官能基へ変換が可能であることから、[20] 本法は生物活性物質の骨格構築の強力な手段として期待できる。

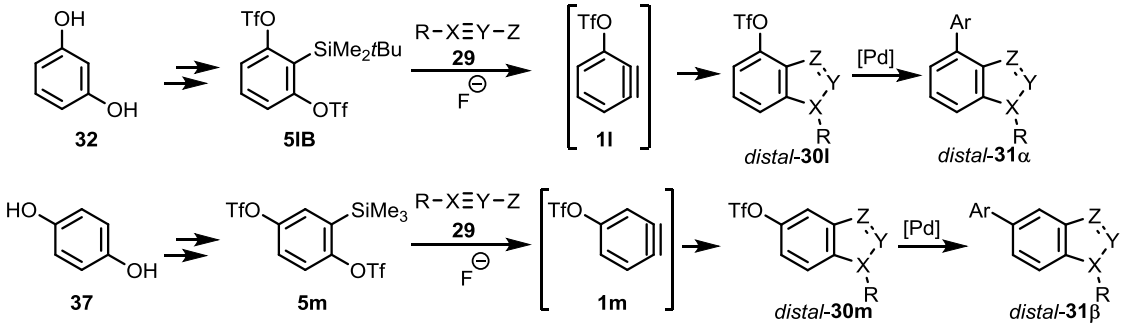


Scheme 10. Concept of this work.

著者は、上記の計画（Scheme 10）に基づいて、TfO ベンザインを活用する縮合複素環の位置制御合成構築に関して研究を行い、 得られた研究成果を 2 つの章にまとめた。

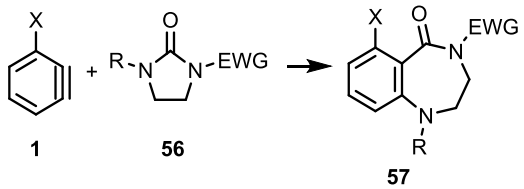
第一章 (トリフリルオキシ) ベンザインの開発とベンゾ縮合複素環の位置制御合成 [21]

TfO ベンザイン **1l**、**1m** の発生に適した前駆体 **5lB**、**5m** を創出した。また、**1l**、**1m** と種々の 1,3-双極子との付加環化反応が既知の置換基よりも高い位置選択性で進行することを見出した。次に、得られた環化体 **30l**、**30m** 上の TfO 基を Pd 触媒反応により炭素置換体 **31α**、**31β** へと変換した。さらに、TfO 基が高い位置制御能を有する理由を計算科学的に解析した。

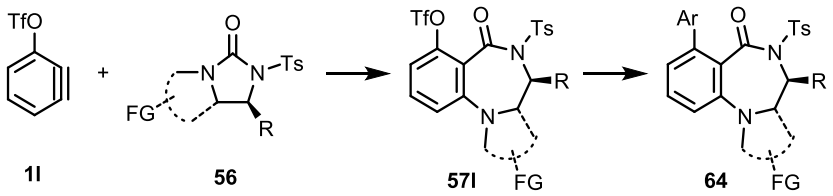


第二章 3-(トリフリルオキシ) ベンザインとイミダゾリジノン誘導体を用いたベンゾジアゼピンの位置制御合成法の開発 [22]

多様な置換基 X を有するベンザイン **1** とイミダゾリン-2-オン類を用いて、ベンゾジアゼピンを単一の位置異性体として合成する方法を検討した。その結果、2 つの窒素原子上に各々アルキル基とトシル (Ts) 基を持つイミダゾリン-2-オン類 **56** と、X として TfO 基を有するベンザインの組み合わせが、反応の進行及び位置選択性に必須であることを見出した。



また、TfO ベンザイン **1l** と Ts 基を有する様々なイミダゾリン-2-オン **56** を用いて、多様なベンゾジアゼピン **57l** を合成した。得られた **57l** は Pd 触媒反応によって **64** へと変換した。さらに、本反応の反応機構を計算科学的に解析した。



本　　論

第一章 （トリフリルオキシ）ベンザインの開発とベンゾ縮合複素環の位置制御合成

総論にて論述したように、ベンザインの (3+2) 付加環化反応は、生物活性物質の活性発現に極めて重要なベンゾ縮合複素環化合物を一挙に合成できるため、有用な反応の 1 つである。しかし、非対称なベンザイン **1** を反応に用いた場合、その配向選択性が低く、分離困難な位置異性体混合物 *distal*-**31** α 、*proximal*-**31** α を与えることが多い (Fig. 1-1)。[14] 一方、3 位に MeO 基を有するベンザイン **1c** はしばしば高い配向選択性を発現する (Fig. 1-2)。[15] また、3 位にシリルやホウ素官能基を有するベンザイン **1d** (M = $SiMe_3$)、**1f** (M = B(pin))は MeO 基と逆向きの配向選択性を発現することが多い (Fig. 1-3)。これらの結果から、ベンザイン上の置換基が持つ誘起効果が配向選択性に大きな影響を及ぼしていると考えられる。[16–18] 誘起効果の小さいアルキル基やアリール基を有するベンゾ縮合複素環を合成する場合、シリル、ホウ素ベンザイン **1d**、**1f** で反応位置制御をした後、生成物 **30d**、**30f** 上に残されたこれらの官能基を金属触媒反応でアルキル基やアリール基に変換することで解決することが出来る。一方、3-アルコキシベンザインで、3-シリルや 3-ホウ素ベンザインと逆の配向制御を行った場合、生成物上に残されたアルコキシ基の変換は容易でないため、上記問題の解決策にはならない。そのため、アルコキシ基と同様に電子求引性誘起効果を有し、且つ金属触媒反応によって変換が可能な新しい配向基の開発が必要である。そこで本章で著者は、

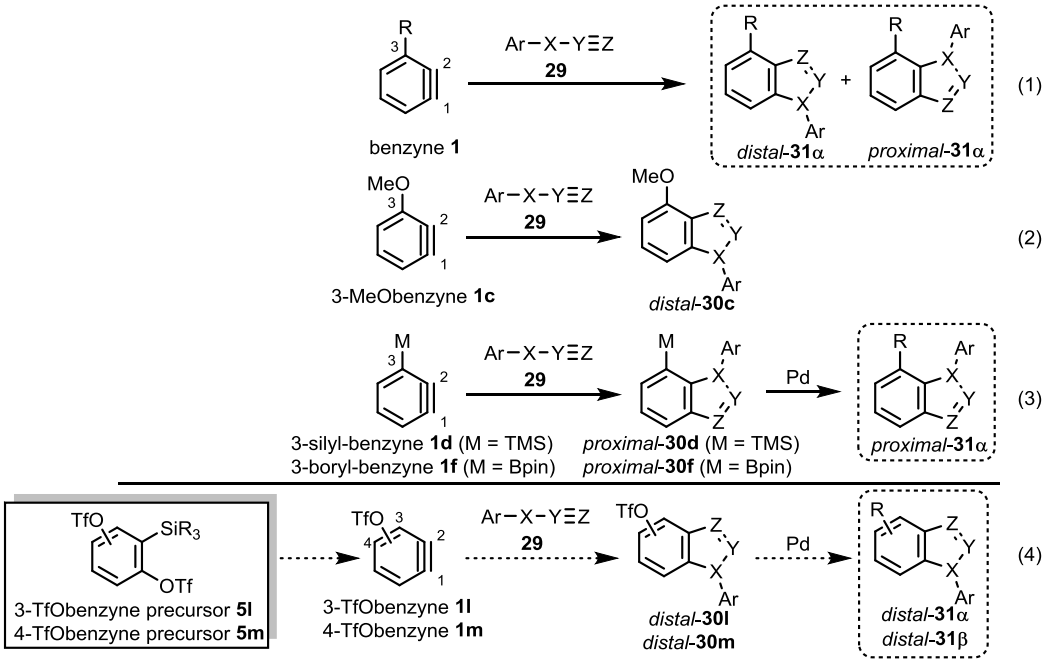
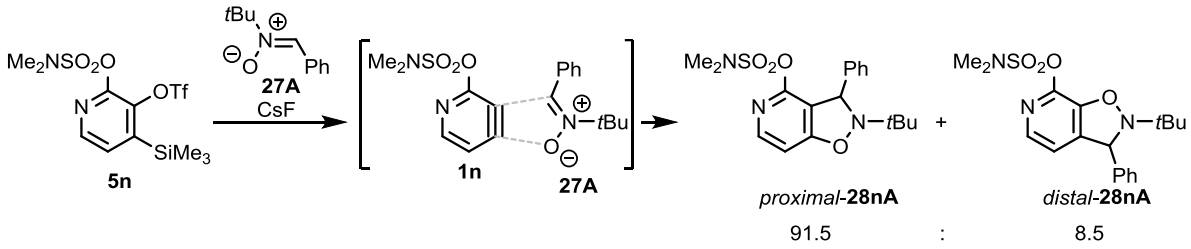


Figure 1. Concept of regiocontrolled reactions of TfO-benzynes **1l**, **1m** with 1,3-diploles **29** and design of TfO-benzyne precursors **5l**, **5m**.

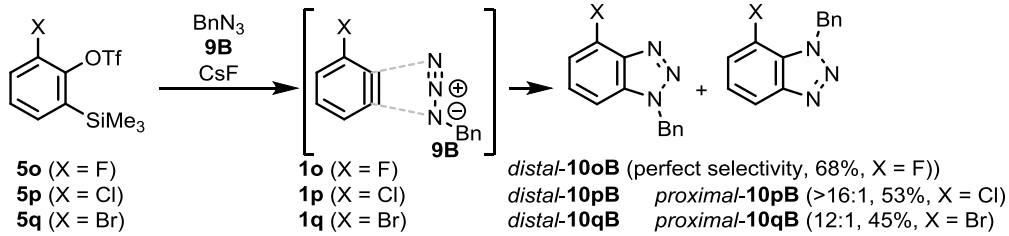
金属触媒反応によって変換容易なトリフリルオキシ (TfO)基が上述の目的に適う配向基になると考え、3 位または 4 位に TfO 基を有するベンザイン **1l**、**1m** を用いる配向制御法の開発に着手した (Fig. 1-4)。[注 4]

注 4: 著者が本研究を開始した 2013 年に Garg らは、電子求引性誘起効果を有するスルファモイルオキシ (Me_2NSO_2O)基を有するアザベンザイン **1n** を発生し、配向選択的な (3+2)付加環化反応を達成した (Scheme 11)。[23a] また、生成物 **28nA** 上の Me_2NSO_2O 基は Ni 触媒反応によって炭素官能基へと変換が可能であるが、Ni 触媒を用いた変換反応は Pd 触媒を用いた変換反応より基質適用性が低い。[24]



Scheme 11. (3+2) Cycloaddition reaction of 2-Me_2NSO_2O-azabenzyne **1n** and nitrone **27A**.

また、ハロベンザインによる反応位置制御も多くのグループによって研究されており、[26] 中でもフルオロベンザイン **1o**、クロロベンザイン **1p** は高い配向選択性を発現することが報告された (Scheme 12)。[26j] しかし、酸素官能基を配向基として用いる場合と比較し、ベンザイン前駆体 **5o, 5p** の合成が難しい。

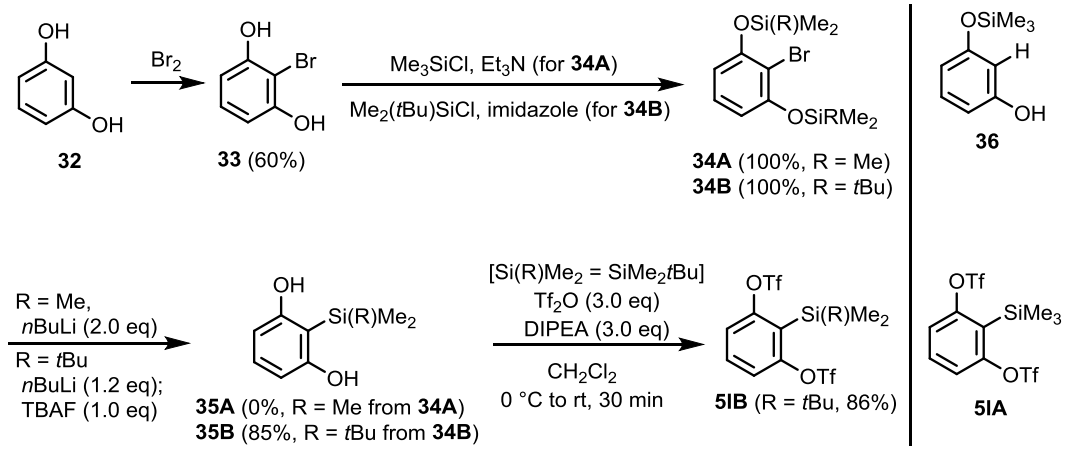


Scheme 12. (3+2) Cycloaddition reaction of 3-halobenzynes **1o**, **1p** and **1q** and benzyl azide **9B**.

第一節 （トリフリルオキシ）ベンザイン前駆体の合成

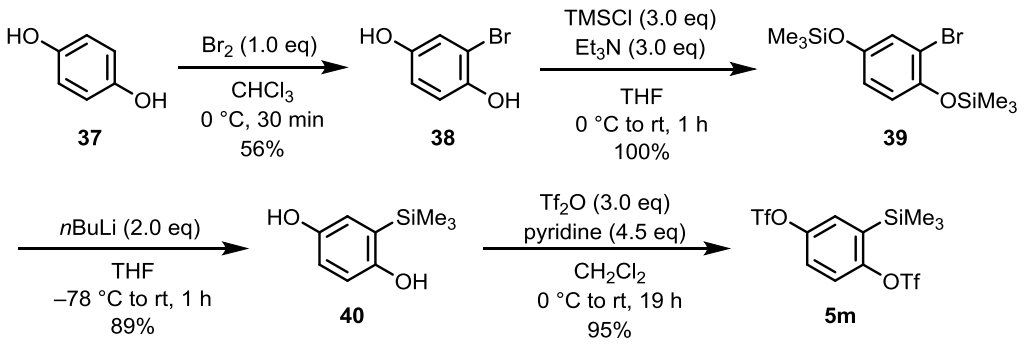
著者は、3 位又は 4 位に TfO 基を有するベンザイン **1l**, **1m** を発生させるベンザイン前駆体 **5l** 及び **5m** を設計した（Figure 1-4）。これら **5l** 及び **5m** はフッ素アニオンを用いた温和な条件下、TfO-ベンザイン **1l**, **1m** へと変換できるため幅広い反応に適用可能と考えられた。

レゾルシノール **32** を出発原料とし、前駆体 **5l** の合成を試みた（Scheme 13）。まず、臭素を用いて **32** から 2-ブロモレゾルシノール **33** を得た。[27, 28] 次に、トリメチルシリル基を有する前駆体 **5lA** の合成を目指して、2 つのフェノール性水酸基をトリメチルシリル化後、ブチルリチウムによるハロゲン-リチウム交換の後に retro-Brook 転位反応を試みた。しかし、目的とする化合物 **35A** は全く得られず、**36** が主生成物として得られた。[29] そこで、**33** により安定な TBDMS 基を導入した後、retro-Brook 転位とそれに引き続く水酸基上のシリル基の脱保護を行ったところ、収率 85%で **35B** を合成することができた。最後に、**35B** の 2 つの水酸基をトリフルオロメタンスルホン酸無水物によりビストリフラート化することで、目的のベンザイン前駆体 **5lB** を合成した。



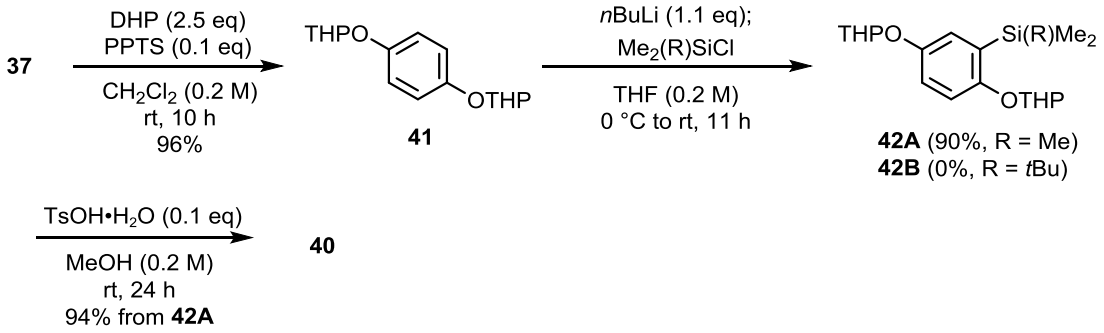
Scheme 13. Synthesis of a 3-TfO-benzyne precursor **5lB**.

次に、ヒドロキノン **37** を出発原料とし、4-TfO-ベンザイン前駆体 **5m** の合成を試みた（Scheme 14）。まず、**37** のモノブロモ化により **38** を合成した。[30, 31] 続いて 2 つの水酸基をトリメチルシリル化後、retro-Brook 転位により **40** へと変換した。[32] 最後に、**40** のビストリフラート化によって **5m** を合成した。



Scheme 14. Synthesis of a 4-TfO-benzyne precursor **5m**.

しかし、上記合成ルートは最初の **38** の収率が低く、且つ副生するジブロモ体の位置異性体混合物との分離が容易でなかった。そこで、**40** の改良合成法を考案した（Scheme 15）。まず、**37** の 2 つの水酸基が THP 基で保護されたヒドロキノン **41** を合成した。次に、ブチルリチウムを用いたオルトリチオ化[33] の後、TMSCl にてトラップすることで、トリメチルシリル基が 1 つ導入された **42A** を得た。最後に、THP 基を脱保護し、**40** を合成した。この手法により大量スケールでの **5m** の合成が可能となった。同様にして、**5m** の TMS 基を TBDMS 基に置き換えた前駆体の合成を試みたが、**41** への TBDMS 基の導入は全く進行しなかったので断念した。



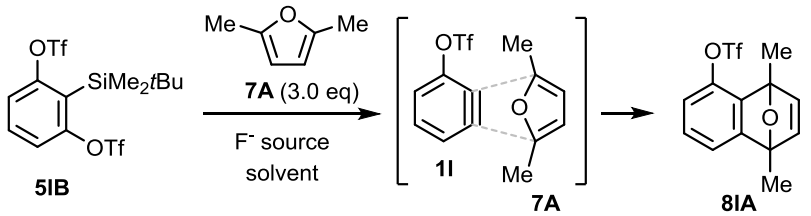
Scheme 15. An alternative route for the synthesis of 2-(trimethylsilyl)dihydroquinone **40**.

第二節　3-(トリフリルオキシ) ベンザインの発生と (3+2)付加環化反応の配向選択性

過去に 3-TfO-ベンザイン **1l** を発生させた前例が皆無だったため、[注5] 本節ではまず、第一節にて合成した新規ベンザイン前駆体 **5lB** から **1l** の発生の可否と、その最適な発生条件を調査した。なお、ベンザインは非常に不安定で単離することが出来ないため、ジメチルフラン **7A** との Diels–Alder 反応でその発生を検出した（Table 2）。すなわち、3 当量の **7A** の存在下、**5lB** の溶液中にフッ素アニオンを加え、撹拌した。その結果、Bu_4NF (TBAF)を用いた場合には、目的の付加環化体 **8lA** は全く生成しなかったが（entry 1）、CsF をフッ素源として用いること

で、**8lA** を得ることができた（entry 2）。さらに、減圧下、加熱乾燥した CsF と **7A** の MeCN 溶液中に、室温で前駆体 **5lB** の MeCN 溶液を加えたとき、最も効率よく **1l** が発生し、**8lA** を収率 79%で与えた（entry 3）。従って、この反応条件を **1l** 調製の最適条件とし、次に 1,3-双極子分子との (3+2)付加環化反応を検討した。

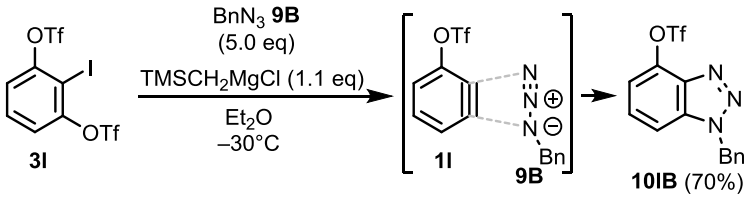
Table 2. Diels–Alder reactions of 3-TfO-benzyne **1l** and 2,5-dimethylfuran **7A**.



entry	F⁻ source	solvent	temp	time (h)	Isolated yield (%) of **8lA**
1	TBAF (1.0 eq)	THF	0 °C	0.5	0
2	CsF (3.0 eq)	MeCN	60 °C	1	56
3	CsF (3.0 eq)[a]	MeCN	rt	3	79

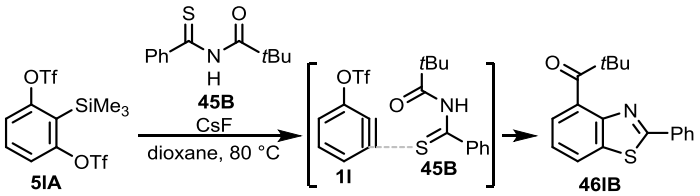
[a]CsF was dried over a flame under reduced pressure 1 mmHg before use.

注 5: 著者が第一章の成果を論文発表した直前に、細谷らも 3-TfO ベンザイン **1l** の発生とアジドとの(3+2)付加環化反応を報告した。なお、彼らは、**3l** を前駆体とし、trimethylsilylmethyl Grignard 反応剤を用いて **1l** を発生した（Scheme 16）。[24a]



Scheme 16. Hosoya's related work.

その後の 2015 年、Shi らは前駆体 **5lA** に CsF を反応させて 3-TfO ベンザインを発生し、チオアミド **45B** とのドミノ型反応を報告した (Scheme 17)。[24b]

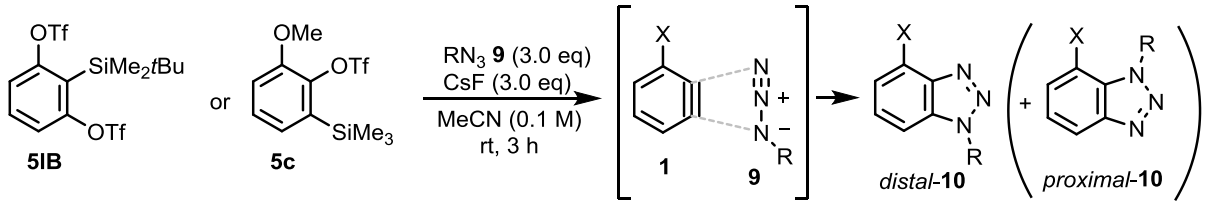


Scheme 17. Domino benzyne reaction of 3-TfO benzyne **1l** and thioamide **45B**.

また、その後、細谷らおよび Shi らは 3-TfO ベンザインを用いたジアミノ化反応、3 成分反応などを報告した。[24c-f]

まず、**1l** とアジド化合物 **9** との (3+2) 付加環化反応を検討した（Table 3）。すなわち、アルゴン雰囲気下、MeCN 中、3-TfO-ベンザイン前駆体 **5lB** と種々のアジド **9** と CsF を室温で攪拌した。その結果、反応系中で発生した **1l** と **9** との (3+2) 付加環化反応が進行し、ベンゾトリアゾール *distal*-**10l** を生成した。なお、配向選択性は **9** の置換基 R によらず、いずれの場合も *distal* 体のみが得られた（entries 1–4）。この高い配向選択性は、3-MeO-ベンザイン **1c** をアジドとの反応に用いた場合とほぼ同等の結果である (entry 5)。[11a]

Table 3. (3+2) Cycloaddition reactions of 3-TfO-benzyne **1l** or 3-MeO-benzyne **1c** with azides **9**.

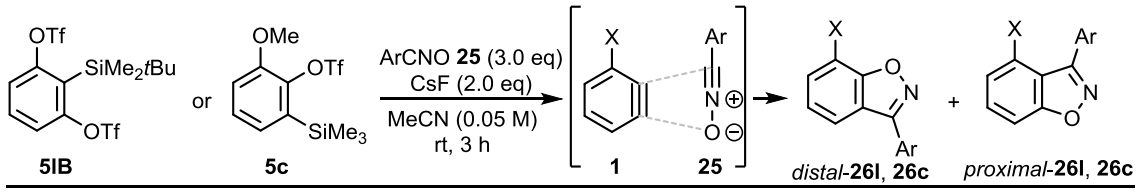


entry	5	1		9		10				
			X		R		X	R	*distal* : *proximal*[b]	yield (%)[c]
1	**5lB**	**1l**	OTf	**9A**	C_6H_4-4-OMe	**10lA**	OTf	C_6H_4-4-OMe	>98 : 2	48
2	**5lB**	**1l**	OTf	**9B**	Bn	**10lB**	OTf	Bn	>98 : 2	74
3	**5lB**	**1l**	OTf	**9C**	$CH_2C_6H_4$-4-NO_2	**10lC**	OTf	$CH_2C_6H_4$-4-NO_2	>98 : 2	70
4	**5lB**	**1l**	OTf	**9D**	Cyclohexyl	**10lD**	OTf	Cyclohexyl	>98 : 2	63
5	**5c**[a]	**1c**	OMe	**9B**	Bn	**10lB**	OMe	Bn	>98 : 2	78[d]

[a]1.2 eq of **5c** and 2.0 eq of CsF were used. [b]Determined by ^{1}H NMR analysis of a crude product. [c]Isolated yield of *distal*-**10**. [d]The yield is based on **9B**.

次に、ニトリルオキシド **25** との（3+2）付加環化反応を検討した。まず、嵩高く安定なニトリルオキシド **25A-C** を事前に調製した。[34] そしてアルゴン雰囲気下、MeCN 中、ベンザイン前駆体 **5lB** と **25A-C** と CsF を室温で攪拌した（Table 4）。その結果、系内で発生した **1l** と **25** との (3+2) 付加環化反応が配向選択的に進行し、TfO 基を有する *proximal*-**26l** を生成した（収率65～77%）。このとき、いずれの **25** を用いた場合にも *proximal*-**26l** のみが生じ、*distal*-**26l** は全く観測されなかった（entries 1–3）。次に、**25A** を用いて 3-MeO-ベンザイン **1c** との付加環化反応を行ったところ、20:80 の比で付加環化体 *distal*-**26cA** と *proximal*-**26cA** を与えた（entry 4）。以上の結果より、ベンザインの (3+2) 付加環化反応において、トリフリルオキシ基は、メトキシ基よりも強力な配向基として働くことが明らかになった。

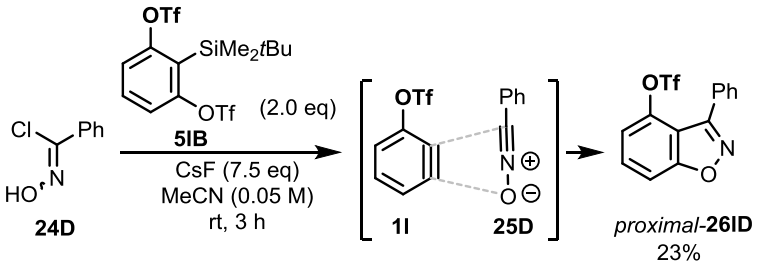
Table 4. (3+2) Cycloaddition reactions of 3-TfO-benzyne **1l** or 3-MeO-benzyne **1c** with nitrile oxides **42**.



entry	5	1		25	Ar	26l, 26c			
			X				X	*distal* : *proximal*[a]	yield (%)[b]
1	**5lB**	**1l**	OTf	**25A**	C_6H_2-2,4,6-Me_3	**26lA**	OTf	<2 : 98	77
2	**5lB**	**1l**	OTf	**25B**	C_6H_2-2,4,6-OMe_3	**26lB**	OTf	<2 : 98	69
3	**5lB**	**1l**	OTf	**25C**	C_6H_2-2,4-OMe_2-6-Me	**26lC**	OTf	<2 : 98	65
4	**5c**	**1c**	OMe	**25A**	C_6H_2-2,4,6-Me_3	**26cA**	OMe	20 : 80	67

[a]Determined by ^{1}H NMR analysis of a crude product. [b]Isolated yield of *proximal*-**26l** or **26c**.

一方、フェニル上に置換基がないニトリルオキシド **25D** をベンザインと共に系中で発生させ、 (3+2)付加環化反応を行う手法も Larock らによって報告されている。[12a] そこで著者も同様に、クロロオキシム **24D** を原料とし、2 当量のベンザイン前駆体 **5lB**、7.5 当量の CsF を MeCN 中撹拌したところ、低収率ながら TfO 基を有するベンゾイソオキサゾール *proximal*-**26lD** を合成することが出来た (Scheme 18)。さらにその配向選択性は完全であり、この場合においても TfO 基による反応位置制御が可能であることが分かった。なお、低収率の原因は、**25D** が系中に発生する前に **1l** が発生し、分解してしまったためだと考えられる。



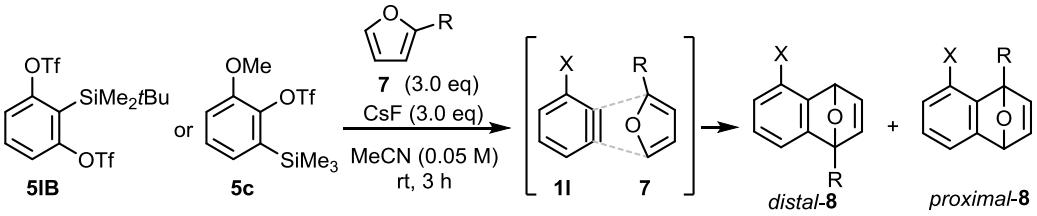
Scheme 18. (3+2) Cycloaddition reactions of 3-TfO-benzyne **1l** with nitrile oxide **25D**, generated from chloro oxime **24D**.

第三節　3-(トリフリルオキシ) ベンザインと他の求ベンザイン体との反応

このような高い反応位置制御能力を有するTfOベンザイン**1l**の、ベンゾ縮合複素環以外の化合物合成への適用を検討した。ベンザインとフランとのDiels–Alder反応は、ナフタレン骨格を構築する優れた反応として重要である。[3a–3c] 特に、3-(アルコキシ)ベンザイン**1c**と2-メトキシフラン**7C**との[4+2]付加環化反応は、*proximal*-**8cC**のみを与える（Table 5, entry 1）[3b] ため、しばしば天然物の全合成に利用されてきた。[35] そこで、著者も**1l**と非対称フラン**7**との [4+2]付加環化反応を検討した (entries 3~6)。すなわち、非対称フラン**7C**, **7D**, **7E**と共に、**5lB**とCsFをMeCN中、室温で攪拌した。その結果、いずれの場合も3-TfO-ベンザイン**1l**と**7**とのDiels–Alder反応生成物**8l**を収率71～86％で与えた。しかし、配向選択性は低く、特に**7C**との付加環化反応では、*distal*-**8lC** と*proximal*-**8lC** を 21 : 79の比で生じ（entry 5）、これは3-MeO-ベンザイン**1c**と反応させた場合の選択性（entry 1, *distal*-**8cC** : *proximal*-**8cC** = <2 : 98）より低かった。これらの結果は、電子的な効果と置換基どうしの立体反発による効果が相反したためと考えられる。そこで、よりかさ高い*t*Bu基を有するフラン**7B**を本反応に適用したところ、*distal*体**8lB**の生成比が増加した（entry 6）。この結果は、3-MeOベンザイン**1c**と**7B**の反応で*proximal*体**8cB**が主生成物となる結果 (entry 2) とは対照的である。

以上の結果より、TfOベンザイン**1l**はフラン**7**とのDiels-Alder反応において、置換基どうしの立体反発が顕著に表れるため、電子的な効果を凌駕し、配向選択性が低下することが分かった。

Table 5. Diels–Alder reactions of 3-TfO-benzyne **1l** with furans **7**.

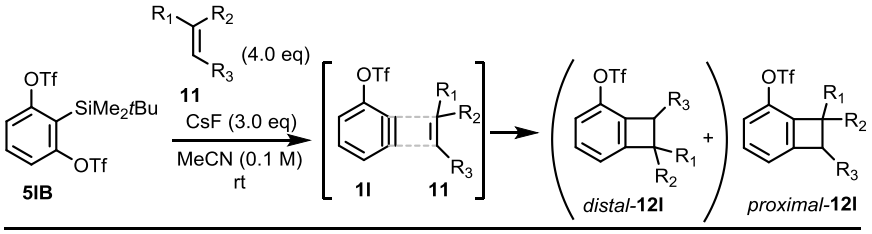


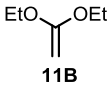
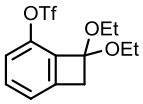
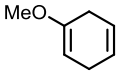
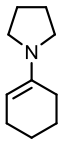
entry	5	1		7		8				
			R		R		X	R	*distal* : *proximal*[a]	yield (%)[b]
1	**5c**	**1c**	OMe	**7C**	OMe	**8cC**	OMe	OMe	<2 : 98	75[(ref:3b)]
2	**5c**	**1c**	OMe	**7B**	*t*Bu	**8cB**	OMe	*t*Bu	15 : 85	34[(ref:3c)]
3	**5lB**	**1l**	OTf	**7D**	*n*Bu	**8lD**	OTf	*n*Bu	38 : 62	81
4	**5lB**	**1l**	OTf	**7E**	Ac	**8lE**	OTf	Ac	46 : 54	71
5	**5lB**	**1l**	OTf	**7C**	OMe	**8lC**	OTf	OMe	21 : 79	85
6	**5lB**	**1l**	OTf	**7B**	*t*Bu	**8lB**	OTf	*t*Bu	75 : 25	86

[a]Isolated product ratio. [b]Total isolated yield of *distal*-**8** and *proximal*-**8**.

続いて、電子豊富アルケンとの[2+2]付加環化反応を検討した (Table 6)。アルゴン雰囲気下、MeCN中、**5lB**より発生させた3-TfOベンザイン**1l**と、ケテンアセタール**11B**を反応させると、TfO基を有する置換ベンゾシクロブテン*proximal*-**12lB**が単一の位置異性体として得られた。一方、エノールエーテル**11C**、エナミン**11D**との反応は複雑化した。以上の結果から、TfOベンザインの [2+2]付加環化反応には、更なる検討が必要である。

Table 6. [2+2] Cycloaddition reaction of 3-TfO-benzyne **1l** with olefins **11**.



entry	11	12l		
		Product	*distal* : *proximal*[a]	yield (%)[b]
1	 **11B**	 **12lB**	<2 : 98	72%
2	 **11C**		complex mixture	
3	 **11D**		complex mixture	

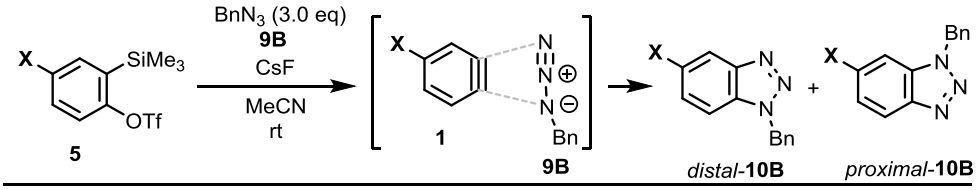
[a]Determined by ^{1}H NMR analysis of a crude product. [b]Isolated yield of *proximal*-**12l**.

第四節　4-(トリフリルオキシ) ベンザインの発生と(3+2)付加環化反応の配向選択性

一般的に、三重結合から離れた 4 位に置換基を有するベンザインの反応は配向選択性を発現しにくいことが知られている。[19、注 6]

さらに、過去に報告されたベンザイン **1** とベンジルアジド **9B** の(3+2)付加環化反応の結果を Table 7 にまとめた。[19h] この Table より、メトキシ基[注 7] やメトキシカルボニル基は、4 位では全く配向基として機能しないが（entries 1 and 2）、シアノ基やブロモ基では、約 2 : 1 の選択性を生じることが分かる（entries 3 and 4）。著者は、強力な電子求引性を有し、3 位で高い配向選択性を発現したトリフリルオキシ（TfO）基なら、4 位においても高い配向選択性が期待出来ると考えた。

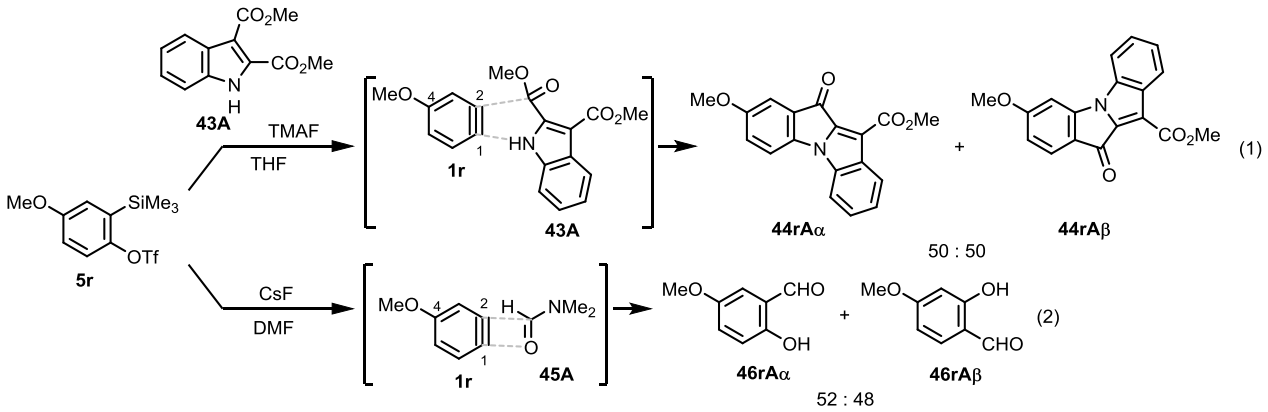
Table 7. (3+2) Cycloaddition reactions of 4-substituted benzynes **1** and benzyl azide **9B**.



entry	5	1	X	10B			ref
					distal : *proximal*[b]	yield (%)	
1	**5r**	**1r**	OMe	**10rB**	52 : 48	80	–[c]
2	**5j**	**1j**	CO_2Me[a]	**10jB**	50 : 50	67	19)
3	**5i**	**1i**	CN[a]	**10iB**	67 : 33	65	19)
4	**5k**	**1k**	Br[a]	**10kB**	67 : 33	70	19)

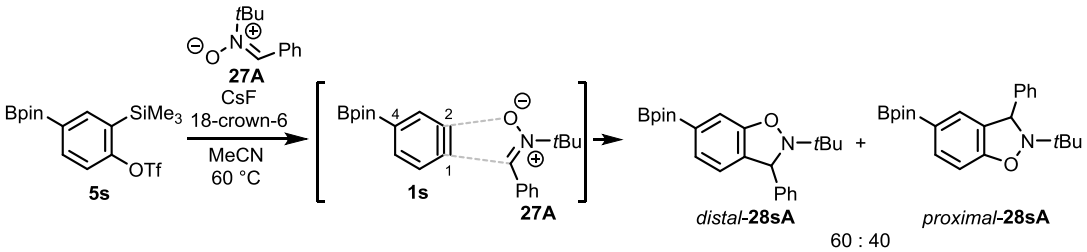
[a]A regioisomer mixture of 4- and 5-substituted material was used as a benzyne precursor.
[b]Determined by ^{1}H NMR. [c]Our result.

注 6: 総論や第一章の導入部分にて論述したように、3 位の MeO 基はベンザインの配向制御に極めて有効であるが 4 位の MeO 基は殆ど効果を発揮せず、多くの反応でほぼ 1:1 の位置異性体混合物となる (Scheme 19)。[19a, 19b]



Scheme 19. Cycloaddition reactions of 4-methoxybenzyne **1r**.

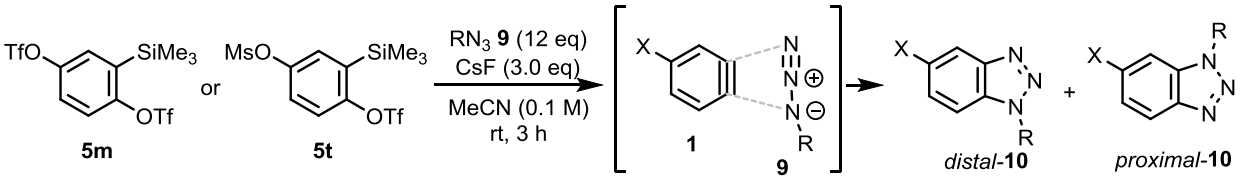
また、4-ホウ素置換ベンザイン **1s** の反応が Pilarski によって精力的に研究されているが、同様に選択性をほとんど発現しない (Scheme 20)。[18d, 18f]



Scheme 20. (3+2) Cycloaddition reaction of 4-borylbenzyne **1s** and nitrone **27A**.

そこで、第一節にて合成した 4-TfO-ベンザイン前駆体 **5m** を、アジド **9B** 、CsF とともに MeCN 中室温で攪拌したところ､系内で 4 位に TfO 基を有するベンザイン **1m** を発生し､(3+2) 付加環化反応が進行して TfO-ベンゾトリアゾールの位置異性体混合物 *distal*-**10mB**、*proximal*-**10mB** を 75:25 の比で与えた（Table 8, entry 1）。この配向選択性は、過去に報告された 4 位置換ベンザインの (3+2) 付加環化反応（Scheme 20, Table 7）の中で最も高かった。次に、酸素原子上のトリフリル基の効果を調べるために、4 位に MsO 基を有する **1t** [注6] で同様の反応を行った。その結果、TfO 基とほぼ同等の 72 ： 28 の比で **10tB** の位置異性体混合物を生成した（entry 2）。この結果と Table 7, entry 1、Table 8, entry 1 の結果を合わせて考える

Table 8. (3+2) Cycloaddition reactions of 4-TfO-benzyne **1m** and azides **9**.

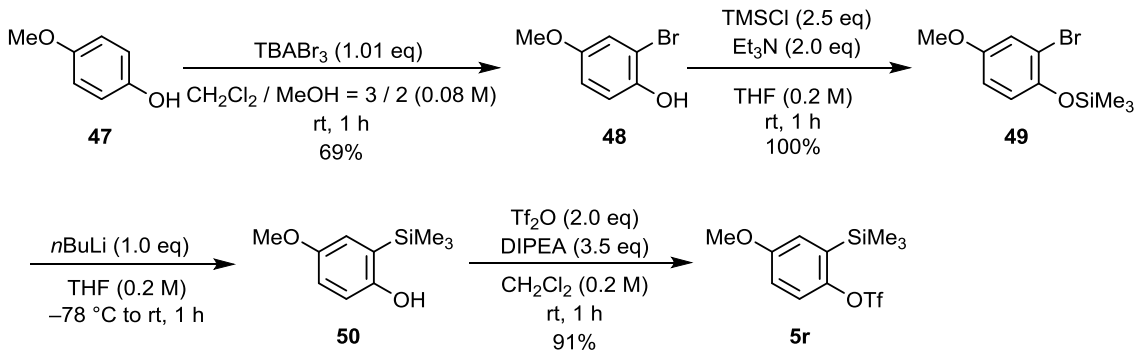


entry	5	1		9		10				
			X		R		X	R	*distal* : *proximal*[b]	yield (%)[c]
1	**5m**	**1m**	OTf	**9B**	$C_6H_4CH_2$	**10mB**	OTf	$C_6H_4CH_2$	75 : 25	60
2	**5t**	**1t**	OMs	**9B**[a]	$C_6H_4CH_2$	**10tB**	OMs	$C_6H_4CH_2$	72 : 28	65
3	**5m**	**1m**	OTf	**9A**	*p*-MeO-C_6H_4	**10mA**	OTf	*p*-MeO-C_6H_4	76 : 24	61
4	**5m**	**1m**	OTf	**9C**	*p*-NO_2-$C_6H_4CH_2$	**10mC**	OTf	*p*-NO_2-$C_6H_4CH_2$	77 : 23	53
5	**5m**	**1m**	OTf	**9D**	cyclohexyl	**10mD**	OTf	cyclohexyl	76 : 24	60

[a]3.0 eq of azide **9B** was used. [b]Isolated product ratio. [c]Total isolated yield of *distal*-**10** and *proximal*-**10**.

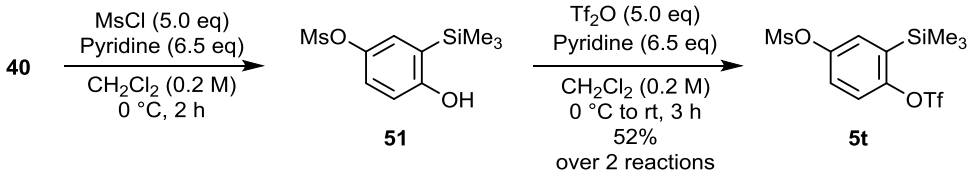
と、電子求引性スルホニル基とトリフルオロメチル基が配向選択性発現に重要な役割を果たしていることが明確になった。さらに、**1m** との反応に他のアジド **9A**、**9C**、**9D** を用いた場合でも約 3:1 の比で TfO-ベンゾトリアゾール **10m** の位置異性体混合物を与えた (entries 3~5)。

注 7: 4-MeO ベンザイン前駆体 **5r** は *p*-MeO フェノール **47** から 4 工程で合成した（Scheme 21）。



Scheme 21. Synthesis of 4-MeO-benzyne precursor **5r**.

4-MsO ベンザイン前駆体 **5t** は **5m** の合成中間体 **40** から 2 工程で合成した (Scheme 22)。

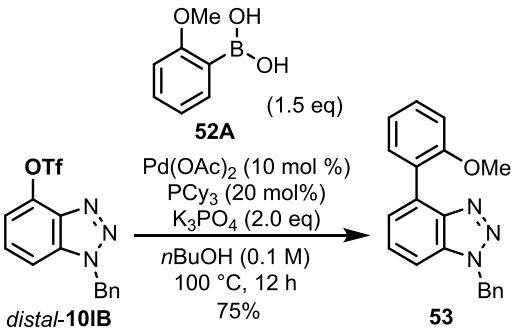


Scheme 22. Synthesis of 4-MsO-benzyne precursor **5t**.

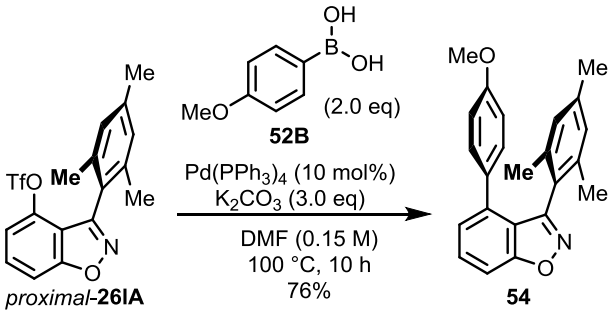
第五節　生成物上の官能基変換

総論で述べたように、誘起効果の小さいアルキル基やアリール基が3位に結合したベンザインの反応位置制御を行うことは困難である。しかし、TfO基で反応位置制御を行なった後、金属触媒反応によって官能基変換を施すことで、実質、これらの炭素置換基によって反応位置制御したことと同じ結果を得ることが出来る。

そこで、第二節で得た環化体（*distal*-**10lB**, *proximal*-**26lA**）において、トリフリルオキシ (TfO) 基からアリール基への変換を試みた。その結果、$Pd(OAc)_2$, PCy_3, K_3PO_4存在下、環化体*distal*-**10lB**とボロン酸**52A**のブタノール溶液を、100 °Cにて12時間加熱撹拌することで鈴木カップリングが良好に進行し、4位にアリール基が導入されたベンゾトリアゾール**53**を75%の収率で合成することができた（Scheme 23）。また、より立体的に込み合った*proximal*-**26lA**の場合は、触媒として$Pd(PPh_3)_4$を用いることで、4位にアリール基を有するベンゾイソキサゾール**54**が収率76%で得られた（Scheme 24）。



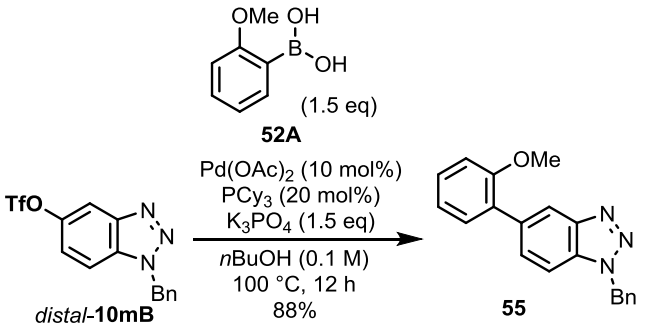
Scheme 23. Suzuki-coupling reaction of *distal*-**10lB**.



Scheme 24. Suzuki-coupling reaction of *proximal*-**26lA**.

さらに、第三節で得た環化体*distal*-**10mB**についても同様に官能基変換を試みた。その結果、$Pd(OAc)_2$, PCy_3, K_3PO_4存在下、環化体*distal*-**10mB**とボロン酸**52A**のブタノール溶液を、100 °Cにて12時間加熱撹拌することで鈴木カップリングは良好に進行し、5位にアリール基が導入さ

れたベンゾトリアゾール**55**を88%の収率で合成することができた（Scheme 25）。



Scheme 25. Suzuki-coupling reaction of *distal*-**10mB**.

このように、配向選択的ベンザイン反応と続く官能基変換は、本来困難な炭素官能基を用いた配向制御を可能にしたことと同じ意味をなしており、本法の有用性を示すことができた。

第六節　配向選択性発現機構の計算科学的解析

ベンザイン反応について、これまでに数多くの計算科学的反応解析の研究が報告されてきた。その主な手法を Figure 2 にまとめた。古典的かつ最も広く利用されてきた手法として、電荷支配モデル (Figure 2-(i))と立体障害モデル (Figure 2-(ii))の組み合わせが挙げられる。[36] 電荷支配モデルは、電子豊富な求核剤がベンザインの正に帯電した三重結合炭素へ求核攻撃すると考えるモデルであるが、ベンザイン上の置換基（M）によって生じる炭素上の電荷は極めて小さいため、配向選択性発現の起源になりうるのか、さらに、三次元的な広がりを持たない三重結合炭素上の点電荷がベンザインの反応性を正確に反映しているかは大いに疑問である。一方、立体障害モデルは、直感的に理解しやすいモデルではあるが、定量的に評価することは難しく、また、説明出来ない反応例も数多く存在する。

一方、著者の研究室では立教大学理学部の常盤研究室と共同で、natural bond orbital (NBO) 解析 [37] を用いて、ベンザインの反応性 *p* 軌道の電子密度を計算する軌道電子密度モデル (Figure 2-(iii))を提案し、立体障害モデルとの組み合わせによりベンザインの配向選択性の起源を解析している。[21,38] 本法では、三次元的に広がる軌道の電子密度を定量化し、求核剤がより電子密度の低い *p* 軌道と相互作用するとの合理的な理論に基づく考察が可能である。実際、電荷支配モデルで正電荷を有する炭素と軌道電子密度モデルで電子密度の低い軌道を持つ三重結合炭素は一致せず、軌道電子密度モデルを用いた場合のみ合理的に実験結果を説明可能な反応が存在する。[38c] 従って、軌道電子密度モデルはより正確に実験結果を解析する上で有用であると言える。

一方、Garg、Houk らは、非対称な置換ベンザインの形状と、その反応の配向選択性に相関

があることに注目し、アライン歪みモデル (Figure 2-(iv))を開発した。[39] すなわち、最適化されたベンザインの内角を求め、より大きな内角を持つ三重結合炭素が求電子部位となる新しい解析法である。アライン歪みモデルは、その解析手法が極めて簡便であるという大きな利点を有しているが、その理論には少なからず論理の飛躍があり、全ての置換ベンザインの反応に適用可能かどうか不明である。

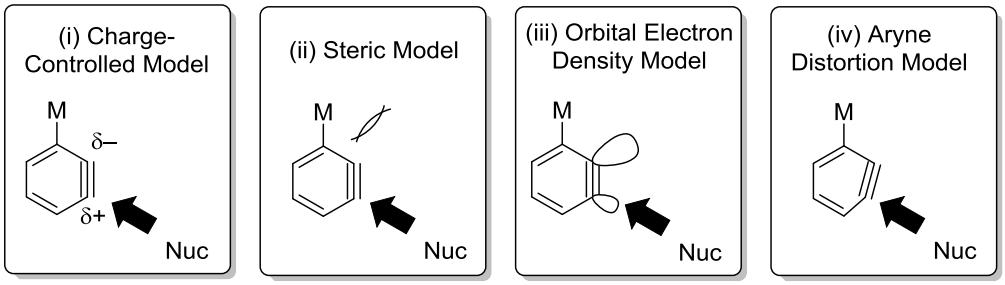


Figure 2. Various models for analyzing benzyne reaction.

そこで本節では、トリフリルオキシベンザイン**1l**、**1m**とアルコキシベンザイン**1c**、**1r**の配向選択性を、軌道電子密度モデル及びアライン歪みモデルの両者を用いて解析した（Figures 4 and 5）。

理論解析結果を議論する前に、3章にて議論した種々ベンザイン**1c**, **1l**, **1m**, **1r**の (3+2) 付加環化反応の配向選択性（実験結果）をFigure 3にまとめた。**1l** はアジドとの付加環化反応において3-MeOベンザイン **1c** と同等の高い配向選択性を示すが（Table 3）、**1l**はニトリルオキシド**25A**との反応において **1c** より高い配向選択性を示す（Table 4）。一方、4-TfO-ベンザイン **1m** は**1c**より選択性が低く（Table 8)、4-MeOベンザイン **1r** は多くの反応で選択性がほとんど発現しない（Table 7, entry 1）。従って、(3+2) 付加環化反応の配向選択性は**1r** < **1m** < **1c** < **1l**の順に大きくなると言える。

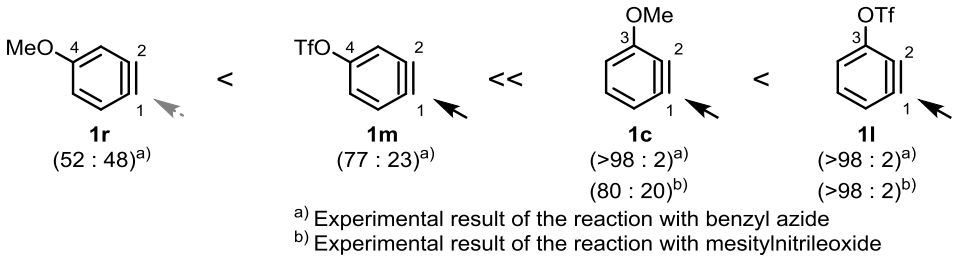
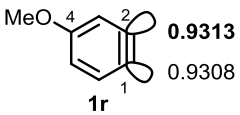
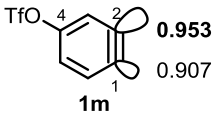
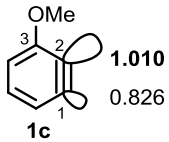
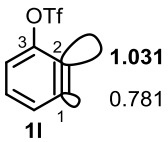
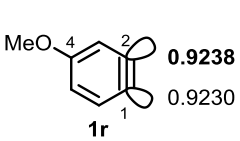
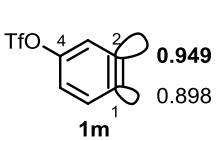
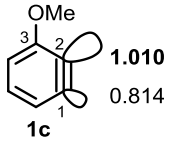
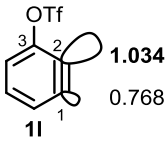
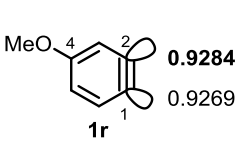
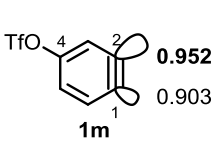
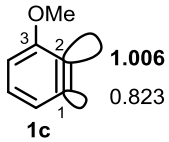
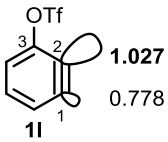
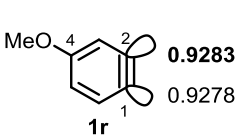
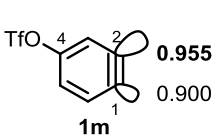
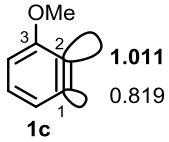
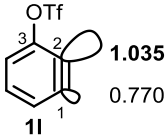


Figure 3. The more electrophilic site of **1c**, **1l**, **1m** and **1r** based on experimental results and the order of the regioselectivity with benzyl azide and mesitylnitrooxide.

まずは、軌道電子密度モデルを用いて解析を行った（Figure 4）。**1c**, **1l**, **1m**, **1r** の構造を density functional theory（DFT）計算により最適化後 [B3LYP/6-31G(d)]、反応性 *p* 軌道の電子

密度を NBO6 により求めた。[40, 41, 注8] その結果、**1c**, **1l**, **1m**, **1r** は、いずれも C1 軌道の電子密度は C2 軌道の電子密度より低かった。また、それぞれの電子密度差（C2–C1）は、**1r** < **1m** < **1c** < **1l** であり、Figure 3 に示す実際の配向選択性の大小関係とほぼ同等であった。従って、オキシベンザインの (3+2) 付加環化反応が配向選択的に進行した理由として、より電子密度の低い反応性 *p* 軌道を持つベンザイン 1 位炭素と 1,3-双極子分子の求電子的部位[注9] が選択的に反応すること、電子密度差は選択性と相関があることが示唆された。なお、異なる基底関数 [B3LYP/6-311+G(d,p), M06-2X/aug-cc-pVDZ] を用いて同様の DFT 計算、NBO 解析を行なったが、これらの結果に大差はなく、本解析の結果は基底関数依存性がないことを示している。

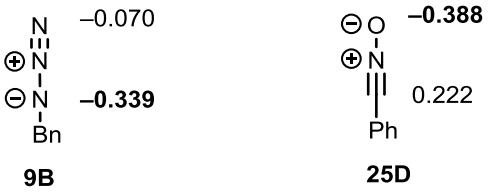
NLMO[a]//Opt[b]				
B3LYP/6-31G(d)//B3LYP/6-31G(d)	 C2 - C1 = 0.0005	 C2 - C1 = 0.046	 C2 - C1 = 0.184	 C2 - C1 = 0.250
B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p)	 C2 - C1 = 0.0008	 C2 - C1 = 0.051	 C2 - C1 = 0.196	 C2 - C1 = 0.266
M06-2X/aug-cc-pVDZ//B3LYP/6-31G(d)	 C2 - C1 = 0.0015	 C2 - C1 = 0.049	 C2 - C1 = 0.183	 C2 - C1 = 0.249
M06-2X/aug-cc-pVDZ//M06-2X/aug-cc-pVDZ	 C2 - C1 = 0.0005	 C2 - C1 = 0.055	 C2 - C1 = 0.192	 C2 - C1 = 0.265

[a]Basis set for Natural Localized Molecular Orbital (NLMO) caluculation. [b]Basis set for structure optimization.

Figure 4. Natural bond orbital (NBO) analysis of substituted benzynes **1c**, **1l**, **1m** and **1r**.[注10]

注 8: ベンザイン三重結合炭素 C_A (A = 1 or 2)における i^{th} NBO (反応性 π 軌道) の電子密度は、$\rho^i_{CA} = n_i \times d_{CA}$ （ここでの n_i とは i^{th} NBO の占有率を表し、d_{CA} は i^{th} NBO に対する炭素原子 C_A からの寄与率を表す）で評価した。

注 9: **9B** と **25D** の電荷を以下に示す。



9B **25D**

注 10: NBO に基づく NLMO は、基底関数依存性がない。[41]

次に、アライン歪みモデルを用いて解析を行った（Figure 5）。すなわち、最適化されたベンザイン **1c**、**1l**、**1m**、**1r** の内角を求め、それらを比較した。その結果、**1c**、**1l**、**1m** はいずれも、1 位の内角が 2 位の内角より大きく、その差は選択性が高いほど大きくなる傾向にあった。この計算結果は、1 位がより求電子的であること、**1l**、**1c**、**1m** の順に配向選択性が発現しやすいことを意味しており、実験結果と一致した。一方、**1r** については 2 位の内角が 1 位の内角より大きく、2 位が求電子部位であるという計算結果を与えた。しかし、実験結果からはわずかながら 1 位の方がより求電子的であり(Table 7, entry 1)、これらは一致しない。また、内角差（C2–C1）がわずか 2.2 °の **1m** の配向選択性は発現するにも関わらず、2.0 °の **1r** の場合はほとんど発現しないという点には違和感が残る。以上の結果より、アライン歪みモデルは内角差が小さい場合（選択性が低い場合）の信頼性に欠けており、本反応系の解析には不適であった。

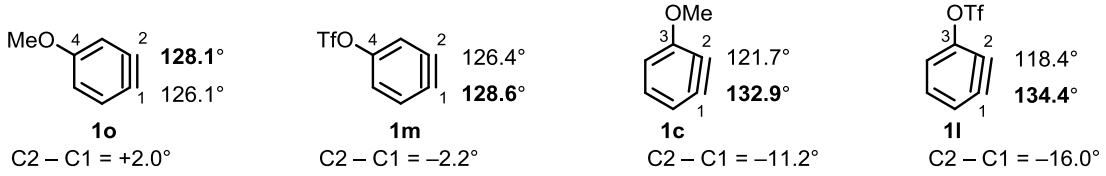


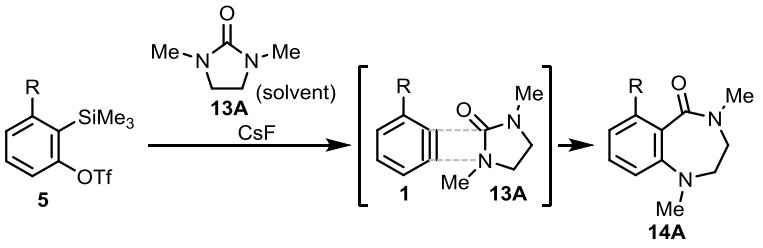
Figure 5. Aryne distortion analysis of substituted benzynes**1c**, **1l**, **1m** and **1r**.

以上著者は、計算科学的解析により、ベンザインの反応性 *p* 軌道の電子密度の偏りが(3+2)付加環化反応の配向選択性に大きく影響していることと、それを起源とする軌道電子密度モデルが反応解析に最適であることを明らかにした。

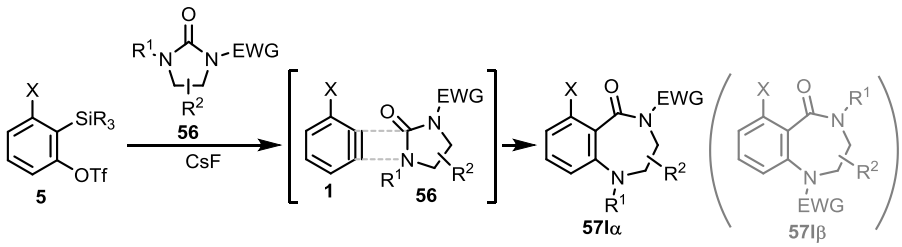
第二章　3-(トリフリルオキシ) ベンザインとイミダゾリジノン誘導体を用いたベンゾジアゼピンの位置制御合成

第一章においてはベンゼン環に四、五、六員環が縮環した化合物を合成した。本章で著者は、生物活性物質の中で、七員環を含むベンゾ縮合複素環として知られるベンゾジアゼピンを、トリフリルオキシベンザインを用いて合成する方法の開発に着手した。

以前、吉田らは対称的な五員環化合物、*N,N'*-ジメチルイミダゾリジノン(以下 DMI と略す) **13A** 中でベンザインを発生させると、2 つの窒素原子上に Me 基を有するベンゾジアゼピン **14A** が得られることを報告した (Scheme 26)。[8a] 本法ではベンザインの三重結合がイミダゾリジノン誘導体の C-N σ 結合に挿入する反応が進行し、ベンゾジアゼピンを 1 工程で合成する優れた手法ではあるが、対称的で且つ単純なイミダゾリジノン誘導体 **13A** のみが用いられ、生成物中のジアゼピン構造は 1 種類に限定されていた。また、**13A** を溶媒として大量に用いていた。そこで著者は、本法をより多様な置換様式のベンゾジアゼピンの合成に拡張すべく、1) 多様な非対称イミダゾリジノン誘導体 **56** を用い、2 つの窒素原子のうちベンザインに求核付加する窒素を制御し、単一の生成物を得ることと、2) 溶媒量使用していたイミダゾリジノン誘導体を少過剰量に減らすことを目標に、種々の研究を行なった (Scheme 27)。[22]



Scheme 26. σ bond insertion reaction of benzynes **1** with symmetrical imidazolidinone **13A**.



Scheme 27. Concept for benzodiazepines.

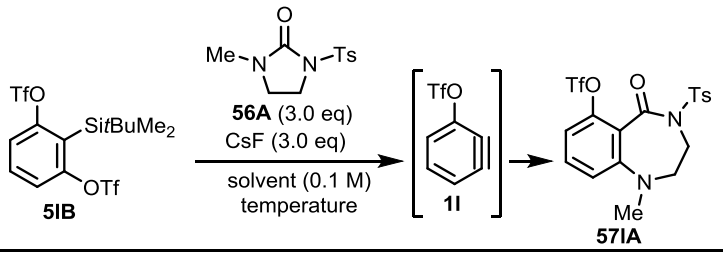
第一節　トリフリルオキシベンザインの発生条件の検討

先に述べたように、ベンゾジアゼピンを単一の位置異性体として合成するためには、イミ

ダゾリジノン誘導体が有する 2 つの窒素原子のうち、ベンザインに求核攻撃をする窒素を制御する必要がある。まずは、窒素原子の電子密度に違いを生じることで 2 つの窒素原子を区別化しようと試みた。

その一例として、2 つの窒素原子上に Me 基とトシル (Ts) 基を有する **56A** を使用し、第一章で見出した TfO-ベンザイン **1l** との反応の可能性について溶媒の種類と反応温度を種々変えて検討した(Table 9)。すなわち、減圧下、加熱乾燥した CsF (3.0 当量)に **56A** を加え、**1l** の溶液をカニュレーションし、一定温度で攪拌した。その結果、MeCN 中では、収率 56%で TfO 基を有するベンゾジアゼピン **57lA α** が得られたが (entry 1)、TLC 上に副生成物のスポットが複数見られた。含ハロゲン溶媒中では、**56A** と CsF がほとんど溶解せず、原料 **5lB** が回収された(entries 2 and 3)。一方、ジオキサン中では温度の増加に伴い **57lA α** の収率が向上し (entries 4–6)、80 °C で最も高い収率を与えた (entry 6)。しかし、同じエーテルでも cyclopentyl methyl ether (CPME) 中では CsF の溶解性が低いためベンザインの生成が遅く、**57lA α** の収率も低かった (entry 7)。これらの結果より、entry 6 を最適条件とした。

Table 9. Optimization of generation conditions of TfO benzyne **1l** and its reaction with **56A**



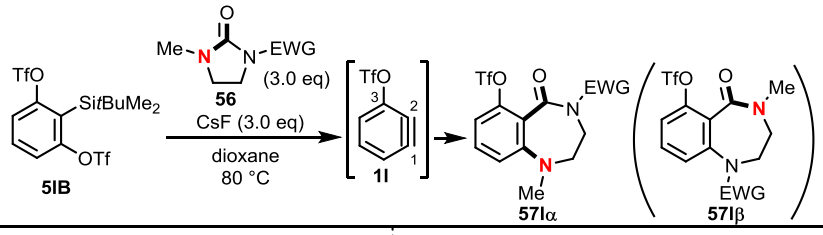
entry	solvent	temperature	time (h)	yield (%)
1	MeCN	rt	3	56
2	CH_2Cl_2	rt	49	7
3	$(CHCl_2)_2$	80 °C	24	no reaction
4	dioxane	rt	49	14
5	dioxane	50 °C	14	30
6	dioxane	80 °C	1	69
7	CPME	80 °C	300	33

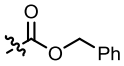
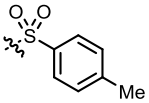
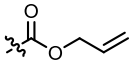
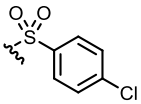
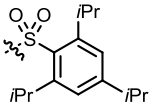
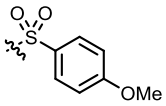
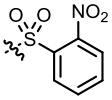
第二節　イミダゾリジノン誘導体上の置換基の検討

次に、窒素上に Me 基と、多様な電子求引基を有する非対称イミダゾリジノン誘導体を **1l** との反応に適用し、電子求引基 (electron withdrawing group: EWG) の最適化を試みた (Table 10)。その結果、カルボニル基を有するイミダゾリジノン誘導体 **56B**–**56D** を用いた場合 (entries

1–3) よりも、スルホニル基を有するイミダゾリジノン誘導体 **56A**, **56E~56I** を用いた場合 (entries 4~9) の方が全体として高い収率で **57l α** を与えることが分かった。最終的に Ts 基を有する **56A** の場合に最も高い収率を与えた (entry 6)。さらに特筆すべき事は、いずれの場合も、Me 基が置換した窒素原子が求核付加した生成物 **57l α** を単一の生成物として与え、その位置異性体 **57l β** は全く観察されなかった。

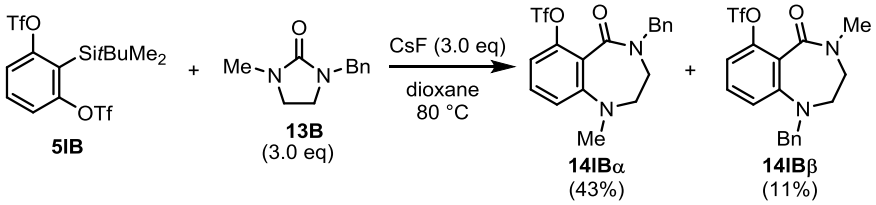
Table 10. Optimization of electron withdrawing group on imidazolidinones **56** for the reaction with **1l**..



entry	56 EWG	57l yield (%)[a]	entry	56 EWG	57l yield (%)[a]
1	**56B** 	**57lB** 23	6[b]	**56A** 	**57lA** 69
2	**56C** 	**57lC** 34	7	**56G** 	**57lG** 68
3	**56D**	**57lD** 42			
4	**56E**	**57lE** 43	8	**56H** 	**57lH** 55
5	**56F** 	**57lF** 56	9	**56I** 	**57lI** 34

[a]Isolated yield of **57lα**. [b]The result of Table 9, entry 6 is reposted.

一方、電子状態はほぼ変わらないものの、嵩高さが異なる 2 つのアルキル基を有するイミダゾリジノン誘導体 **13B** を適用したところ、約 80:20 の選択性で **14lB α** と **14lB β** の位置異性体混合物を得た (Scheme 28)。



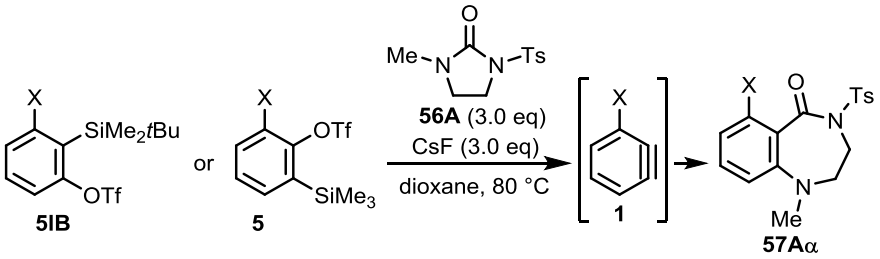
Scheme 28. The regioselectivity of the reaction of imidazolidinone **13B** with TfO-benzyne generated from **5lB**..

以上の結果から、イミダゾリジノン誘導体の反応位置制御には、2 つの窒素原子の電子密度の違いが必須であることが分かった。以下の研究は Ts 基置換イミダゾリジノン誘導体を用いて行うことにした。

第三節　ベンザイン上の置換基効果

本節ではベンザイン **1** の 3 位置換基の効果を調べるために、種々のベンザイン **1** と Ts 置換イミダゾリジノン誘導体 **56A** との反応を試みた (Table 11)。前節でも述べたように、TfO 基を有するベンザイン **1l** は **56A** と良好に反応し、ベンゾジアゼピン **57lA**α を与えるのに対し (entry 1)、無置換ベンザイン前駆体 **5a** 及び MeO ベンザイン前駆体 **5c** を **56A** との反応に適用したところ、どちらも複雑な混合物を与え、ベンゾジアゼピン **57aA**α、**57cA**α は全く観測されなかった (entries 2 and 3)。以上の結果から、TfO 基の強力な電子求引性誘起効果によって **1f** の三重結合は **1a**、**1c** の三重結合よりも求電子性が高まっているため、非常に弱い求核種である **56A** とも反応することが出来たと考えられる。すなわち、本反応において **1l** 上の TfO 基は、ベンザインの反応位置制御だけでなく、三重結合の求電子性向上という 2 つの役割を果たしていることが分かった。なお、同様に強力な電子求引性を有するフルオロベンザイン **1o** も **56A** と反応してベンゾジアゼピン **57oA**α を単一の位置異性体として与えたが、**1l** の反応と比較すると収率は大幅に低下した (entry 4)。

Table 11. Substituent effects of X on benzynes **1** for the reaction with **56A**.



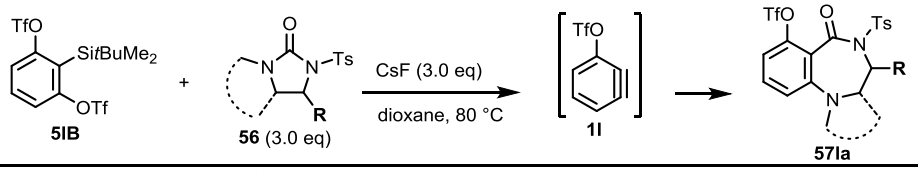
entry	5		1		57Aα		
		X		X		X	yield
1[a]	**5lB**	OTf	**1l**	OTf	**57lA**α	OTf	69%
2	**5a**	H	**1a**	H	**57aA**α	H	N.D.
3	**5c**	OMe	**1c**	OMe	**57cA**α	OMe	N.D.
4	**5o**	F	**1o**	F	**57oA**α	F	34%

[a]The result of Table 9, entry 6 is reposted.

第四節　多様な置換ベンゾジアゼピンの合成

3-TfO ベンザイン **1l** と *N*-Ts イミダゾリジノン誘導体 **56** を用いて、多様な置換ベンゾジアゼピン **57lα** の合成を検討した (Table 12)。まず、アルキル基として Me 基、アリル基、Bn 基を有するイミダゾリジノン誘導体 **56A**、**56J**、**56K** から、それぞれベンゾジアゼピン **57lAα**、**57lJα**、**57lKα** を合成することが出来た (entries 1~3)。また、環内に Me 基、*i*Pr 基を有するイミダゾリジノン誘導体 (*R*)-**56L**、(±)-**56M** から、ベンゾジアゼピン(*R*)-**57lLα**、(±)-**57lMα** が合成出来た (entries 4, 5)。一方、五員環が縮環した二環性イミダゾリジノン誘導体 (*R*)-**56N** からはより高い収率で三環性ベンゾジアゼピン(*R*)-**57lNα** を合成することが出来た (entry 6)。なお、不斉点を 1 つだけ有する光学活性イミダゾリジノン誘導体 (*R*)-**56L**、(*R*)-**56N** の光学純度は、ベンザイン反応生成物(*R*)-**57lLα**, (*R*)-**57lNα** に於いて完全に保たれていた (entries 4 and 6)。さらに、AcO 基やアセタールのような官能基を有するイミダゾリジノン誘導体 **56O**、**56P**、(*S*)-**56Q** や、嵩高い置換基を有するイミダゾリジノン誘導体 (±)-**56R**、(±)- **56S** も良好に反応し、対応するベンゾジアゼピン **57lOα**、**57lPα**、(*S*)-**57lQα**、(±)-**57lRα**、(±)-**57lSα** を生成した (entries 7–11)。一方、テトラヒドロピリミジノン誘導体 **56T** からは、対応する八員環化合物 **57lTα** は全く得られず、複雑な混合物を与えた (entry 12)。また、2 つの窒素原子のうち片方が硫黄原子に置き換わったチアゾリジノン誘導体 **56U** は複雑な混合物を与えた (entry 13)。

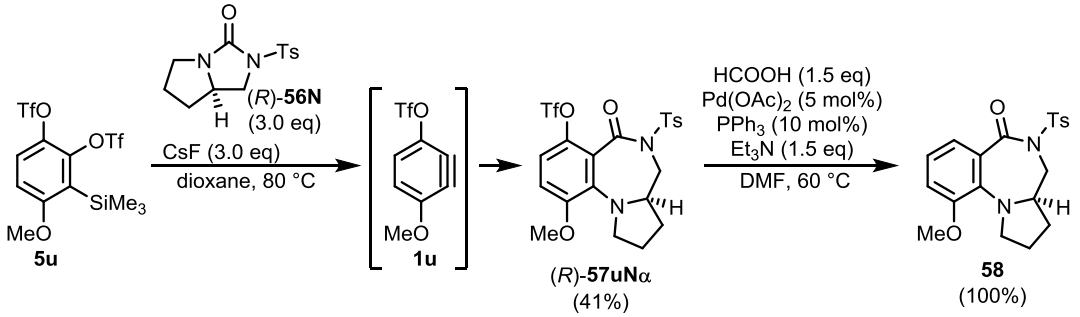
Table 12. Synthesis of benzodiazepines **57l α** using 3-TfO benzyne **1l** and asymmetrically substituted *N*-Ts-imidazolidinones **56**.



entry	56	product, yield
1[a]	**56A** (R = Me)	**57lAα** (R = Me: 69%)
2	**56J** (R = Allyl)	**57lJα** (R = Allyl 43% (11%)[b]
3	**56K** (R = Bn)	**57lKα** (R = Bn: 69%)
4	(*R*)-**56L** (R = Me) (89% ee)	(*R*)-**57lLα** (R = Me: 44%) (89% ee)
5	(±)-**56M** (R = *i*Pr)	(±)-**57lMα** (R = *i*Pr: 24%)
6	(*R*)-**56N** (88% ee)	(*R*)-**57lNα** (70%) (88% ee)
7	**56O** (R = OAc)	**57lOα** (R = OAc: 63%)
8	**56P** (R = H)	**57lPα** (R = H: 73%)
9	(*S*)-**56Q**	(*S*)-**57lQα** (77%)
10	(±)-**56R**	(±)-**57lRα** (75%)
11	(±)-**56S**	(±)-**57lSα** (49%)
12	**56T**	**57lTα** (0%)
13	**56U**	**57lUα** (0%)

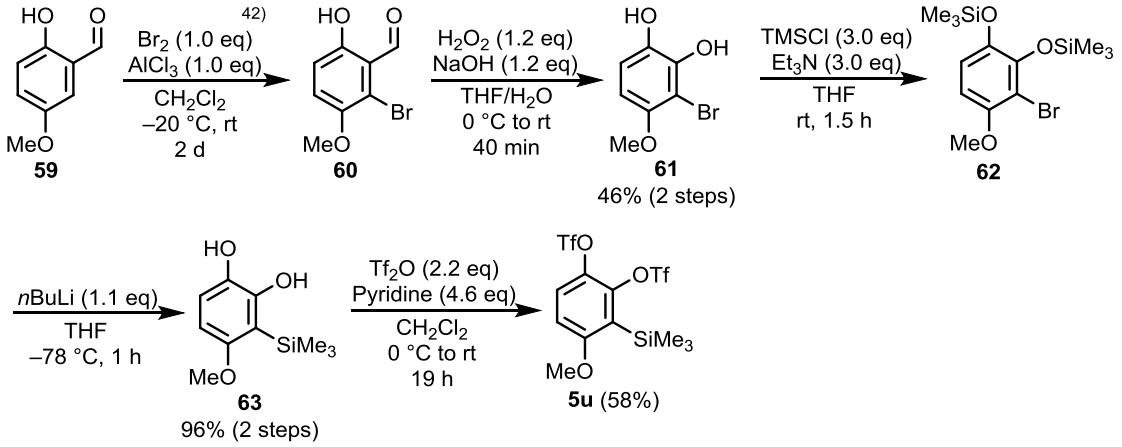
[a]The result of Table 9, entry 6 is reposted. [b]The corresponding phenol **57lJα'**, generated by hydrolysis of the TfO group, was also isolated in 11% yield.

次に、新たに合成したベンザイン前駆体 **5u** 注11 から発生した 3-methoxy-6-(triflyoxy)benzyne **1u** とイミダゾリジノン誘導体 (*R*)-**56N** を同様の条件下で反応させた結果、9-MeO-6-TfO ベンゾジアゼピン(*R*)-**57uNα** を単一の位置異性体として得た (Scheme 29)。この結果は、6-MeO-3-TfO ベンザイン **1u** が系中で発生したこと、イミダゾリジノン誘導体 (*R*)-**56N** の求核攻撃が TfO 基のメタ位で選択的に進行したことを示している。さらに注目すべき点は、TfO 基が MeO 基よりも強力な電子求引効果を有していることである。次いで、得られた環化体 (*R*)-**57uNα** 上の TfO 基を Pd 触媒反応で除去することにより、9-位に酸素官能基が置換した **58** を定量的に得ることが出来た。本化合物は、ベンゾジアゼピン(*R*)-**57lN α** (Table 12, entry 6) の酸素置換基の位置異性体であり、同じイミダゾリジノン誘導体 (*R*)-**56N** と反応させるベンザインを使い分けることで、両者を作り分けることが出来た。



Scheme 29. Regiocontrolled synthesis of 9-methoxy-1,4-benzodiazepine **58** by the reaction of 6-MeO-3-TfO benzyne **1u** and asymmetrical imidazolidinone (*R*)-**56N**.

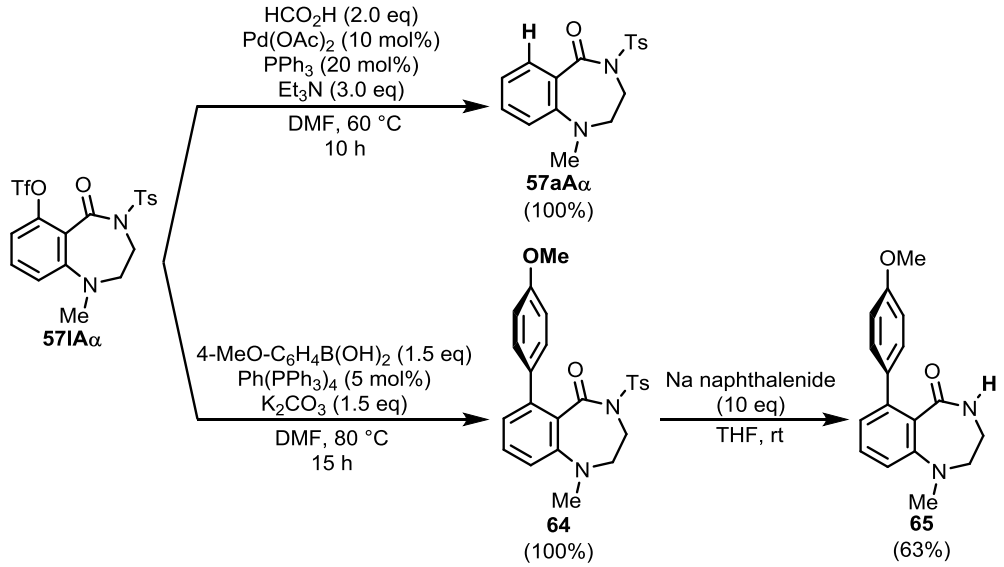
注 11: 6-MeO-3-TfO ベンザイン前駆体 **5u** は、市販されているベンズアルデヒド **59** から 5 工程で合成した (Scheme 30)。



Scheme 30. Synthesis of 6-MeO-3-TfO-benzyne precursor **5u**.

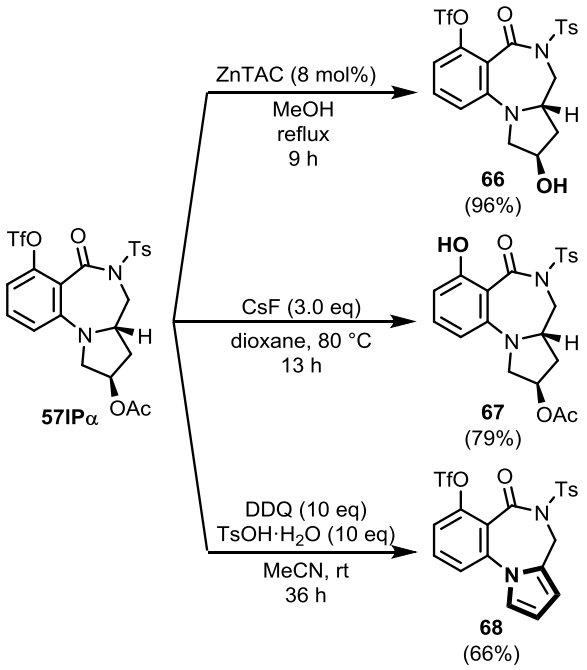
第五節　生成物上の官能基変換

第四節で合成したベンゾジアゼピン **57lA α**、**57lPα** の置換基の変換を種々検討した。まず、**57lA α** の TfO 基を Pd 触媒を用いて還元的に除去し、**57aA α** を定量的に得ることが出来た (Scheme 31)。また、鈴木カップリング反応によりアリール基へと変換し、ビアリール **64** を定量的に得た。このように、TfO 基をベンザイン反応の位置制御と他の置換基への変換に 2 回利用するという本法の有用性を実証することが出来た。さらに **64** の *N*-Ts 基を Na ナフタレニドにより除去し、**65** を得た。



Scheme 31. Transformations of product **57lA α** .

また、**57lP α** 上の AcO 基は ZnTAC 触媒[42] を用いて定量的に脱保護し、アルコール **66** へ変換した (Scheme 32)。一方、**57lP α** を CsF と共に加熱攪拌すると、AcO 基を残したまま TfO 基が加水分解され、フェノール **67** を得ることが出来た。さらに、**57lP α** を DDQ と TsOH を用いて酸化し、ピロリジン環をピロール環 **68** へ変換した。このように本法によって合成した環化体から、多様なベンゾジアゼピンを合成することが出来た。



Scheme 32. Transformations of product **57lP** α .

第六節　計算科学及び実験による反応機構の解析

まず、縮環形式や環の大きさが異なる 3 つの Ts 置換化合物 **56A**、**56N**、**56T** の構造を、計算科学を用いて比較し、これらとベンザインとの反応性の違いについて考察した。

第四節の実験結果から、ベンザインとの反応の収率は、**56T** < **56A** < **56N** の順に大きくなっていることが分かった。これは、環構造によりアミド窒素原子が本来の平面構造から外れてピラミッド状をなすことで、孤立電子対が剥き出しになることと、sp^3 混成軌道の性質を持つことにより、求核力が向上したためであると考えられる。

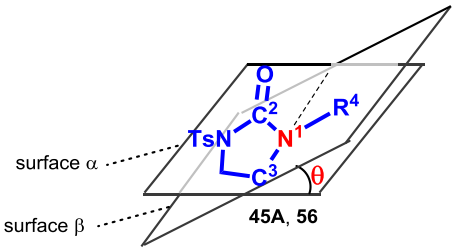
そこで、これら環状化合物の反応性窒素原子と周辺置換基の立体構造を計算科学により解析することで、窒素原子のピラミッド性と混成軌道を求めることにした。すなわち、カルボニル基炭素 (C2)、窒素原子 (N1)、環内の隣接した炭素原子 (C3) の 3 つの原子からなる平面 α と、残りの置換基 R (C4)、N1、C3 からなる平面 β がなす角度 θ を計算した (Table 13)。もし θ が小さい場合は、窒素原子は sp^2 と sp^3 の両方の性質を持つ。一方、θ が大きい場合、窒素原子は部分的に sp^3 性を有し、求核性を帯びる。

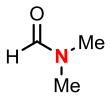
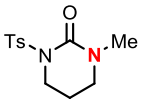
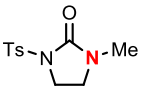
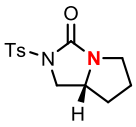
主な 3 つの環状化合物 **56A**、**56N**、**56T** の構造を DFT (density functional theory) 計算により最適化 [B3LYP/6-31G(d)]し、角度 θ を求めた (Table 13)。ここで、比較のために *N,N*-ジメチルホルムアミド (DMF)**45A** についても同様に計算した。まず、DMF **45A** の窒素原子、カルボニル炭素原子、1 つの Me 基を同一平面上に置き、その平面と、2 つの Me 基、窒素原子からなる平面がなす角度 θ を求めたところ、予想通り 0.1 °という極めて小さい角度であった。

なお、DMF **45A** の窒素原子はベンザイン **1** に対して求核攻撃をおこさないことが既に報告されている。[19b] 次に、Ts 置換テトラヒドロピリミジノン誘導体 **56T** の θ を求めたところ、3.7°であった。よって、**56T** の窒素原子は DMF **45A** の窒素原子と近い反応性を有している。一方、Ts 置換イミダゾリジノン誘導体 **56A** について同様に θ を求めたところ、27.1°であった。つまり、この窒素原子はピラミッド状をなしており、比較的 sp^3 に近くなっている。さらに、二環性イミダゾリジノン誘導体 **56N** の θ は 40.6°であり、最も大きかった。つまり、この窒素原子はこの 3 つの誘導体の中で最も sp^3 の性質が強いため、求核性も高いと言える。

以上の計算結果をまとめると、Ts 基置換環状化合物 **56A**、**56N**、**56T** の反応性窒素原子がなす θ は **56T** < **56A** < **56N** の順に大きい。この序列はベンザイン反応成績体 **57l** の収率の大小関係に完全に一致し、これらの間には相関があることが分かった。

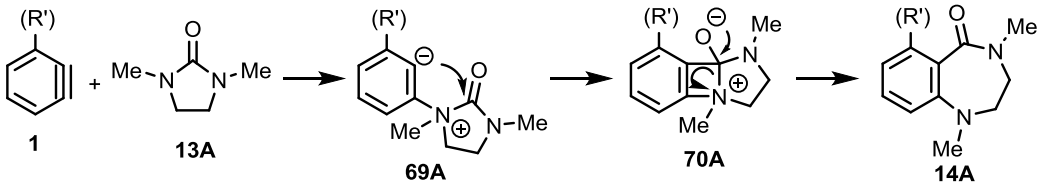
Table 13. Correlation between the dihedral angle θ of *N*-Ts-compounds **56** and isolated yield of benzyne reaction products **57l**.



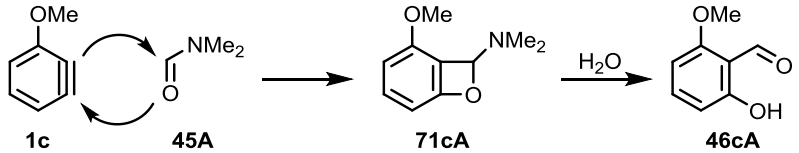
entry	urea/ amide	θ	isolated yield of **57l**
1	 **45A**	0.1 °	– [19b)]
2	 **56T**	3.7 °	N.D.
3	 **56A**	27.1°	69%
4	 **56N**	40.6°	70%

最後に反応機構の考察を行なった。以前吉田らはベンザイン **1** と DMI **13A** との反応において、まず **13A** の窒素原子が付加した後、ベンゼン環上に生成したアニオンがカルボニル炭素

に求核攻撃し、最後に四員環 **70A** の環拡大が進行することでベンゾジアゼピン **14A** を与えるという反応機構を提唱したが、それを裏付ける実験事実はなかった (Scheme 33)。[8a] また、一般に、窒素原子よりも酸素原子の方がより電子豊富であり、そのため DMF**45A** は酸素原子からベンザインに求核攻撃をおこすにもかかわらず (Scheme 34)、[19b] イミダゾリジノン誘導体 **13, 56** との反応は窒素原子から付加した生成物のみを与えることなど、不明な点が多い。

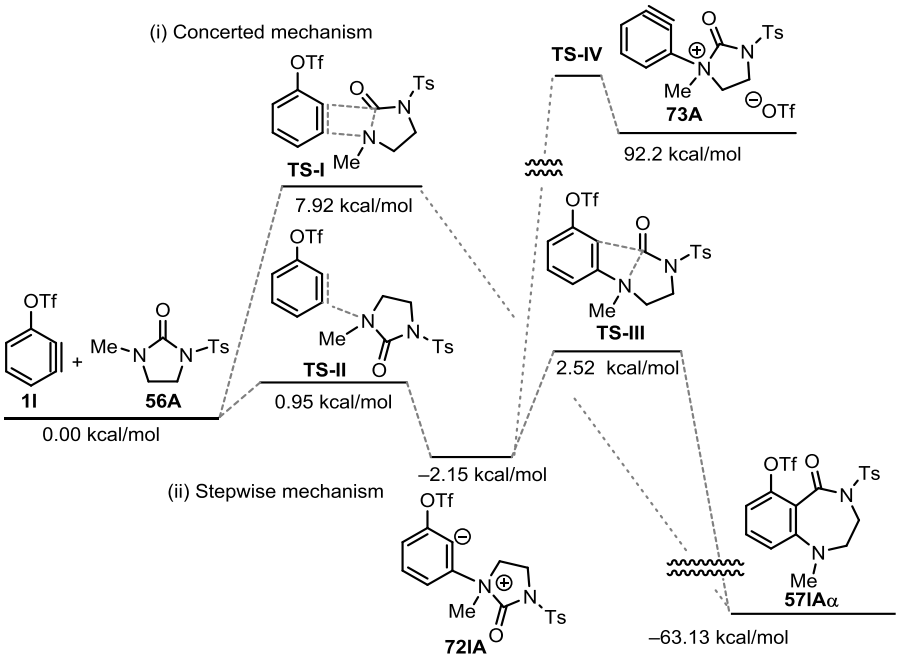


Scheme 33. Putative mechanism of the reaction of benzynes **1** and imidazolidinone **13A** proposed by Yoshida et al.



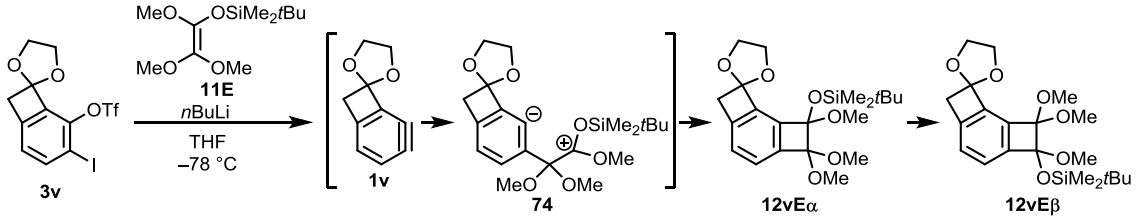
Scheme 34. The reaction of benzyne **1c** and DMF **45A**.

そこで著者は、イミダゾリジノン誘導体の窒素原子とカルボニル炭素が協奏的に付加する反応機構と、窒素原子の付加及びフェニルアニオンからカルボニル炭素への求核攻撃が段階的に進行する反応機構の 2 通りを想定した (Scheme 35)。そしてそれぞれの反応機構の遷移状態を B3LYP-D3/6-31G(d)を用いて計算した。[44] まず、協奏的反応機構において、ベンザイン三重結合とイミダゾリジノン誘導体の N－C 結合がほぼ平行になって近づく遷移状態 **TS-I** が見つかり、その活性化エネルギーは 7.92 kcal/mol であった。その後、ベンゾジアゼピン **57lA** α が得られた。一方、段階的な反応機構では、**1l** の TfO 基のメタ位にイミダゾリジノン誘導体の窒素原子が近づく遷移状態 **TS-II** が見つかり、その活性化エネルギーは 0.95 kcal/mol であった。続いて、C-C 結合を形成した **72lA** を経由した後、生じたアニオンがカルボニル炭素に接近する遷移状態 **TS-III** が見つかり、その活性化エネルギーは 2.52 kcal/mol であった。後者の場合、2 段階目に律速段階が存在するものの、**TS-I** と比較すると明らかに **TS-III** の方が有利であり、本反応は段階的に進行している可能性が高いと考えられる。[45, 注 12] なお、後者の場合、**72lA** のベンゼン環上のアニオンは隣接する TfO 基の脱離を伴って、新たなベンザイン **73A** を発生するルートも考えられるが、この遷移状態 **TS-IV** の活性化エネルギーは極めて高い (92.2 kcal/mol)ため、ベンザイン **73A** 生成の可能性は極めて低いと考えられる。



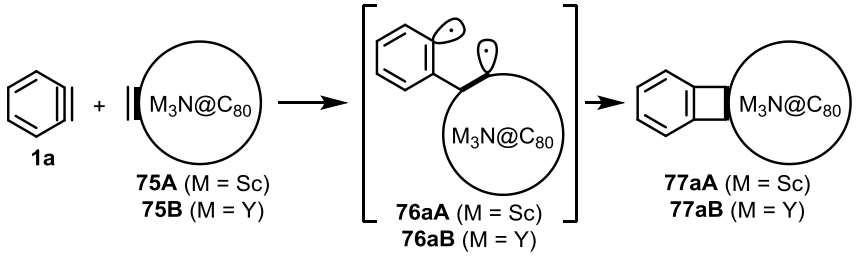
Scheme 35. Plausible reaction mechanisms for the formation of benzodiazepines **57lA** α via benzynes **1l**.

注 12: 他にも段階的な反応機構をとっていると考えられているベンザイン反応は存在する。[45] ここにその一部を示す。鈴木らはベンザイン **1v** とシリルエノールエーテル **11E** との [2+2]付加環化反応は、双性イオン中間体 **74vE** を経由していると主張している (Scheme 36)。[45b]



Scheme 36. [2+2] Cycloaddition reaction of benzyne **1v** with silyl enol ether **11E**.

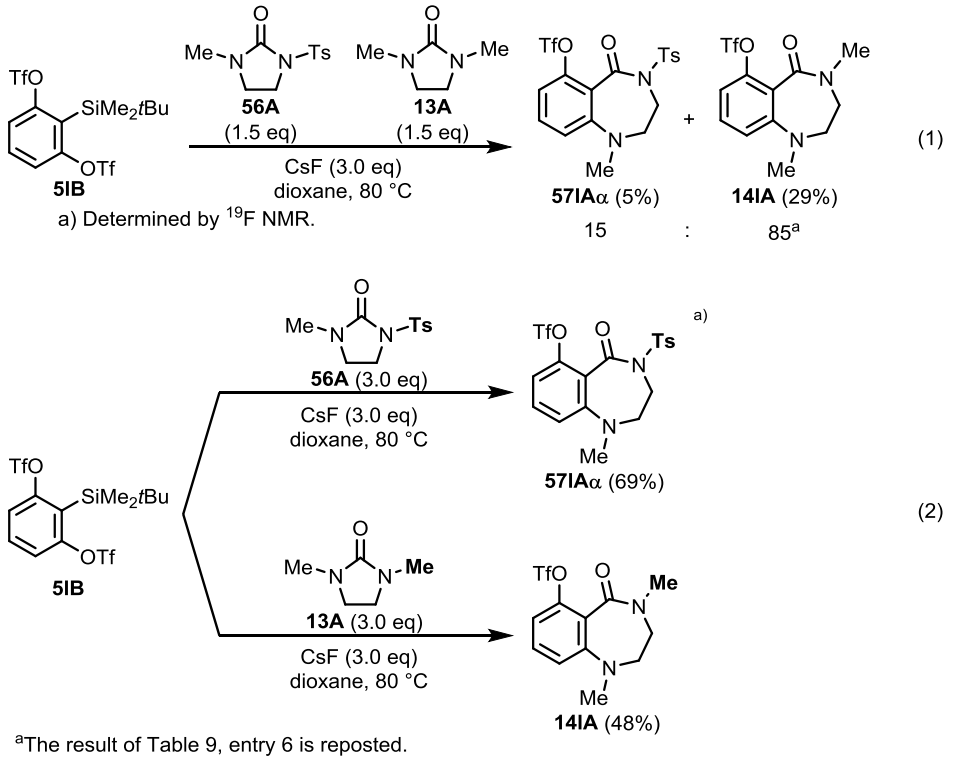
また、Houk らは、ベンザイン **1a** と金属内包フラーレン **75** との [2+2]付加環化反応が、ビラジカル中間体 **76a** を経由する段階的反応機構をとっていることを計算科学的に裏付けた (Scheme 37)。[45c]



Scheme 37. [2+2] Cycloaddition reactions of benzyne **1a** and endohedral metallofullerenes $M_3N@C80$ **75**.

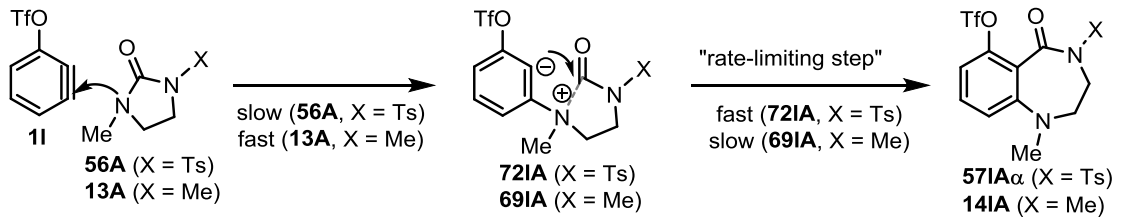
次に、反応機構に関して更なる知見を得るため、2 種類のイミダゾリジノン誘導体 **56A** と **13A** を用いた競争実験を行い、反応性の違いを比較した (Scheme 38)。すなわち、同一反応容器に、TfO ベンザイン前駆体 **5lB**、3.0 当量の CsF、各々1.5 当量の Ts 基置換イミダゾリジノン誘導体 **56A** 及び DMI **13A**、ジオキサンを加え、この反応溶液を 80 ° C で撹拌した (Scheme 38–1)。その結果、**56A** から生じた環化体 **57lA α** と **13A** から生じた環化体 **14lA** の混合物が 15:85 の比、総収率 34%で生じた。すなわち、DMI **13A** の方が明らかに多くの生成物を与えた。一方、それぞれのイミダゾリジノン誘導体 3.0 当量を単独で、**1l** との反応に用いた。その結果、Ts 基置換イミダゾリジノン誘導体 **56A** からは生成物 **57lA α** が 69%、DMI **13A** から生成物 **14lA** が 48%で得られた (Scheme 38–2)。すなわち、今度は逆に Ts 基置換イミダゾリジノン誘導体 **56A** の方がより多くの生成物を与えた。

Scheme 38-1 における **57lA α**、**14lA** の収率の合計が Scheme 38-2 のものより低い理由として、以下の 2 つが考えられる。1 つ目として、イミダゾリジノン誘導体 **56A**、**13A** をそれぞれ 1.5 当量しか用いていないため、3.0 当量用いている Scheme 38–2 と比較すると全体的に収率が低下したと考えられる。2 つ目として、Scheme 38–1 では求核性の比較的高い DMI **13A** が先にベンザイン **1l** を捕捉する。しかし、この反応の中間体は環化段階が不利なため、高収率で **14lA** を生成することは出来ない。また、付加段階が遅い **56A** は、**1l** を少量しか捕捉できないため、勿論低収率で **57lA α** を生成する。よって、Scheme 38–2 より、全体的に収率が低下したと考えられる。



Scheme 38. Competition experiment between Ts-substituted imidazolidinones **56A** and DMI **13A** and reactions carried out separately.

なお、DMI **13A** とベンザイン **1l** の付加環化反応について同様に計算科学的に解析を試みたが、現時点では遷移状態が見つかっていないために、本反応が同様の 2 段階機構で進行しているかどうか、また、後半に律速段階があるかどうか不明であるが、**13A** と **56A** が類似の反応機構で進行していると仮定すると、以下のように考察することができる (Scheme 39)。**56A** では Ts 基の電子求引性誘起効果により求核性窒素原子が電子不足になっており、最初の求核付加は遅い。一方、その後の **72lA** の環化反応は、電子求引性 Ts 基により促進されるために速い。また、本反応はこの 2 段階目に律速段階が存在するため (Scheme 35)、**56A** を単独で用いた実験では、**13A** 単独で用いる反応より高い収率で生成物を与えたと考えられる。一方、**13A** の求核性窒素原子は **56A** のそれよりも相対的に電子豊富であるため、最初の求核付加は **13A** の方が **56A** よりも速い。よって競争実験においては、過剰量存在する **13A** が TfO ベンザイン **1l** を **56A** より先に捕捉するため、より高い収率で生成物 **14lA** を与えたと考えられる。一方、律速段階においては、**69lA** の環化は **72lA** ほど促進されていないため、**13A** を単独で用いた場合は **56A** を単独で用いた場合よりも反応全体が進行しづらくなっており、生成物 **14lA** の収率が低いと考えられる。



Scheme 39. Plausible reaction mechanisms of reactions of two different imidazolidinones **13A** and **56A**.

他のイミダゾリジノン誘導体とベンザイン **1l** との反応機構が **56A** のそれと同じであると仮定した場合に、置換基効果に関する考察は、第二節で得た実験結果とも一致する。すなわち、Ts 基より強力な電子求引性を有する Ns 置換イミダゾリジノン誘導体 **56I** の反応で得られるベンゾジアゼピン **57lIα** の収率(34%)は、Ts 置換イミダゾリジノン誘導体 **56A** が生成する **57lAα** の収率(69%)と比較して明らかに低い。この理由は、**56l** は Ns 基の強力な電子求引性誘起効果により、求核性窒素原子の電子密度が低下し、その結果、ベンザイン **1l** に対する求核力が低下したためであると考えられる(Figure 7)。

一方、Ts 基よりも電子求引性が低い Ac 基が置換した **56D** や Cbz 基が置換した **56B** が与えるベンゾジアゼピン **57lDα**、**57lBα** の収率は、それぞれ 42%、23%とやはり低い。この理由は、本反応の 2 段階目に存在する律速段階を Ts 基のように促進していないためであると考えられる。

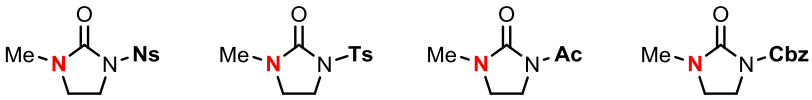
				
	56I	**56A**	**56D**	**56B**
Strength of EWG	high ⟸			low
Nucleophilicity of **N**	low ⟹			high
Promotion of cyclization step	Strong ⟸			Weak
Isolated yield (%) of **57Iα**	34	69	42	23

Figure 7. Substituent effects of EWG on cyclic imidazolidinones **56**.

以上、本章において著者は TfO ベンザインと電子求引基置換イミダゾリジノン誘導体を用いた多置換ベンゾジアゼピン合成法を開発した。本法において TfO 基は反応の位置制御だけでなく、反応の進行においても必須であり、TfO ベンザインの更なる知見を得ることが出来た。

結　　論

著者は、強力な電子求引性を有し、且つ金属触媒反応によって他の置換基に変換可能なトリフリルオキシ (TfO)基を用いてベンザイン反応の位置制御を行うというコンセプトを立案し、それによって多くの生物活性物質の骨格構造であるベンゾ縮合複素環を迅速に合成する研究を行なった。その結果、以下の成果を得た。

1) 3 位または 4 位トリフリルオキシベンザイン前駆体をデザインし、合成した。これらは室温でフッ素アニオンを用いる温和な反応条件によって、それぞれ 3 位、4 位に TfO 基を有するベンザインを発生した。

2) 3-TfO ベンザインをアジドやニトリルオキシドとの (3+2)付加環化反応に適用した。その結果、TfO 基を有するベンゾトリアゾール並びにベンゾイソオキサゾールを単一の位置異性体として得ることに成功した。また、TfO 基が従来ベンザインの配向基として汎用されてきた MeO 基よりも強力な配向制御能力を有していることが明らかになった。

3) 4-TfO ベンザインをアジドとの (3+2)付加環化反応に適用した。その結果、これまで報告されている 4 位置換ベンザインの (3+2)付加環化反応の中で最も高い配向選択性を発現し、TfO 基が 4 位においても高い配向制御能力を有していることが明らかになった。

4) 3 位または 4 位トリフリルオキシベンザインの(3+2)付加環化反応生成物の TfO 基は炭素官能基へと容易に変換出来た。TfO 基をベンザイン反応の配向制御と置換基変換に 2 回活用する本法は、従来困難であった炭素官能基によるベンザインの配向制御に変わる有効な手段を提示するものである。

5) 計算科学による解析の結果、TfO 基はベンザインの反応性 *p* 軌道の電子密度を大きく偏らせることで反応位置を制御していることが明らかになった。

6) 3-TfO ベンザインは種々の 1-アルキル-3-トシルイミダゾリン-2-オンと反応し、ベンゾジアゼピンを単一の位置異性体として生成することがわかった。また、この反応では、強力な電子求引性を有する TfO 基が、反応位置制御だけでなく、反応の進行においても必須であることを見出した。さらに、生成物の構造変換を行い、TfO 基を活用する多置換ベンゾジアゼピンの新合成法の有用性を実証した。

7) 3-TfO ベンザインと 3-トシルイミダゾリン-2-オンの反応機構を計算科学によって解析した結果、2 つの結合形成が段階的に進行している可能性が高いことがわかった。

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実 験 の 部

General considerations:

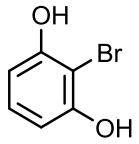
Reagents: All reactions were carried out under an argon or nitrogen atmosphere. A round-bottomed flask containing a stir-bar with a three-way stopcock was used as a reactor. 1.6 and 2.3 M solutions of *n*BuLi in hexane were purchased from Kanto Chemical. Anhydrous THF, CH_2Cl_2 and MeCN were obtained from Wako Pure Chemical Industries or Kanto Chemical and used without further purification. Anhydrous DMF was purchased from Kanto Chemicals, and purified by Glass Contour solvent dispensing system (Nikko Hansen & Co., Ltd., Osaka, Japan) using two packed columns of activated molecular sieves and an isocyanate column. 4-Methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **5r** (Table 7, entry 1),[46, 47] 4-methoxyphenyl azide **9B**,[48] 4-nitrophenylmethyl azide **9C**,[49] cyclohexyl azide **9D**,[50] 2,4,6-trimethylbenzonitrile oxide **25A**[51] 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **5a**,[2d] 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **5c**,[64] 2,6-bis(trifluoromethansulfonyloxy)phenyl trimethylsilyl ether **5lA**[24b] and 1-methyl-2-imidazolidone **S8**[52] were prepared according to the literatures.[53] CsF was dried over a flame in vacuobefore use. All other reagents were purchased from Wako Pure Chemical Industries, Tokyo Chemical Industry, Aldrich Chemical, and Kishida Chemical and used without further purification. Flash chromatography[54] was performed with Silica gel 60N, spherical neutral (40–50 μm), purchased from Kanto Chemical.

Analytical methods: Elemental analyses were performed by YANACO CHN CORDER MT-5 instrument. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were obtained on a SHIMADZU FTIR-8400S. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JMN-ECA-500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) or a JEOL JMNECS-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) or a JEOL AL-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) instrument with chemical shifts reported in ppm relative to the residual deuterated solvent. GC spectra were taken on SHIMADZU GC-2010. The mass spectra were recorded on a JEOL JMS-S3000 (MALDI), or a JMS-T100TD (APCI) spectrometer. Yield refers to isolated yields of compounds greater than 95% purity as determined by ^{1}H NMR analysis. ^{1}H NMR and melting points (where applicable) of all known compounds were taken. All new products were further characterized by high resolution mass spectrum (HRMS) or Elemental analysis. Each regiochemistry of representative cycloaddition products (*distal*-**8lB**, *distal*-**10lB**, *distal*-**10mA**, *distal*-**10mB**, **14lBα**, **57lAα**, (*R*)-**57uNα**) was confirmed by NOESY or dNOE experiment and that of *proximal*-**26lA** was confirmed by NOESY experiment of **54**. The regiochemistries of all other cycloaddition products were predicted by the similarity of ^{1}H NMR data.

第一章　第一節の実験

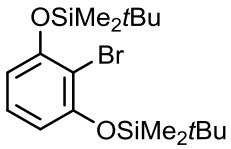
ベンザイン前駆体及び求ベンザイン体の合成

Synthesis of 3-TfO-benzyne precursor 5lB (Scheme 13):



33

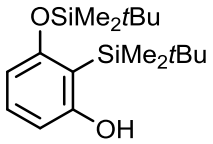
2-Bromoresorcinol (33):[55] To a solution of resorcinol **32** (11 g, 0.10 mol) in $CHCl_3$ (63 mL, 0.50 M) was added Br_2 (15 mL, 0.30 mol) at 0 °C. After stirring for 10 h at rt, the mixture was concentrated in vacuo. The residue was recrystallized from $CHCl_3$ to give 2,4,6-tribromoresorcinol (27 g, 77%). To a solution of 2,4,6-tribromoresorcinol (17 g, 50 mmol) in H_2O/MeOH (0.35 L, H_2O/MeOH = 6:1, 0.14 M) were added NaOH (4.0 g, 0.10 mol) and Na_2SO_3 (13 g, 0.10 mol) at rt. After stirring for 10 h at rt, the reaction was quenched by adding 1N HCl (20 mL) and the mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to provide the titled compound **33** (7.3 g, 78%) as a colorless solid. Mp: 101–102 °C (Lit. 101–102 °C).[55] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.39 (2 OH, s), 6.60 (2 H, d, J = 8.5 Hz), 7.11 (1 H, t, J = 8.5 Hz).



34B

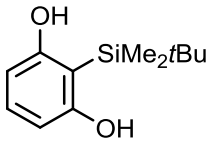
1,3-Bis(*tert*-butyldimethylsilyloxy)-2-bromobenzene (34B): To a solution of **33** (6.0 g, 32 mmol) in DMF (63 mL, 0.50 M) were added imidazol (6.5 g, 95 mmol) and TBSCl (14 g, 95 mmol) at 0 °C. After stirring for 1 h at rt, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted twice with hexane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to provide the titled compound **34B** (13 g, quant) as a colorless solid. Mp: 40–42 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.23 (12 H, s), 1.04 (18 H, s), 6,51

(2 H, d, J = 8.5 Hz), 6.99 (1 H, t, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: –4.22, 18.4, 25.8, 109.3, 113.0, 127.3, 154.1. IR (neat): 1252, 1464 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{34}O_2Si_2Br$ $[M+H]^+$: 417.1275, found 417.1257.



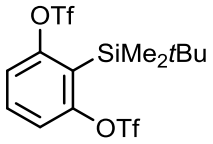
S1

2-(*tert*-Butyldimethylsilyl)-3-[(*tert*-butyldimethylsilyl)oxy]phenol (S1): To a solution of **34B** (10 g, 24 mmol) in THF (0.12 L, 0.20 M) was added 1.6 M *n*BuLi in hexane (18 mL, 29 mmol) slowly at –78 °C. After stirring for 40 min, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted twice with hexane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1) to provide the titled compound **S1** (8.1 g, 85%) as a colorless solid. Mp: 57–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.31 (6 H, s), 0.37 (6 H, s), 0.93 (9 H, s), 1.00 (9 H, s), 4.87 (OH, s), 6.30 (1 H, d, J = 8.0 Hz), 6.40 (1 H, d, J = 8.0 Hz), 7.05 (1 H, t, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –2.95, –1.37, 18.6, 19.5, 26.9, 27.0, 107.8, 110.5, 112.0, 130.6, 162.3, 162.3. IR (neat): 1254, 1437, 3512 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{35}O_2Si_2$ $[M+H]^+$:339.2170, found 339.2170.



35B

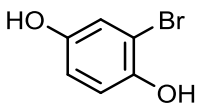
2-(*tert*-Butyldimethylsilyl)benzene-1,3-diol (35B): To a solution of **S1** (2.0 g, 5.0 mmol) in THF (50 mL, 0.10 M) was added 1.0 M TBAF in THF (5.0 mL, 5.0 mmol) slowly at 0 °C. After stirring for 30 min, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from $CHCl_3$ to provide the titled compound **35B** (0.86 g, 77%) as a colorless solid. Mp: 128–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.41 (6 H, s), 0.94 (9 H, s), 4.90 (2 OH, s), 6.29 (2 H, d, J = 8.0 Hz), 7.07 (1 H, t, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –2.09, 18.4, 26.8, 107.7, 108.0, 131.4, 162.1. IR (neat): 1263, 1327, 1445, 3518 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{21}O_2Si$ $[M+H]^+$: 225.1305, found 225.1298.



5lB

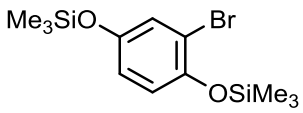
2-(*tert*-Butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (5lB): To a solution of **35B** (0.20 g, 0.89 mmol) in CH_2Cl_2 (4.5 mL, 0.20 M) were added DIPEA (0.47 mL, 2.7 mmol) and Tf_2O (0.45 mL, 2.7 mmol) at 0 °C. After stirring for 30 min at rt, the reaction was stopped by adding $NaHCO_3$ aq. and the mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to provide the titled compound **5lB** (0.37 g, 86%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.53 (6 H, s), 0.98 (9 H, s), 7.49 (2 H, d, J = 9.0 Hz), 7.56 (1 H, t, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –2.00, 18.6, 26.5, 117.9, 118.6 (q, J = 318 Hz), 122.4, 132.3, 156.0. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –73.8. IR (neat): 1215, 1424 cm^{-1}. Anal. Calcd for $C_{14}H_{18}F_6O_6S_2Si$: C, 34.42; H, 3.71. Found: C, 34.54; H, 3.72.

Synthesis of 4-TfO-benzyne precursor 5m (Scheme 14):



38

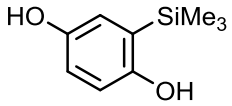
2-Bromohydroquinone (38):[56] To a solution of hydroquinone **37** (6.4 g, 58 mmol) in $CHCl_3$ (0.29 L, 0.20 M) was added Br_2 (3.0 mL, 58 mmol) at 0 °C. After stirring for 30 min at rt, the mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to provide the titled compound **38** (6.0 g, 56%) as a colorless solid. Mp: 111–114 °C (Lit. 112 °C).[56] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.12 (2 OH, brs), 6.73 (1 H, dd, J = 3.0, 9.0 Hz), 6.90 (1 H, d, J = 9.0 Hz), 6.99 (1 H, d, J = 3.0 Hz).



39

1,4-Bis(trimethylsilyloxy)-2-bromobenzene (39): To a solution of **38** (2.5 g, 13 mmol) in THF (65 mL, 0.20 M) were added Et_3N (5.4 mL, 39 mmol) and TMSCl (4.9 mL, 39 mmol). After stirring for 1

h at rt, the mixture was concentrated in vacuo. The residue was filtered through Celite pad (washed with hexane) and concentrated in vacuo to provide the titled compound as a colorless oil (4.3 g, quant). This compound **39** was used for next reaction without purification due to the instability on silica gel column chromatography.

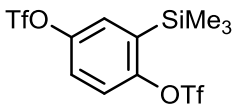


40

2-(Trimethylsilyl)hydroquinone (40):[57]

For Scheme 21: To a solution of **39** (4.3 g, 13 mmol) in THF (65 mL, 0.20 M) was added 2.3 M *n*BuLi in hexane (11 mL, 26 mmol) slowly at –78 °C. After stirring for 1 h at rt, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to provide the titled compound **40** (2.1 g, 89%) as a colorless solid.

For Scheme 22: To a solution of **42A** (13 g, 36 mmol) in MeOH (0.18 L, 0.2 M) was added TsOH・H_2O (0.68 mg, 3.6 mmol) at rt. After stirring for 90 min at rt, the reaction was stopped by adding a saturated aqueous solution of $NaHCO_3$ and the mixture was concentrated in vacuo. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to provide the titled compound **40** (6.1 g, 94%) as a colorless solid. Mp: 126–127 °C (Lit. 126–127 °C).[57] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.30 (9 H, s), 4.49 (OH, s), 4.54 (OH, s), 6.57 (1 H, d, J = 8.5 Hz), 6.70 (1 H, dd, J = 3.5, 8.5 Hz), 6.82 (1 H, d, J = 3.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –1.08, 115.5, 116.2, 117.0, 121.4, 149.0, 154.2. IR (neat): 1362, 3349 cm^{-1}. HRMS (MALDI) Calcd for $C_9H_{14}O_2Si$ $[M+H]^+$: 182.0758, found 182.0759.

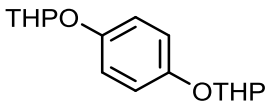


5m

1,4-Bis(trifluoromethanesulfonyloxy)-2-(trimethylsilyl)benzene (5m): To a solution of **40** (1.0 g, 5.5 mmol) in CH_2Cl_2 (28 mL, 0.20 M) were added pyridine (2.0 mL, 25 mmol) and Tf_2O (2.8 mL, 17 mmol) at 0 °C. After stirring for 19 h at rt, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash

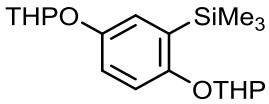
column chromatography on silica gel (hexane/EtOAc = 15:1) to provide the titled compound **5m** (2.3 g, 95%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.39 (9 H, s), 7.34 (1 H, dd, *J* = 3.0, 9.0 Hz), 7.38 (1 H, d, *J* = 3.0 Hz), 7.44 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: –1.21, 118.4 (q, *J* = 318 Hz), 118.7 (q, *J* = 319 Hz), 121.5, 123.9, 128.6, 136.7, 147.9, 153.3. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –73.7, –72.6. IR (neat): 1427 cm^{-1}. HRMS (APCI) Calcd for $C_{12}H_{13}F_6O_6S_2Si$ $[M+H]^+$: 446.98270, found 446.98508.

Synthesis of 4-TfO-benzyne precursor 5m (Scheme 15):



41

1,4-Bis((tetrahydro-2*H*-pyran-2-yl)oxy)benzene (41): To a solution of hydroquinone **37** (0.77 g, 7.0 mmol) in CH_2Cl_2 (35 mL, 0.20 M) was added DHP (1.5 mL, 18 mmol) and PPTS (0.18 g, 0.70 mmol) at rt. After stirring for 10 h at rt, the reaction was stopped by adding a saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8 : 1) to provide the titled compound **41** (1.9 g, 96%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57–1.70 (6 H, m), 1.83–1.86 (4 H, m), 1.95–2.02 (2 H, m), 3.57–3.61 (2 H, m), 3.91–3.96 (2 H, m), 5.30–5.31 (2 H, m), 6.97 (4 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.9, 25.2, 30.4, 62.0, 97.1, 97.1, 117.5, 117.5, 151.8, 151.8.

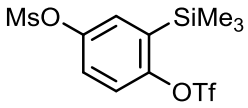


42A

1,4-Bis((tetrahydro-2H-pyran-2-yl)oxy)-2-(trimethylsilyl)benzene (42A): To a solution of **41** (11 g, 40 mmol) in THF (0.20 L, 0.20 M) was added 2.7 M *n*BuLi in hexane (16 mL, 43 mmol) slowly at 0 °C. After stirring for 8 h at rt, TMSCl (7.5 mL, 59 mmol) was added at rt. After stirring for 2 h at rt, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to provide the titled compound **42A** (13 g, 90%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.29 (9 H, s), 1.58–1.73 (6 H, m), 1.84–1.88 (4 H, m), 1.96–2.02 (2 H, m), 3.57–3.63 (2 H, m), 3.86–3.97 (2 H, m), 5.29–5.32 (1 H, m), 5.37–5.38 (1 H, m), 7.00–7.05 (3 H, m). ^{13}C

NMR (125 MHz, $CDCl_3$) δ: –0.78, 18.7, 19.0, 25.3, 30.4, 30.5, 61.5, 61.5, 62.1, 96.1, 96.2, 97.2, 97.3, 113.2, 113.3, 118.0, 118.2, 123.4, 123.6, 129.0, 151.1, 151.2, 156.8, 156.8.

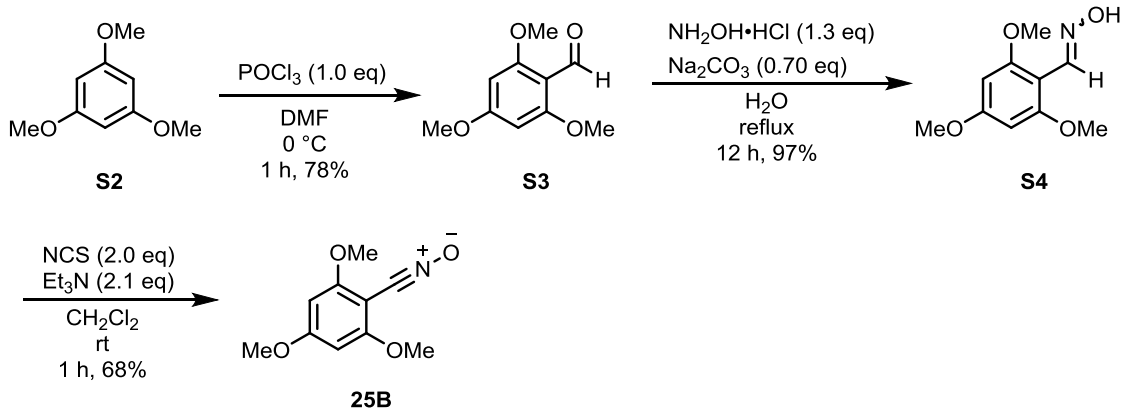
Synthesis of 4-MsO-benzyne precursor 5t (Scheme 22):



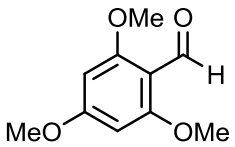
5t

1-(Methanesulfonyloxy)-3-(trimethylsilyl)-4-(trifluoromethanesulfonyloxy)benzene (5t): To a solution of **40** (0.90 g, 4.9 mmol) in CH_2Cl_2 (25 mL, 0.20 M) were added pyridine (2.6 mL, 32 mmol) and MsCl (1.9 mL, 25 mmol) at 0 °C. After stirring for 2 h at rt, the reaction was stopped by adding H_2O and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (toluene/EtOAc = 6:1) to provide the mixture of 3-(trimethylsilyl)-4-(methansulfonyloxy)phenol **51** and 1,4-bis(methansulfonyloxy)-3-(trimethylsilyl)benzene (1.3 g). To a solution of the mixture in CH_2Cl_2 (14 mL) was added pyridine (1.9 mL, 24 mmol) and Tf_2O (3.1 mL, 18 mmol) at 0 °C. After stirring for 3 h at rt, the reaction was stopped by adding H_2O and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to provide the titled compound **5t** [1.0 g, 52% (2 steps)] as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.38 (9 H, s), 3.18 (3 H, s), 7.36 (1 H, dd, J = 3.0, 8.5 Hz), 7.21 (1 H, d, J = 8.5 Hz), 7.40 (1 H, d, J = 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –1.21, 37.6, 118.3 (q, J = 317 Hz), 121.2, 124.5, 129.3, 135.9, 147.5, 152.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.8. IR (neat): 1373, 1420 cm^{-1}. HRMS (APCI) Calcd for $C_{11}H_{16}F_3O_6S_2Si$ $[M+H]^+$: 393.01097, found 393.01356.

Synthesis of 2,4,6-trimethoxybenzonitrile oxide (25B):

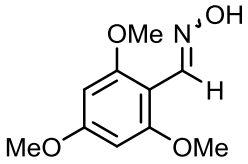


Scheme 40



S3

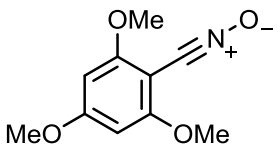
2,4,6-Trimethoxybenzaldehyde (S3):[58] To a solution of 1,3,5-trimethoxybenzene **S2** (0.80 mg, 4.8 mmol) in DMF (15 mL, 0.30 M) was added $POCl_3$ (0.45 mL, 4.8 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **S3** (0.73 g, 78%) as a colorless solid. Mp: 119–120 °C (Lit. 119–121 °C).[58] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (9 H, s), 6.06 (2 H, s), 10.3 (1 H, s).



S4

2,4,6-Trimethoxybenzaldehyde oxime (S4): To a solution of **S3** (0.69 g, 3.5 mmol) in H_2O (35 mL, 0.10 M) was added Na_2CO_3 (0.27 g, 2.5 mmol) and $NH_2OH{\cdot}HCl$ (0.32 g, 4.6 mmol) at rt. After stirring for 12 h at rt, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on

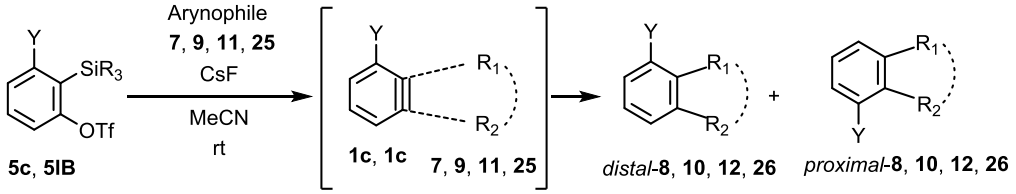
silica gel (EtOAc/hexane = 1:15) to provide the titled compound **S4** (0.72 g, 97%) as a colorless solid. Mp: 216–218 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.77 (6 H, s), 3.80 (3 H, s), 6.26 (2 H, s), 8.13 (OH, s), 10.8 (1 H, s). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 55.4, 55.8, 91.0, 102.4, 142.4, 159.2, 161.6. IR (neat): 1464, 1611, 3181 cm^{-1}. HRMS (MALDI) Calcd for $C_{10}H_{14}NO_4$ $[M+H]^+$: 212.0917, found 212.0919.



25B

2,4,6-Trimethoxyphenylnitrile oxide (25B): To a solution of **S4** (0.22 g, 1.1 mmol) in CH_2Cl_2 (11 mL, 0.10 M) was added Et_3N (0.30 mL, 2.2 mmol) and *N*-chlorosuccinimide (0.28 g, 2.1 mmol) at rt. After stirring for 1 h at rt, the reaction was stopped by adding H_2O and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/hexane = 2:1) to provide the titled compound **25B** (0.15 g, 68%) as a colorless solid. Mp: 164–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.83 (9 H, s), 6.06 (2 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.6, 55.9, 84.3, 90.4, 163.4, 163.7. IR (neat): 1333, 1582 cm^{-1}. HRMS (MALDI) Calcd for $C_{10}H_{11}NO_4$ $[M+H]^+$: 209.0683, found 209.0683.

第二、三節のベンザイン反応の一般操作法

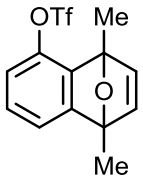


General Procedure I: CsF (2.0–3.0 equiv) was flame-dried under reduced pressure in a flask equipped with a three-way stopcock, and back-filled with Ar. Furan **7** or azide **9** or nitrile oxide **25** or alkene **11** (3.0–4.0 equiv) with a stir bar was loaded into the flask and evacuated and backfilled with Ar (This process was repeated three times). MeCN (One-fifth of its total volume) was added into the flask via a syringe. A solution of precursor **5c** or **5lB** (1.0 equiv) in anhydrous MeCN (one-fifth of its total volume) was added to the flask through a cannula and washed with MeCN (three-fifth of its total volume). The mixture was stirred at rt for the period shown in Tables 1–6 and 30. H_2O and EtOAc

were added to the reaction mixture, and the aqueous phase was extracted thrice with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to ^{1}H NMR analysis for calculating the ratio of the two regioisomers (*distal*- and *proximal*-**8**, **10**, **12** or **26**). The crude product was purified by flash column chromatography on silica gel (hexane, a mixture of hexane and EtOAc, or CH_2Cl_2) to afford *distal*- and *proximal*-**8, 10, 12** or **26**.

第二節の実験

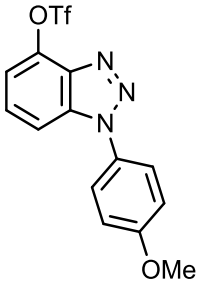
Diels–Alder reaction of 3-TfO-benzyne 1l with furan 7A (Table 2):



8lA

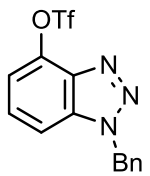
1,4-Dimethyl-1,4-dihydro-1,4-epoxy-5-(trifluoromethanesulfonyloxy)naphthalene 8lA (Table 2, entry 3): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 2,5-dimethylfuran **7A** (32 μL, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL, 0.10 M) for 3 h at rt. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to provide the titled compound **8lA** (25 mg, 79%) as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.91 (3 H, s), 2.03 (3 H, s), 6.78–6.89 (3 H, m), 7.03–7.13 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0, 16.3, 88.8, 89.3, 118.1, 118.4, 118.5 (q, J = 318 Hz), 127.7, 142.2, 144.1, 146.3, 146.7, 157.5. ^{19}F NMR (280MHz, $CDCl_3$) δ: –72.9.

Reaction of 3-triflyloxybenzyne 1l with azides 9 (Table 3):



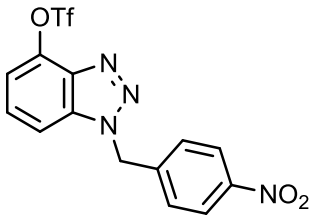
distal-**10lA**

1-(4-Methoxyphenyl)-4-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10lA) (Table 3, entry 1): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 4-methoxyphenyl azide **9A**[57)] (45 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL, 0.10 M) for 3 h at rt. The crude product (*distal*-**10lA**/*proximal*-**10lA** = >98:2, determined by 300 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:3) to provide the titled compound, *distal*-**10lA** (18 mg, 48%) as a colorless solid. Mp: 109–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.92 (3 H, s), 7.13 (2 H, d, *J* = 8.0 Hz), 7.36 (1 H, d, *J* = 7.0 Hz), 7.54–7.70 (4 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 110.9, 115.1, 116.5 118.8 (q, *J* = 318 Hz), 124.9, 128.3, 129.1, 135.2, 139.0, 139.6, 160.3. ^{19}F NMR (280MHz, $CDCl_3$) δ: –72.4. IR (neat): 1423 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_4F_3S$ $[M+H]^+$: 374.0417, found 374.0416.



distal-**10lB**

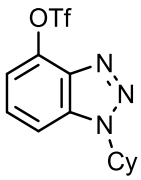
1-Benzyl-4-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10lB) (Table 3, entry 2): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), benzyl azide **9B** (37 μL, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*distal*-**10lB**/*proximal*-**10lB** = >98:2, determined by 300 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:4) to provide the titled compound, *distal*-**10lB** (26 mg, 74%) as a colorless solid, and its regiochemistry was determined by dNOE experiments. Mp: 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.86 (2 H, s), 7.25–7.44 (8 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.8, 110.4, 116.2, 118.8 (q, *J* = 318 Hz), 127.7, 127.7, 128.8, 129.1, 133.8, 135.3, 139.1, 139.6. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.6. IR (neat): 1427 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_3F_3S$ $[M+H]^+$: 358.0468, found 358.0471.



distal-**10lC**

1-(4-Nitrobenzyl)-4-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10lC) (Table 3, entry 3):

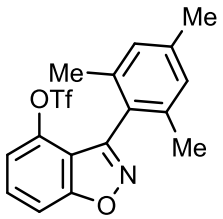
Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 4-nitrobenzyl azide **9C**[49] (53 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*distal*-**10lC**/*proximal*-**10lC** = >98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound, *distal*-**10lC** (28 mg, 70%) as a colorless solid. Mp: 106–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.98 (2 H, s), 7.32 (1 H, d, *J* = 4.0 Hz), 7.34–7.45 (3 H, m), 7.51 (1 H, t, *J* = 7.5 Hz), 8.21 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.6, 109.7, 116.7, 118.8 (q, *J* = 320 Hz), 124.4, 128.4, 128.5, 135.1, 139.2, 139.8, 140.8, 148.1. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.5. IR (neat): 1424, 1522 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{10}N_4O_5F_3S$ $[M+H]^+$: 403.0319, found 403.0321.



distal-**10lD**

1-Cyclohexyl-4-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10lD) (Table 3, entry 4): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), cyclohexyl azide **9D**[50] (38 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*distal*-**10lD**/*proximal*-**10lD** = >98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:6) to provide the titled compound, *distal*-**10lD** (22 mg, 63%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32–1.61 (4 H, m), 1.81–2.20 (6 H, m), 4.62–4.73 (1 H, m), 7.28 (1 H, d, *J* = 8.0 Hz), 7.49 (1 H, t, *J* = 8.0 Hz), 7.61 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.1, 25.4, 32.5, 59.7, 110.4, 116.0, 118.8 (q, *J* = 320 Hz), 127.0, 134.8, 138.8, 139.7. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.6. IR (neat): 1427 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{15}N_3O_3F_3S$ $[M+H]^+$: 350.0781, found 350.0783.

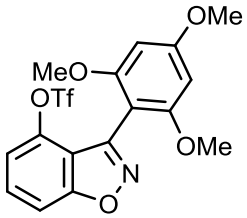
Reaction of 3-triflyloxybenzyne 1l with nitrile oxides 42 (Table 4 and Scheme 18):



proximal-**26lA**

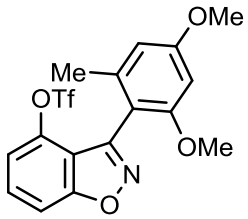
3-(2,4,6-Trimethylphenyl)-4-(trifluoromethanesulfonyloxy)-1,2-benzisoxazole (*proximal*-26lA)

(Table 4, entry 1): Following General Procedure I, a mixture of CsF (30 mg, 0.20 mmol), 2,4,6-trimethylphenylnitrileoxide **25A** (48 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (2.0 mL) for 3 h at rt. The crude product (*proximal*-**26lA**/*distal*-**26lA** = >98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (CH_2Cl_2/hexane = 2:5) to provide the titled compound, *proximal*-**26lA** (30 mg, 77%) as a colorless solid. Mp: 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.12 (6 H, s), 2.38 (3 H, s), 7.03 (2 H, s), 7.23 (1 H, d, *J* = 8.5 Hz), 7.65 (1 H, t, *J* = 8.5 Hz), 7.72 (1 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.9, 21.1, 110.6, 115.7, 116.1, 118.4 (q, *J* = 320 Hz), 122.8, 128.5, 130.9, 137.7, 139.9, 142.0, 155.5, 164.9. ^{19}F NMR (280 MHz, $CDCl_3$) δ: −73.2. IR (neat): 1435, 1626 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{15}NO_4F_3S$ $[M+H]^+$: 386.0668, found 386.0668.



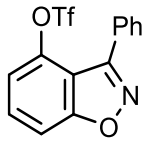
proximal-**26lB**

3-(2,4,6-Trimethoxyl)phenyl-4-(trifluoromethanesulfonyloxy)-1,2-benzisoxazole (*proximal*-26lB) (Table 4, entry 2): Following General Procedure I, a mixture of CsF (30 mg, 0.20 mmol), 2,4,6-trimethoxyphenylnitrileoxide **25B** (63 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (2.0 mL) for 3 h at rt. The crude product (*proximal*-**26lB**/*distal*-**26lB** = >98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound, *proximal*-**26lB** (30 mg, 69%) as a colorless solid. Mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (6 H, s), 3.87 (3 H, s), 6.25 (2 H, s), 7.16 (1 H, d, *J* = 8.5 Hz), 7.55 (1 H, t, *J* = 8.5 Hz), 7.62 (1 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 55.7, 90.8, 97.0, 110.2, 115.2, 116.6, 118.4 (q, *J* = 318 Hz), 130.0, 142.4, 150.6, 159.8, 163.5, 164.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.3. IR (neat): 1340, 1429 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{15}NO_7F_3S$ $[M+H]^+$: 434.0516, found 434.0521.



proximal-**26lC**

3-(2,4-Dimethoxyl-6-methyl)phenyl-4-(trifluoromethanesulfonyloxy)-1,2-benzisoxazole (*proximal*-26lC) (Table 4, entry 3): Following General Procedure I, a mixture of CsF (30 mg, 0.20 mmol), 2,4-dimethoxy-6-methyl-phenylnitrileoxide **25C** (58 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (2.0 mL) for 3 h at rt. The crude product (*proximal*-**26lC**/*distal*-**26lC** = >98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound, *proximal*-**26lC** (27 mg, 65%) as a colorless solid. Mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.23 (3 H, s), 3.70 (3 H, s), 3.87 (3 H, s), 6.43 (1 H, d, *J* = 2.5 Hz), 6.50 (1 H, d, *J* = 2.5 Hz), 7.18 (1 H, d, *J* = 8.0 Hz) , 7.61 (1 H, t, *J* = 8.0 Hz), 7.67 (1 H, d, *J* = 8.0 Hz). ^{19}F NMR (280 MHz, $CDCl_3$) δ: –73.2.

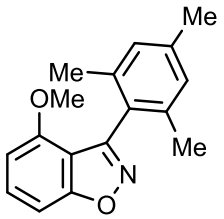


proximal-**26lD**

3-Phenyl-4-(trifluoromethanesulfonyloxy)-1,2-benzisoxazole (*proximal*-26lD) (Scheme 18): CsF (0.11 g, 0.75 mmol) was flame-dried under reduced pressure in a flask equipped with a three-way stopcock, and back-filled with Ar. *N*-hydroxybenzimidoyl chloride **24D** (16 mg, 0.10 mg) with a stir bar was loaded into the flask and evacuated and backfilled with Ar (this process was repeated three times). MeCN (one-fifth of its total volume) was added into the flask *via* a syringe. A solution of 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (98 mg, 0.20 mmol) in anhydrous MeCN (one-fifth of total volume) was added to the flask through a cannula and washed with MeCN (three-fifth of its total volume). The mixture was stirred at rt 3 h. H_2O and EtOAc were added to the reaction mixture, and the aqueous phase was extracted thrice with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:15) to provide the titled compound, *proximal*-**26lD** (18 mg, 48%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (1 H, d, *J* = 8.0 Hz), 7.54–7.59 (3 H, m), 7.68 (1 H, t, *J* = 8.5 Hz), 7.72 (1 H, d, J = 8.5 Hz), 7.75–7.77 (2 H, m). ^{13}C

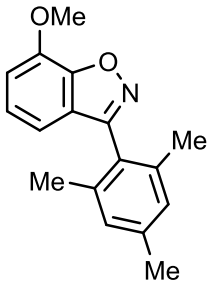
NMR (125 MHz, $CDCl_3$) δ: 110.6, 114.2, 116.2, 118.3(q, J = 320 Hz), 127.1, 128.8, 129.3, 130.5, 130.9, 142.2, 156.9, 165.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.7.

Reaction of 3-methoxybenzyne 1c with nitrile oxide 25A (Table 4, entry 4):



proximal-**26cA**

3-(2,4,6-Trimethyl)phenyl-4-(methoxy)-1,2-benzisoxazole (*proximal*-26cA) (Table 4, entry 4): Following General Procedure I, a mixture of CsF (93 mg, 0.61 mmol), 2,4,6-trimetylphenylnitrileoxide **25A**[59)] (74 mg, 0.46 mmol), and 1-methoxy-2-(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5c**[68)] (50 mg, 0.15 mmol) was stirred in MeCN (1.5 mL) for 3 h at rt. The crude product (*proximal*-**26cA**/*distal*-**26cA** = 85:15, determined by 500 MHz ^1H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:15) to provide the titled compound, *proximal*-**26cA** (23 mg, 57%) as a colorless solid. Mp: 140–141 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.10 (6 H, s), 2.35 (3 H, s), 3.73 (3 H, s), 6.62 (1 H, d, J = 8.5 Hz), 6.95 (2 H, s), 7.22 (1 H, d, J = 8.5 Hz), 7.48 (1 H, t, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0, 21.2, 55.7, 102.6, 103.3, 112.4, 125.6, 128.0, 131.3, 137.4, 138.5, 155.1, 156.5, 165.1. IR (neat): 1283, 1360, 1501 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1332, found 268.1331.



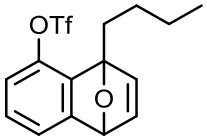
distal-**26cA**

3-(2,4,6-Trimethyl)phenyl-7-(methoxy)-1,2-benzisoxazole (*distal*-26cA) (Table 4, entry 4) was obtained from the above-mentioned reaction mixture by flash column chromatography on silica gel (3.8 mg, 9.5%) as a colorless solid. Mp: 116–119 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.08 (6 H, s), 2.36 (3 H, s), 4.10 (3 H, s), 6.94 (1 H, d, J = 7.5 Hz), 6.99 (2 H, s), 7.01 (1 H, d, J = 7.5 Hz), 7.20 (1 H,

t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0, 21.2, 56.5, 111.0, 113.4, 124.0, 124.1, 124.7, 128.4, 137.7, 139.2, 144.7, 153.7, 158.1. IR (neat): 1273, 1371, 1505 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1332, found 268.1328.

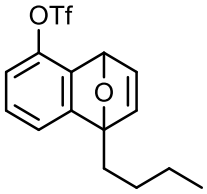
第三節の実験

Diels–Alder reactions of 3-TfO-benzyne 1l with furans 7 (Table 5):



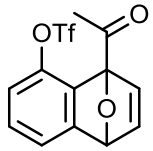
proximal-**8lD**

1-Butyl-1,4-dihydro-1,4-epoxy-8-(trifluoromethanesulfonyloxy)naphthalene (*proximal*-8lD) (Table 5, entry 3): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 2-butylfuran **7D** (42 μL, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*proximal*-**8lD**/*distal*-**8lD** = 61:39, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound, *proximal*-**8lD** (11 mg, 31%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96 (3 H, t, J = 7.5 Hz), 1.42–1.61 (4 H, m), 2.41–2.48 (2 H, m), 5.71 (1 H, s), 6.83 (2 H, d, J = 8.5 Hz), 6.87 (1 H, d, J = 5.0 Hz), 7.04 (1 H, d, J = 7.0 Hz), 7.04 (1 H, dd, J = 5.0, 8.5 Hz), 7.20 (1 H, d, J = 7.0 Hz).



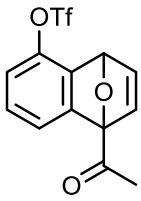
distal-**8lD**

1-Butyl-1,4-dihydro-1,4-epoxy-5-(trifluoromethanesulfonyloxy)naphthalene (*distal*-8lD) (Table 5, entry 3) was obtained from the above-mentioned reaction mixture by flash column chromatography (17 mg, 50%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95–1.01 (3 H, m), 1.44–1.62 (4 H, m), 2.22–2.39 (2 H, m), 5.85 (1 H, s), 6.81–6.83 (2 H, m), 7.06–7.09 (2 H, m), 7.14 (1 H, d, 6.5 Hz).



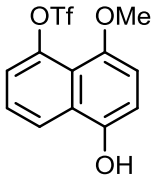
proximal-**8lE**

1-Acetyl-1,4-dihydro-1,4-epoxy-8-(trifluoromethanesulfonyloxy)naphthalene (*proximal*-8lE) (Table 5, entry 4): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 2-acetylfuran **7E** (30 μL, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*proximal*-**8lE**/*distal*-**8lE** = 54:46, determined by 300 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound, *proximal*-**8lE** (11 mg, 38%) as a colorless solid. Mp: 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.41 (3 H, s), 5.87 (1 H, d, *J* = 1.5 Hz), 6.90 (1 H, d, *J* = 8.5 Hz), 7.07–7.14 (2 H, m), 7.24 (1 H, d, *J* = 5.5 Hz) , 7.29 (1 H, d, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.8, 82.7, 95.4, 118.6 (q, *J* = 320 Hz), 119.0, 120.2, 128.7, 140.1, 141.2, 142.3, 143.6, 153.3, 201.7. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.5.



distal-**8lE**

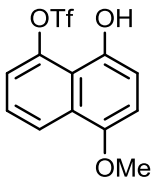
1-Acetyl-1,4-dihydro-1,4-epoxy-5-(trifluoromethanesulfonyloxy)naphthalene (*distal*-8lE) (Table 5, entry 4) was obtained from the above-mentioned reaction mixture by flash column chromatography (11 mg, 33%) as a colorless solid. Mp: 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40 (3 H, s), 6.06 (1 H, d, *J* = 1.5 Hz), 6.88 (1 H, d, *J* = 8.0 Hz), 7.06–7.12 (3 H, m), 7.31 (1 H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.9, 80.4, 95.7, 118.7 (q, *J* = 317 Hz), 118.9, 119.5, 128.2, 140.4, 142.3, 142.5, 143.1, 151.4, 204.3. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.5.



proximal-**8lC**

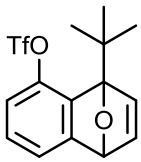
4-Methoxy-5-(trifluoromethanesulfonyloxy)naphthol (*proximal*-8lC) (Table 5, entry 5):

Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 2-methoxyfuran **7C** (28 μL, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*proximal*-**8lC**/*distal*-**8lC** = 79:21, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:4) to provide the titled compound, *proximal*-**8lC** (22 mg, 67%) as a colorless solid, and its regiochemistry was determined by dNOE experiments. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (3 H, s), 5.78 (1 OH, s), 6.67 (1 H, d, *J* = 8.5 Hz), 6.70 (1 H, d, *J* = 8.5 Hz), 7.31 (1 H, d, *J* = 8.0 Hz), 7.43 (1 H, t, *J* = 8.0 Hz) , 8.19 (1 H, d, *J* = 8.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.5.



distal-**8lC**

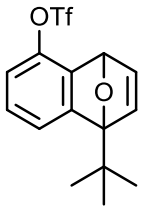
4-Methoxy-8-(trifluoromethanesulfonyloxy)naphthol (*distal*-8lC) (Table 5, entry 5) was obtained from the above-mentioned reaction mixture by flash column chromatography (EtOAc/hexane = 1:4) to provide the titled compound, *distal*-**8lC** (5.7 mg, 18%) as a colorless solid, and its regiochemistry was determined by dNOE experiments. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.95 (3 H, s), 5.70 (1 OH, s), 6.74 (1 H, d, *J* = 8.5 Hz), 6.84 (1 H, d, *J* = 8.5 Hz), 7.36 (1 H, d, *J* = 8.0 Hz), 7.44 (1 H, t, *J* = 8.0 Hz) , 8.29 (1 H, d, *J* = 8.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.9.



proximal-**8lB**

1-Butyl-1,4-dihydro-1,4-epoxy-8-(trifluoromethanesulfonyloxy)naphthalene (*proximal*-8lB) (Table 5, entry 6): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 2-*t*butylfuran **7B** (43 μL, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*proximal*-**8lB**/*distal*-**8lB** = 25:75, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:20) to provide the titled compound, *proximal*-**8lB** (7.4 mg, 21%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (9 H, s), 5.84 (1 H, d, *J* = 1.5 Hz), 6.82 (1 H, d, *J* = 8.0 Hz),

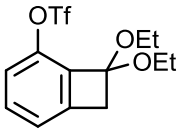
6.99 (1 H, d, J = 5.5 Hz), 7.03–7.07 (2 H, m), 7.38 (1 H, d, J = 7.0 Hz).



distal-**8lB**

1-Butyl-1,4-dihydro-1,4-epoxy-5-(trifluoromethanesulfonyloxy)naphthalene (*distal*-8lB) (Table 5, entry 6) was obtained from the above-mentioned reaction mixture by flash column chromatography (23 mg, 65%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (9 H, s), 5.68 (1 H, d, J = 1.5 Hz), 6.96 (1 H, d, J = 5.0 Hz), 7.02–7.07 (3 H, m), 7.16 (1 H, dd, J = 4.5, 6.0 Hz).

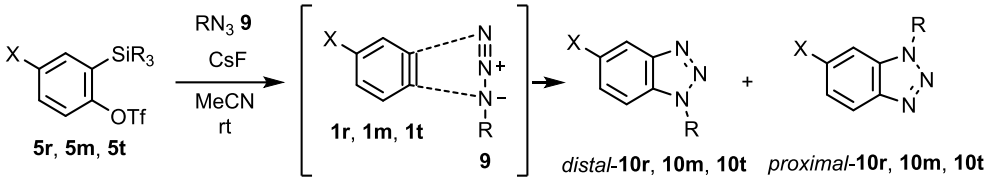
Reaction of 3-triflyloxybenzyne 1l with alkenes 11 (Table 6):



proximal-**12lB**

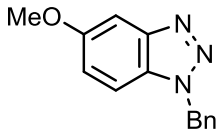
1,1-Diethoxy-6-(trifluoromethanesulfonyloxy)benzocyclobutene (*proximal*-12lB) (Table 6, entry 1): Following General Procedure I, a mixture of CsF (46 mg, 0.30 mmol), 1,1-diethoxyethylene **11B** (54 μL, 0.40 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*distal*-**12lB**/*proximal*-**12lB** = 2:>98, determined by 500 MHz ^{1}H NMR analysis) was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:20) to provide the titled compound, *proximal*-**12lB** (25 mg, 72%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (6 H, t, J = 7.5 Hz), 3.41 (2 H, s), 3.66–3.79 (4 H, m), 7.15 (1 H, d, J = 8.0 Hz), 7.24 (1 H, d, J = 8.0 Hz), 7.39 (1 H, t, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.1, 44.3, 60.0, 104.0, 118.6 (q, J = 318 Hz), 119.5, 124.2, 131.9, 137.0, 140.7, 145.0. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –73.5.

第四節のベンザイン反応の一般操作法



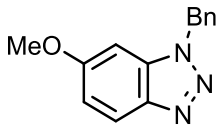
General Procedure II: CsF (3.0 equiv) was flame-dried under reduced pressure in a flask equipped with a three-way stopcock, and back-filled with Ar. Azide **9** (3.0 or 12 equiv) with a stir bar was loaded into the flask and evacuated and backfilled with Ar (This process was repeated three times). MeCN (one-fifth of its total volume) was added into the flask via a syringe. A solution of precursor (**5r**, **5m**, **5t**) (1.0 equiv) in anhydrous MeCN (one-fifth of its total volume) was added to the flask through a cannula and washed with MeCN (three-fifth of its total volume). The mixture was stirred at rt for the period shown in Table 13. H_2O and EtOAc were added to the reaction mixture, and the aqueous phase was extracted thrice with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to ^{1}H NMR analysis for calculating the ratio of the two regioisomers (*distal*- and *proximal*-**10r**, **10m**, **10t**). The crude product was purified by flash column chromatography on silica gel (hexane, a mixture of hexane and EtOAc, or CH_2Cl_2) to afford *distal*- and *proximal*-**10r**, **10m**, **10t**.

(3+2) Cycloaddition reaction of 4-MeO-benzyne 1r with azide 9B (Table 7):



distal-**10rB**

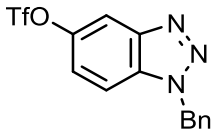
1-Benzyl-5-methoxybenzotriazole (*distal*-10rB) (Table 7, entry 1): Following General Procedure II, a mixture of CsF (91 mg, 0.60 mmol), benzyl azide **9B** (56 μL, 0.45 mmol) and 1-methoxy-4-(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5r** (50 mg, 0.15 mmol) was stirred in MeCN (1.5 mL, 0.10 M) for 3 h at rt. The crude product (*distal*-**10rB**/*proximal*-**10rB** = 52:48, determined by 500 MHz ^{1}H NMR analysis) was purified by preparative TLC (EtOAc/toluene = 1:5) to provide the titled compound, *distal*-**10rB** (15 mg, 42%) as a colorless solid. Mp: 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (3 H, s), 5.80 (2 H, s), 7.05 (1 H, dd, J = 2.0, 9.0 Hz), 7.19–7.37 (7 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.4, 55.7, 98.7, 110.4, 120.3, 127.5, 128.3, 128.5, 129.0, 134.7, 147.3, 157.2. IR (neat): 1205 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{14}N_3O$ $[M+H]^+$: 240.1131, found 240.1131.



proximal-**10rB**

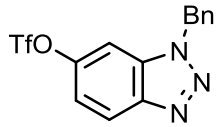
1-Benzyl-6-methoxybenzotriazole (*proximal*-10rB) (Table 7, entry 1) was obtained from the above-mentioned reaction mixture by preparative TLC (14 mg, 38%) as a colorless solid. Mp: 91–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.72 (3 H, s), 5.72 (2 H, s), 6.53 (1 H, d, *J* = 2.0 Hz), 6.91 (1 H, dd, *J* = 2.0, 9.0 Hz), 7.18–7.28 (5 H, m), 7.85 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.9, 55.7, 90.0, 116.1, 120.7, 127.4, 128.4, 129.0, 133.9, 134.8, 141.7, 159.9. IR (neat): 1232 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{14}N_3O$ $[M+H]^+$: 240.1131, found 240.1134.

(3+2) Cycloaddition reactions of 4-substituted-benzyne 1m, 1t and azides 9 (Table 8):



distal-**10mB**

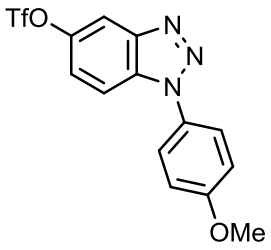
1-Benzyl-5-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10mB) (Table 8, entry 1): Following General Procedure II, a mixture of CsF (50 mg, 0.33 mmol), benzyl azide **9B** (0.16 mL, 1.3 mmol), and 1,4-bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5m** (50 mg, 0.11 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product (*distal*-**10mB**/*proximal*-**10mB** = 75:25, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography on silica gel (Et_2O/hexane = 3:5) to provide the titled compound, *distal*-**10mB** (18 mg, 45%) as a colorless solid, and its regiochemistry was determined by dNOE experiments. Mp: 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.82 (2 H, t, *J* = 7.5 Hz), 7.24–7.40 (7 H, m), 7.93 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.7, 111.3, 112.7, 118.6 (q, *J* = 318 Hz), 121.5, 127.6, 128.8, 129.1, 131.8, 133.8, 145.7, 145.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.5. IR (neat): 1421 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_3F_3S$ $[M+H]^+$: 358.0468, found 358.0470.



proximal-**10mB**

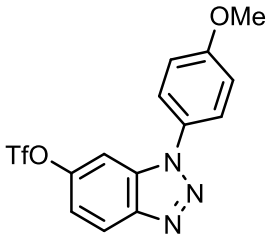
1-Benzyl-6-(trifluoromethanesulfonyloxy)benzotriazole (*proximal*-10mB) (Table 8, entry 1) was obtained from the above-mentioned reaction mixture by flash column chromatography on silica gel

(5.8 mg, 15%) as a colorless solid. Mp: 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.86 (2 H, s), 7.23–7.39 (7 H, m), 8.14 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.8, 103.3, 118.0, 118.6 (q, *J* = 318 Hz), 122.0, 127.7, 129.0, 129.3, 132.6, 133.6, 145.1, 148.2. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.4. IR (neat): 1219, 1427 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_3F_3S$ $[M+H]^+$: 358.0468, found 358.0468.



distal-**10mA**

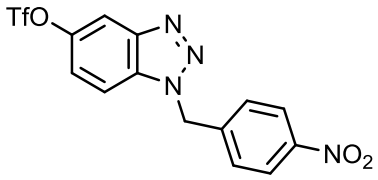
1-(4-Methoxyphenyl)-5-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10mA) (Table 8, entry 2): Following General Procedure II, a mixture of CsF (50 mg, 0.33 mmol), 4-methoxyphenyl azide **9A** (0.19 g, 1.3 mmol), and 1,4-bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5m** (50 mg, 0.11 mmol) was stirred in MeCN (1.0 mL) for 3 h at rt. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:4) to provide the titled compound, *distal*-**10mA** (19 mg, 46%) as a colorless solid and its regiochemistry was determined by NOESY spectra. Mp: 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (3 H, s), 7.12 (2 H, d, *J* = 7.5 Hz), 7.45 (1 H, d, *J* = 9.0 Hz), 7.62 (2 H, d, *J* = 7.5 Hz), 7.73 (1 H, d, *J* = 9.0 Hz), 8.05 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 111.8, 112.9, 115.1, 118.7 (q, *J* = 318 Hz), 122.1, 124.7, 129.1, 131.8, 145.8, 145.9, 160.3. ^{19}F NMR (280MHz, $CDCl_3$) δ: –72.4. IR (neat): 1209, 1427 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_4FS$ $[M+H]^+$: 374.0417, found 374.0417.



proximal-**10mA**

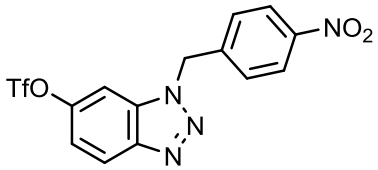
1-(4-Methoxyphenyl)-6-(trifluoromethanesulfonyloxy)benzotriazole (*proximal*-10mA) (Table 8, entry 2) was obtained from the above-mentioned reaction mixture by flash column chromatography on silica gel (6.1 mg, 15%) as a colorless solid (*distal*-**10mA**:*proximal*-**10mA** = 76:24, determined by isolated product yield). Mp: 91–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.92 (3 H, s), 7.15 (2 H, d, *J* =

9.0 Hz), 7.34 (2 H, dd, J = 2.0, 9.0 Hz), 7.61–7.63 (3 H, m), 8.22 (1 H, d, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.7, 103.9, 115.3, 118.3, 118.7 (q, J = 320 Hz), 122.1, 124.7, 129.0, 132.6, 145.0, 148.8, 160.4. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.4. IR (neat): 1211, 1425 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_4F_3S$ $[M+H]^+$: 374.0417, found 374.0416.



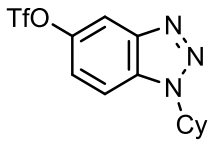
distal-**10mC**

1-(4-Nitrobenzyl)-5-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10mC) (Table 8, entry 3): Following General Procedure II, a mixture of CsF (50 mg, 0.33 mmol), 4-nitrobenzyl azide **39c** (0.23 g, 1.3 mmol), and 1,4-bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5m** (50 mg, 0.11 mmol) was stirred in MeCN (1.1 mL) for 3 h at rt. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound, *distal*-**10mC** (17 mg, 39%) as a colorless solid. Mp: 80–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.98 (2 H, s), 7.38–7.46 (4 H, m), 8.02 (1 H, d, J = 2.5 Hz), 8.21 (2 H, d, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.5, 110.7, 113.1, 118.6 (q, J = 320 Hz), 122.1, 124.3, 128.3, 131.8, 140.9, 145.9, 145.9, 148.0. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.4. IR (neat): 1348, 1424, 1526 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{10}N_4O_5F_3S$ $[M+H]^+$: 403.0319, found 403.0315.



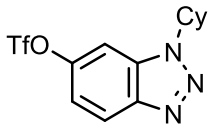
proximal-**10mC**

1-(4-Nitro)benzyl-6-(trifluoromethanesulfonyloxy)benzotriazole (*proximal*-10mC) (Table 8, entry 3) was obtained from the above-mentioned reaction mixture by flash column chromatography on silica gel (5.9 mg, 13%) as a colorless solid (*distal*-**10mC**:*proximal*-**10mC** = 75:25, determined by isolated product yield). Mp: 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.97 (2 H, s), 7.29–7.33 (2 H, m), 7.43 (2 H, d, J = 9.0 Hz), 8.19 (1 H, d, J = 9.0 Hz), 8.23 (2 H, d, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.4, 102.7, 118.4, 118.6 (q, J = 320 Hz), 122.4, 124.4, 128.4, 132.6, 140.7, 145.0, 148.1, 148.6. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.4. IR (neat): 1348, 1424, 1524 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{10}N_4O_5F_3S$ $[M+H]^+$: 403.0319, found 403.0321.



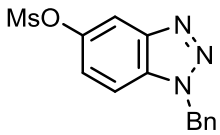
distal-**10mD**

1-Cyclohexyl-5-(trifluoromethanesulfonyloxy)benzotriazole (*distal*-10mD) (Table 8, entry 4): Following General Procedure II, a mixture of CsF (50 mg, 0.33 mmol), cyclohexyl azide **9D**[58)] (0.16 g, 1.3 mmol), and 1,4-bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5m** (50 mg, 0.11 mmol) was stirred in MeCN (1.1 mL) for 3 h at rt. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound *distal*-**10mD** (18 mg, 46%) as a colorless solid. Mp: 98–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32–2.19 (10 H, m), 4.61–4.72 (1 H, m), 7.39 (1 H, brd, *J* = 9.0 Hz), 7.65 (1 H, d, *J* = 9.0 Hz), 7.98 (1 H, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1, 25.4, 32.6, 59.6, 111.2, 112.8, 118.7 (q, *J* = 319 Hz), 121.0, 131.4, 145.6, 145.7. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –72.4. IR (neat): 1223, 1416 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{15}N_3O_3F_3S$ $[M+H]^+$: 350.0781, found 350.0783.



proximal-**10mD**

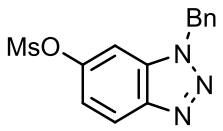
1-Cyclohexyl-6-(trifluoromethanesulfonyloxy)benzotriazole (*proximal*-10mD) (Table 8, entry 4) was obtained from the above-mentioned reaction mixture by flash column chromatography on silica gel (5.6 mg, 15%) as a colorless oil (*distal*-**10mD** : *proximal*-**10mD** = 76:24, determined by isolated product yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33–2.20 (10 H, m), 4.58–4.68 (1 H, m), 7.27 (1 H, dd, *J* = 2.5, 8.5 Hz), 7.52 (1 H, d, *J* = 2.5 Hz), 8.14 (1 H, d, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1, 25.4, 32.6, 59.5, 103.2, 117.7, 118.7 (q, *J* = 318 Hz), 121.9, 132.1, 144.8, 147.9. ^{19}F NMR (280MHz, $CDCl_3$) δ: –72.4. IR (neat): 1425 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{15}N_3O_3F_3S$ $[M+H]^+$: 350.0781, found 350.0781.



distal-**10tB**

1-Benzyl-5-(methanesulfonyloxy)benzotriazole (*distal*-136) (Table 8, entry 5): Following General Procedure II, a mixture of CsF (58 mg, 0.38 mmol), benzyl azide **9B** (47 μL, 0.38 mmol) and 1-methanesulfonyloxy-4-(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)benzene **5t** (50 mg, 0.13

mmol) was stirred in MeCN (1.3 mL) for 3 h at rt. The crude product (*distal*-**10tB**/*proximal*-**10tB** = 72:28, determined by 300 MHz ^{1}H NMR analysis) was purified by preparative TLC (only CH_2Cl_2) to provide the titled compound, *distal*-**10tB** (18 mg, 47%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.19 (3 H, s), 5.86 (2 H, s), 7.27–7.37 (7 H, m), 7.97 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 37.4, 52.7, 111.0, 112.9, 123.0, 127.6, 128.8, 129.2, 131.6, 134.1, 145.4, 146.3. IR (neat): 1364 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{14}N_3O_3S$ $[M+H]^+$: 304.0750, found 304.0756.

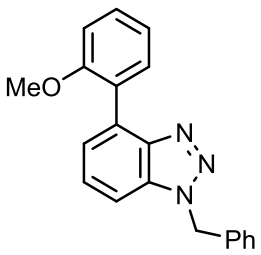


proximal-**10tB**

1-Benzyl-6-(methanesulfonyloxy)benzotriazole (*proximal*-10tB) (Table 8, entry 5) was obtained from the above-mentioned reaction mixture by preparative TLC (7.0 mg, 18%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.14 (3 H, s), 5.85 (2 H, s), 7.24–7.38 (7 H, m), 8.11 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 37.7, 52.6, 103.6, 119.0, 121.6, 127.7, 128.8, 129.2, 132.9, 134.0, 144.8, 148.0. IR (neat): 1364 cm^{-1}. HRMS (MALDI) Calcd for$C_{14}H_{14}N_3O_3S$ $[M+H]^+$: 304.0750, found 304.0745.

第五節の実験

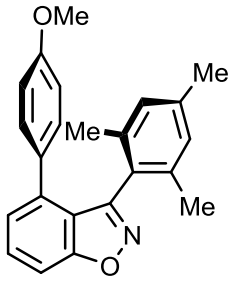
Suzuki-coupling reaction of cycloaddition products *distal*-10lB, *proximal*-26lA and *distal*-10oB (Schemes 23–25):



53

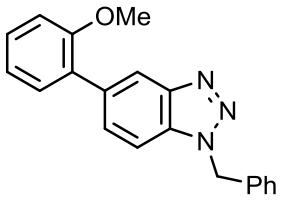
1-Benzyl-4-(2-methoxyphenyl)-benzotriazole (53) (Scheme 23): An oven dried Schlenk tube was charged with $Pd(OAc)_2$ (1.3 mg, 5.6 μmol), PCy_3 (3.1 mg, 11 μmol), 2-methoxyphenylboronic acid **52A** (13 mg, 84 μmol), K_3PO_4 (23 mg, 0.11 mmol) and *distal*-**10lB** (20 mg, 56 μmol) and evacuated and back-filled with argon. Anhydrous *n*-BuOH (0.56 mL) was added via a syringe, and the reaction mixture was stirred at 100 °C for 14 h and filtered through a pad of silica gel cake using EtOAc. The eluent was concentrated in vacuo. The residue was purified by flash column chromatography on silica

gel (EtOAc/hexane = 1:3) to provide the titled compound **53** (13 mg, 75%) as a colorless solid. Mp: 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (3 H, s), 5.87 (2 H, s), 7.08 (1 H, d, J = 8.5 Hz), 7.12 (1 H, t, J = 7.5 Hz), 7.30–7.50 (9 H, m), 7.68 (1 H, dd, J = 1.5, 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.3, 55.7, 108.4, 111.5, 120.7, 125.0, 125.8, 127.1, 127.6, 128.4, 128.9, 129.6, 130.9, 132.2, 133.1, 134.9, 145.1, 156.9. IR (neat): 1244, 1489 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1444, found 316.1446.



54

3-(2,4,6-Trimethylphenyl)-4-(4-methoxyphenyl)-1,2-benzisoxazole (54) (Scheme 24): An oven dried Schlenk tube was charged with *proximal*-**26lA** (20 mg, 52 μmol), 4-methoxyphenylboronic acid **52B** (16 mg, 0.10 mmol), $Pd(PPh_3)_4$ (6.0 mg, 5.2 μmol), K_2CO_3 (22 mg, 0.16 mmol) and evacuated and back-filled with Ar. Anhydrous DMF (0.15 mL) was added via a syringe, and the reaction mixture was stirred at 100 °C for 10 h and filtered through a pad of silica gel cake using EtOAc. The eluent was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/hexane = 1:2) to provide the titled compound **54** (14 mg, 76%) as a colorless solid and its regiochemistry was determined by NOESY spectra. Mp: 116–118°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89 (6 H, s), 2.25 (3 H, s), 3.71 (3 H, s), 6.51 (2 H, d, J = 8.5 Hz), 6.70 (2 H, s), 6.89 (2 H, d, J = 8.5 Hz), 7.22 (1 H, dd, J = 2.5, 5.0 Hz), 7.60–7.62 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.0, 21.0, 55.2, 108.4, 112.5, 119.5, 124.1, 125.7, 127.9, 129.1, 129.7, 129.8, 137.0, 138.5, 138.6, 157.3, 158.9, 163.8. IR (neat): 1252, 1518 cm^{-1}. HRMS (MALDI) Calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$: 344.1645, found 344.1648.



55

1-Benzyl-5-(2-methoxyphenyl)-benzotriazole (55) (Scheme 25): An oven dried Schlenk tube was charged with $Pd(OAc)_2$ (1.3 mg, 5.6 μmol), PCy_3 (3.1 mg, 11 μmol), 2-methoxyphenylboronic acid **52A** (13 mg, 84 μmol), K_3PO_4 (23 mg, 0.11 mmol) and *distal*-**10mB** (20 mg, 56 μmol) and evacuated and back-filled with argon. Anhydrous *n*BuOH (0.56 mL) was added via a syringe, and the reaction mixture was stirred at 100 °C for 11 h and filtered through a pad of silica gel cake using EtOAc. The eluent was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:4) to provide the titled compound **55** (16 mg, 88%) as a colorless solid. Mp: 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.81 (3 H, s), 5.86 (2 H, s), 7.03 (1 H, t, J = 8.5 Hz), 7.06 (1 H, t, J = 6.0 Hz), 7.33–7.38 (8 H, m), 7.61 (1 H, dd, J = 1.0, 8.5 Hz), 8.19 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 55.5, 108.9, 111.2, 120.3, 121.0, 127.6, 128.5, 129.0, 129.0, 129.8, 129.9, 131.1, 131.9, 134.8, 146.7, 156.4. IR (neat): 1244, 1456 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1444, found 316.1444.

第六節の実験

All calculations were performed using the Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

For a natural bond orbital (NBO) method, see: (a) Wiberg, K. B. *Tetrahedron* 1968, **24**, 1083–1096; (b) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211–7218; (c) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.

For NBO6, see: Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. Theoretical Chemistry Institute, University of Wisconsin, Madison, 2013.

The natural "localized" molecular orbital (NLMO) based on the natural bond orbital (NBO) interpretations could give chemists actual chemical and even quantitative insights without methodology/basis set-dependency. For a review on NBO analysis, see: Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.

Electron density ρ^{i}_{CA} of the ith (reacting π) NBO of carbon atom C_A (A = 1 or 2) was evaluated as follows,

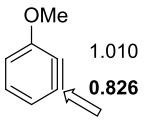
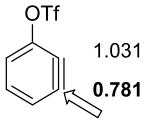
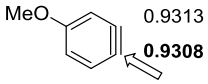
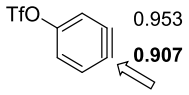
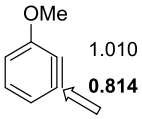
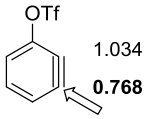
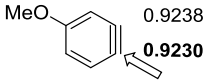
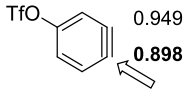
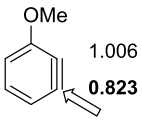
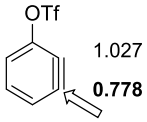
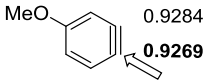
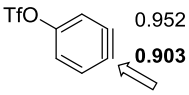
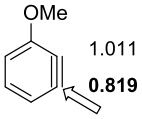
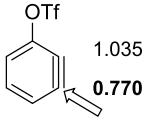
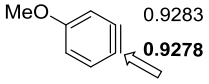
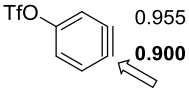
$$\rho^{i}_{\mathrm{CA}} = n_i \times d_{\mathrm{CA}} \qquad (1)$$

where n_i is occupancy of the ith NBO and d_{CA} is percentage contribution from each carbon atom C_A for the ith NBO (Figure 4).

Validation of basis-set independency of NBO analyses of benzynes **1c**, **1l**, **1m**, **1r**:

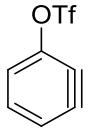
We have performed validation of the independency for our NBO results by using some DFT methods with more flexible basis sets (B3LYP/6-31G(d), B3LYP/6-311+G(d,p), M06-2X/aug-cc-pVDZ). These results indicate that actual computational levels would hardly affect the results of NBO analysis.

Table 14. Validation of basis set independency of electron densities of benzynes **1c**, **1l**, **1m**, **1r** .

NLMO[a]//Opt[b]	**1c**	**1l**	**1m**	**1r**
B3LYP/6-31G(d)//B3LYP/6-31G(d)				
C2–C1	0.184	0.250	0.0005	0.046
B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p)				
C2–C1	0.196	0.266	0.0008	0.051
M06-2X/aug-cc-pVDZ//B3LYP/6-31G(d)				
C2–C1	0.183	0.249	0.0015	0.049
M06-2X/aug-cc-pVDZ//M06-2X/aug-cc-pVDZ				
C2–C1	0.192	0.265	0.0005	0.055

[a]Basis set for Natural Localized Molecular Orbital (NLMO) calculation. [b]Basis set for structure optimization.

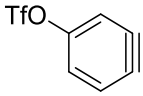
Cartesian coordinates of benzynes 1c, 1l, 1m, 1r optimized by DFT [B3LYP/6-31G(d)]:



1l

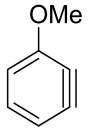
1	C	4.3439170	-0.2734480	0.1237090
2	C	3.6576610	0.8861480	-0.3087160
3	C	3.4306290	-1.2899530	0.2561410
4	C	2.2733950	0.8935130	-0.5421010
5	C	2.1922790	-1.3843920	0.0853730
6	C	1.4991100	-0.2667160	-0.3443450
7	O	0.1273570	-0.2625480	-0.6436730

8	S	-0.8790360	0.4800390	0.4392730
9	O	-0.6407650	-0.0237720	1.7819550
10	O	-0.9431840	1.9058860	0.1551360
11	C	-2.4299840	-0.3205410	-0.2419350
12	F	-2.5560360	-0.0344860	-1.5332930
13	F	-2.3725230	-1.6356990	-0.0688780
14	F	-3.4608530	0.1810980	0.4358830
15	H	5.4112710	-0.3017160	0.3051570
16	H	4.2260420	1.7989860	-0.4693410
17	H	1.7826580	1.7996830	-0.8836890



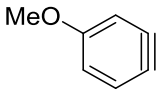
1m

1	C	4.1542530	0.1867320	0.0374970
2	C	3.5231410	1.2591820	0.1528490
3	C	3.6682440	-1.0721760	-0.2749900
4	C	2.1624450	1.4323430	-0.0206410
5	C	2.2777630	-1.0170790	-0.4805580
6	C	1.5721070	0.1972860	-0.3554460
7	O	0.1882850	0.1985220	-0.6399990
8	S	-0.8166170	-0.3014280	0.5746410
9	O	-0.7760820	-1.7512270	0.6944780
10	O	-0.6777500	0.5676940	1.7326400
11	C	-2.3795120	0.1685260	-0.3456610
12	F	-2.3990000	1.4792340	-0.5627340
13	F	-2.4395190	-0.4861010	-1.5001040
14	F	-3.4078130	-0.1779310	0.4257360
15	H	4.2368590	-1.9912340	-0.3644410
16	H	1.5776020	2.3405960	0.0703910
17	H	1.7221380	-1.9121290	-0.7415520



1c

1	C	-1.4012340	-1.9820040	0.0000000
2	C	-1.9158900	-0.7017010	0.0000000
3	C	-1.3844100	0.4289210	0.0000000
4	C	0.0000000	0.5868860	0.0000000
5	C	0.6889330	-0.6532870	0.0000000
6	C	0.0065520	-1.8841970	0.0000000
7	O	0.5727830	1.8141540	0.0000000
8	C	1.9923020	1.8880390	0.0000000
9	H	-1.9371320	-2.9231500	0.0000000
10	H	1.7741190	-0.6693630	0.0000000
11	H	0.5924200	-2.8015940	0.0000000
12	H	2.2351920	2.9518010	0.0000000
13	H	2.4178110	1.4165660	0.8952410
14	H	2.4178110	1.4165660	-0.8952410



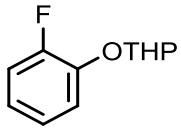
1r

1	C	-0.0432360	-2.0214650	0.0000000
2	C	-1.4114160	-1.8134740	0.0000000
3	C	0.6633850	-0.8007590	0.0000000
4	C	-1.9883820	-0.7032780	0.0000000
5	C	-1.4185880	0.5496390	0.0000000
6	C	0.0000000	0.4510130	0.0000000
7	O	0.6476630	1.6538600	0.0000000
8	C	2.0659780	1.6683100	0.0000000
9	H	0.4687220	-2.9788100	0.0000000
10	H	1.7473430	-0.8334450	0.0000000
11	H	-1.9064250	1.5181370	0.0000000
12	H	2.3537110	2.7213890	0.0000000
13	H	2.4744510	1.1809660	0.8953100
14	H	2.4744510	1.1809660	-0.8953100

第二章の実験

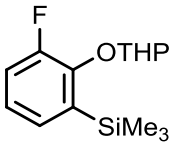
ベンザイン前駆体及び求ベンザイン体の合成

Synthesis of benzyne precursor 5o and 5u



S5

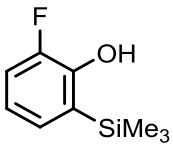
2-(2-Fluorophenoxy)tetrahydro-2*H*-pyran (S5): To a solution of 2-fluorophenol (1.4 mL, 15 mmol) in CH_2Cl_2 (75 mL, 0.2 M) were added dihydropyran (2.5 mL, 30 mmol) and pyridinium *p*-toluenesulfonate (0.19 g, 0.75 mmol). After stirring for 12 h at room temperature, the reaction was quenched by adding $NaHCO_3$ aq. and the mixture was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_3N/hexane = 1:19) to give the titled compound **S5** as a colorless oil (2.7 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59–1.76 (3 H, m), 1.84–2.10 (3 H, m), 3.62 (1 H, tdd, *J* = 2.0, 4.5, 11.0 Hz), 3.96 (1 H, dt, *J* = 3.0, 11.0 Hz), 5.44 (1 H, t, *J* = 3.0 Hz), 6.93–6.97 (1 H, m), 7.02–7.10 (2 H, m) , 7.20 (1 H, dt, *J* = 2.0, 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4, 25.1, 30.1, 61.9, 97.5, 116.2 (d, *J* = 18.0 Hz), 118.6, 122.2 (d, *J* = 7.5 Hz), 124.2 (d, *J* = 4.0 Hz), 144.8 (d, *J* = 10.5 Hz), 153.3 (d, *J* = 245 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –133.5–(–133.4) (m). IR (neat): 2946, 1505 cm^{-1}. HRMS (MALDI) Calcd for $C_{11}H_{13}O_2FNa$ $[M+Na]^+$: 219.0792, found 219.0785.



S6

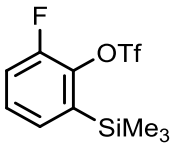
(3-Fluoro-2-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)trimethylsilane (S6): To a solution of **S5** (2.7 g, 13.8 mmol) in THF (46 mL) at 0 °C under argon *n*-BuLi (2.6 M in THF, 5.6 mL, 14.4 mmol) was added dropwise over 10 min. The reaction mixture was warmed to ambient temperature and stirred rt for 5 h. TMSCl (1.9 mL, 15.2 mmol) was added dropwise over 10 min at 0 °C. The mixture was allowed to warm to ambient temperature for 30 min and quenched with NH_4Cl aq. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_3N/hexane = 1:19) to provide the titled compound **S6** as a colorless oil (3.6 g,

98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.33 (9 H, s), 1.57–1.65 (3 H, m), 1.83–1.86 (1 H, m), 1.94–1.98 (2 H, m), 3.54–3.58 (1 H, m), 3.98–4.02 (1 H, m), 5.49 (1 H, d, *J* = 6.0 Hz), 6.95–6.99 (1 H, m), 7.06 (1 H, ddd, *J* = 1.5, 8.5, 13 Hz), 7.15 (1 H, dd, *J* = 2.0, 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –0.41, 20.0, 25.1, 30.9, 64.1, 100.3 (d, *J* = 9.5 Hz), 118.3 (d, *J* = 20.0 Hz), 123.1 (d, *J* = 7.0 Hz), 130.1 (d, *J* = 3.5 Hz), 147.7, 153.6 (d, *J* = 247 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: –129.84–(–129.80). IR (neat): 2952 cm^{-1}. HRMS (MALDI) Calcd for $C_{14}H_{21}O_2FNaSi$ $[M+Na]^+$: 291.1187, found 291.1169.



S7

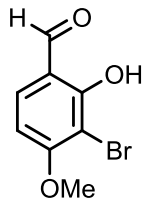
2-Fluoro-6-(trimethylsilyl)phenol (S7):[59] To a solution of **S6** (3.1 g, 11.5 mmol) in MeOH (30 mL, 0.38 M) was added TsOH·H_2O (0.11 g, 0.58 mmol) at room temperature. After stirring for 30 min, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and the mixture was concentrated under reduced pressure. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound **S7** as a colorless oil (2.0 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.31 (9 H, s), 5.26 (1 H, d, *J* = 6.0 Hz), 6.84 (1 H, ddd, *J* = 4.5, 7.0, 8.5 Hz), 7.04–7.11 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: –1.15, 116.1 (d, *J* = 18.0 Hz), 120.4 (d, *J* = 5.5 Hz), 128.3, 129.9 (d, *J* = 5.0 Hz), 147.7 (d, *J* = 11.5 Hz), 150.5 (d, *J* = 237.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –143.1–(–143.0) (m). IR (neat): 3586 cm^{-1}.



5o

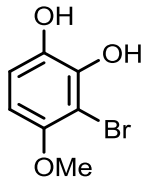
2-Fluoro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (5o) (Table 1):[26j] To a solution of **S7** (2.0 g, 10.9 mmol) in CH_2Cl_2 (36 mL, 0.30 M) were added pyridine (1.3 mL, 16 mmol) and Tf_2O (2.2 mL, 13 mmol) at 0 °C. After stirring for 100 min at room temperature, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:8) to provide the titled compound **5o** as a yellow oil (2.9 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ:

0.40 (9 H, s), 7.23 (1 H, ddd, J = 1.5, 8.0, 9.5 Hz), 7.28–7.30 (1 H, m), 7.32–7.36 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.62, 118.4 (d, J = 19.0 Hz), 118.7 (q, J = 318.5 Hz), 129.2 (d, J = 4.0 Hz), 130.9 (d, J = 4.0 Hz), 137.2 (d, J = 3.0 Hz), 140.6 (d, J = 11.5 Hz), 153.2 (d, J = 250 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –125.9–(–125.7) (m), –71.9 (d, J = 22.0 Hz). IR (neat): 2961, 1578 cm^{-1}.



60

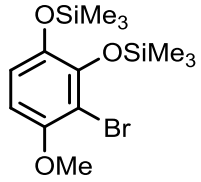
3-Bromo-2-hydroxy-4-methoxybenzaldehyde (60):[42] A solution of aldehyde **59** (0.61 g, 4.0 mmol) in dichloromethane (24 mL) was cooled to −20 °C. Then aluminum chloride (0.53 g, 4.0 mmol) was added in three portions. The suspension was stirred for 15 min before a solution of bromine (0.21 mL, 4.0 mmol) in dichloromethane (10 mL) was added over 10 min. After stirring for 2 days at room temperature, the reaction was quenched by adding 1N HCl and Na_2SO_3 aq. The mixture was extracted with CH_2Cl_2 twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:3) to provide the titled compound **60** as a colorless solid (0.66 mg, 71%). Mp: 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.00 (3 H, s), 6.63 (1 H, d, J = 8.5 Hz), 7.51 (1 H, d, J = 8.5 Hz), 9.72 (1 H, s), 11.9 (OH, s). IR (neat): 1636 cm^{-1}.



61

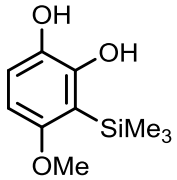
3-Bromo-4-methoxy-resorcinol (61): A solution of aldehyde **60** (0.23 g, 1.0 mmol) in THF (5.0 mL, 0.20 M) was cooled to 0 °C. Then NaOH aq. (0.80 mL, 1.5 M) and H_2O_2 (0.13 mL, 1.2 mmol) was added in two portions. After stirring for 40 min, the reaction was quenched by adding a saturated aqueous solution of Na_2SO_3 and 1N HCl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **61** as a colorless oil (0.14 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.84 (3 H, s), 5.11 (OH, s), 5.61 (OH, s), 6.42 (1 H, d, J = 9.0 Hz), 6.84 (1 H, d, J = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.6, 99.7, 103.4, 113.7, 138.4, 141.1, 149.9. IR (neat): 3435, 3414 cm^{-1}. HRMS

(MALDI) Calcd for $C_7H_7O_3Br$ $[M+H]^+$: 217.9573, found 217.9574.



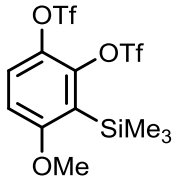
62

1,2-Bis(trimethylsilyloxy)-3-bromo-4-methoxybenzene (62): To a solution of **61** (2.1 g, 9.7 mmol) in THF (48 mL, 0.20 M) were added Et_3N (4.0 mL, 29 mmol) and TMSCl (3.7 mL, 29 mmol). After stirring for 1.5 h at room temperature, the mixture was concentrated under reduced pressure. The residue was filtered through Celite pad (washed with hexane) and concentrated under reduced pressure as a colorless oil (3.5 g, quant). This compound **62** was used for next reaction without purification due to the instability on silica gel column chromatography.



63

3-(Trimethylsilyl)-4-methoxyresorcinol (63): To a solution of **62** (4.3 g, 9.7 mmol) in THF (48 mL, 0.20 M) was added 2.6 M *n*-BuLi in hexane (4.1 mL, 11 mmol) slowly at –78 °C. After stirring for 1 h, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:3) to provide the titled compound **63** as a colorless solid (2.0 g, 96%). This compound **63** was used for next reaction as soon as it has been purified due to the instability.

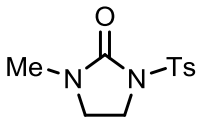


5u

1,2-Bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)-4-methoxybenzene (5u) (Scheme 29): To a solution of **63** (2.0 g, 9.2 mmol) in CH_2Cl_2 (23 mL, 0.40 M) were added pyridine (3.3 mL, 42 mmol) and Tf_2O (3.4 mL, 20 mmol) at 0 °C. After stirring for 19 h at room temperature, the reaction was

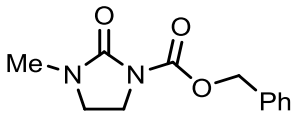
quenched by adding a saturated aqueous solution of NH_4Cl and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:15) and (CH_2Cl_2/hexane = 1:4) to provide the titled compound **5u** as a collarless oil (2.5 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.39 (9 H, s), 3.86 (3 H, s), 6.87 (1 H, d, *J* = 9.0 Hz), 7.39 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.41, 56.0, 110.1, 118.5 (q, *J* = 320 Hz), 118.6 (q, *J* = 320 Hz), 124.6, 126.4, 134.6, 143.2, 163.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –72.45 (q, *J* = 8.0 Hz), –72.90 (q, *J* = 2.5 Hz). IR (neat): 2591, 1597 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{14}O_7F_6NaSiS_2$ [M+Na]$^+$: 498.9747, found 498.9733.

Synthesis of imidazolidinones 56



56A

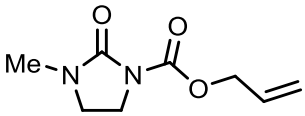
1-Methyl-3-tosyl-2-imidazolidone (56A) (Table 9): To a solution of 1-methyl-2-imidazolidinone (**S8**)[52] (0.29 g, 2.9 mmol) in THF (15 mL, 0.20 M) were added 60% NaH (0.58 g, 15 mmol) and TsCl (0.93 g, 4.9 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **56A** as a colorless solid (0.72 g, 98%). Mp: 185–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (3 H, s), 2.75 (3 H, s), 3.36 (2 H, dd, *J* = 6.5, 9.5 Hz), 3.82 (2 H, dd, *J* = 6.5, 8.0 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.92 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 30.7, 41.7, 43.7, 128.1, 129.6, 134.8, 144.7, 154.1. IR (neat): 1728 cm^{-1}. HRMS (MALDI) Calcd for $C_{11}H_{14}N_2O_3NaS$ [M+Na]$^+$: 277.0617, found 277.0619.



56B

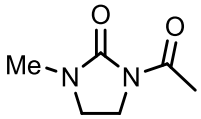
1-Methyl-3-benzyloxycarbonyl-2-imidazolidone (56B) (Table 10, entry 1): To a solution of 1-methyl-2-imidazolidone (**S8**)[52] (0.60 g, 6.0 mmol) in THF (30 mL, 0.20 M) were added 60% NaH (0.48 g, 12 mmol) and CbzCl (1.3 mL, 9.0 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced

pressure. The residue was purified by flash column chromatography on silica gel (only EtOAc) to provide the titled compound **56B** as a colorless solid (1.0 g, 74%). Mp: 63–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.85 (3 H, s), 3.37 (2 H, t, *J* = 8.0 Hz), 3.81 (2 H, t, *J* = 8.0 Hz), 5.27 (2 H, s), 7.28–7.36 (3 H, m), 7.42 (2 H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.7, 40.4, 43.2, 67.6, 127.9, 128.1, 128.5, 135.7, 152.0, 153.9. IR (neat): 1780, 1742 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$: 257.0897, found 257.0902.



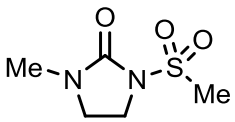
56C

1-Methyl-3-allyloxycarbonyl-2-imidazolidone (56C) (Table 10, entry 2): To a solution of 1-Methyl-2-imidazolidone **S8**[52] (0.60 g, 6.0 mmol) in THF (30 mL, 0.20 M) were added NaH (0.48 g, 12 mmol) and AllocCl (0.95 g, 9.0 mmol) at 0 °C. After stirring for 16 h at rt, the reaction was stopped by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc) to provide the titled compound **56C** (0.72 g, 65%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.82 (3 H, s), 3.37 (2 H, t, *J* = 8.0 Hz), 3.79 (2 H, t, *J* = 8.0 Hz), 4.68 (2 H, dt, *J* = 1.0, 10.5 Hz), 5.21 (1 H, dq, *J* = 1.0, 10.5 Hz), 5.37 (1 H, dq, *J* = 1.0, 17.0 Hz), 5.88–5.97 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.6, 40.3, 43.1, 66.6, 118.3, 131.6, 151.8, 153.8. HRMS (MALDI) Calcd for $C_8H_{12}N_2O_3Na$ $[M+H]^+$: 207.0740, found 207.0738.



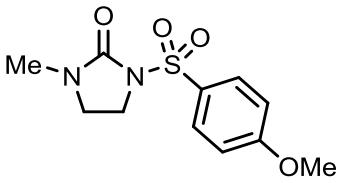
56D

1-Methyl-3-acetyl-2-imidazolidone (56D) (Table 10, entry 4): To a solution of 1-methyl-2-imidazolidinone **S8**[52] (0.25 g, 2.5 mmol) in THF (13 mL, 0.20 M) were added 60% NaH (0.20 g, 5.0 mmol) and AcCl (0.27 mL, 3.8 mmol) at 0 °C. After stirring for 13 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:1) to provide the titled compound **56D** as a colorless solid (0.26 g, 72%). Mp: 71–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (3 H, s), 2.86 (3 H, s), 3.39 (2 H, t, *J* = 8.0 Hz), 3.80 (2 H, t, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.1, 30.6, 39.2, 42.9, 154.9, 170.7. IR (neat): 1724, 1668 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_{10}N_2O_2Na$ $[M+Na]^+$: 165.0634, found 165.0635.



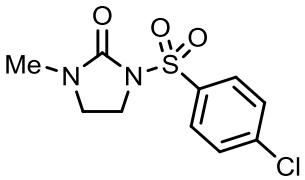
56E

1-Methyl-3-(methanesulfonyl)-2-imidazolidone (56E) (Table 10, entry 4): To a solution of 1-methyl-2-imidazolidinone **S8**[52] (0.40 g, 4.0 mmol) in CH_2Cl_2 (20 mL, 0.20 M) were added Et_3N (1.7 mL, 12 mmol) and MsCl (0.93 mL, 12 mmol) at room temperature. After stirring for 15 h at room temperature, the reaction was quenched by adding H_2O and the mixture was extracted with EtOAc four times. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15) to provide the titled compound **56E** as a colorless solid (0.46 g, 65%). Mp: 147–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.86 (3 H, s), 3.27 (3 H, s), 3.45 (2 H, t, *J* = 7.5 Hz), 3.85 (2 H, t, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7, 40.2, 40.7, 44.0, 154.8. IR (neat): 1715 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_{10}N_2O_3NaS$ $[M+Na]^+$: 201.0304, found 201.0303.



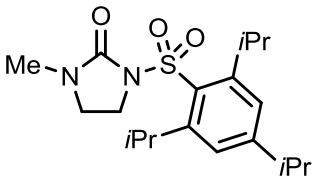
56F

1-Methyl-3-(*p*-methoxybenzenesulfonyl)-2-imidazolidone (56F) (Table 10, entry 5): To a solution of **S8**[52] (0.25 g, 2.5 mmol) in THF (13 mL, 0.20 M) were added NaH (0.20 g, 5.0 mmol) and *p*-MeO-$C_6H_4SO_2Cl$ (0.79 g, 3.8 mmol) at 0 °C. After stirring for 13 h at rt, the reaction was stopped by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:1) to provide the titled compound **56F** (0.51 g, 75%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75 (3 H, s), 3.36 (2 H, dd, *J* = 7.0, 8.5 Hz), 3.81 (2 H, dd, *J* = 7.0, 8.5 Hz), 6.98 (2 H, d, *J* = 9.0 Hz), 7.97 (2 H, d *J* = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7, 41.7, 43.7, 55.6, 114.1, 129.2, 130.3, 154.3, 163.7. HRMS (MALDI) Calcd for $C_{11}H_{14}N_2O_4Na$ S$[M+Na]^+$: 293.0566, found 293.0565.



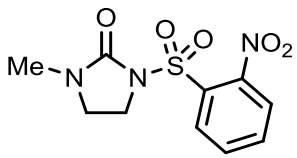
56G

1-Methyl-3-(*p*-chloro-benzenesulfonyl)-2-imidazolidone (56G) (Table 10, entry 7): To a solution of **S8**[52] (0.25 g, 2.5 mmol) in THF (13 mL, 0.20 M) were added NaH (0.20 g, 5.0 mmol) and *p*-Cl-$C_6H_4SO_2Cl$ (0.80 g, 3.8 mmol) at 0 °C. After stirring for 13 h at rt, the reaction was stopped by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:1) to provide the titled compound **56G** (0.48 g, 70%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.76 (3 H, s), 3.37–3.40 (2 H, m), 3.81–3.84 (2 H, m), 7.49 (2 H, d, *J* = 9.0 Hz), 7.98 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.7, 41.7, 43.7, 129.3, 129.6, 136.2, 140.4, 153.9. HRMS (MALDI) Calcd for $C_{10}H_{11}N_2O_3NaSCl$ $[M+H]^+$: 297.0071, found 297.0072.



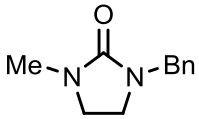
56H

1-Methyl-3-(2,4,6-triisopropylbenzenesulfonyl)-2-imidazolidone (56H) (Table 10, entry 8): To a solution of **S8**[52] (0.25 g, 2.5 mmol) in THF (13 mL, 0.20 M) were added NaH (0.20 g, 5.0 mmol) and 2,4,6-Triisopropylbenzenesulfonyl Chloride (1.2 g, 3.8 mmol) at 0 °C. After stirring for 13 h at rt, the reaction was stopped by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:1) to provide the titled compound **56H** (0.98 g, 70%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (6 H, d, *J* = 7.0 Hz), 1.27 (12 H, d, *J* = 7.0 Hz), 2.77 (3 H, s), 2.88 (1 H, sep, *J* = 7.0 Hz), 3.44 (2 H, dd, *J* = 7.0, 9.0 Hz), 3.94 (2 H, dd, *J* = 7.0, 9.0 Hz), 4.13 (2 H, sep, *J* = 7.0 Hz), 7.17 (2 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.5, 24.5, 29.3, 30.6, 34.1, 40.2, 44.2, 123.8, 131.7, 151.3, 153.5, 155.0. HRMS (MALDI) Calcd for $C_{19}H_{30}N_2O_3NaS$ $[M+Na]^+$: 389.1869, found 389.1870.



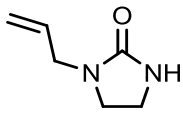
56I

1-Methyl-3-(2-nitrobenzenesulfonyl)-2-imidazolidone (56I) (Table 10, entry 9): To a solution of 1-Methyl-2-imidazolidone **S8**[52] (0.25 g, 2.5 mmol) in dioxane (46 mL, 0.20 M) were added 60% NaH (0.74 g, 18 mmol) and NsCl (3.1 g, 14 mmol) at 0 °C. After stirring for 2 h at 65 °C, the reaction was cooled to 0 °C. To the solution was added NsCl (3.1 g, 14 mmol). After stirring for 11 h at rt, the reaction was stopped by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from MeOH to provide the titled compound **56I** (1.3 g, 45%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.79 (3 H, s), 3.52 (2 H, dd, *J* = 6.5, 8.5 Hz), 4.07 (2 H, dd, *J* = 6.5, 8.5 Hz), 7.67–7.78 (3 H, m), 8.43–8.48 (1 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.6, 41.5, 44.3, 123.9, 131.8, 131.9, 134.0, 134.5, 147.8, 153.5. HRMS (MALDI) Calcd for $C_{10}H_{11}N_3O_5NaS$ $[M+Na]^+$: 308.0312, found 308.0309.



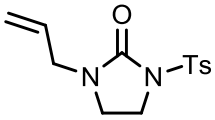
13B

1-Methyl-3-benzyl-2-imidazolidone (13B) (Scheme 28): To a solution of 1-methyl-2-imidazolidinone **S8**[52] (0.56 g, 5.6 mmol) in THF (30 mL, 0.20 M) were added 60% NaH (0.45 g, 11 mmol) and BnBr (0.88 mL, 7.3 mmol) at 0 °C. After stirring for 11 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:1) to provide the titled compound **13B** as a colorless oil (0.98 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.80 (3 H, s), 3.11–3.16 (2 H, m), 3.22–3.26 (2 H, m), 4.35 (2 H, s), 7.21–7.26 (3 H, m), 7.28–7.33 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.3, 41.9, 44.9, 48.3, 127.2, 128.0, 128.4, 137.2, 161.4. IR (neat): 2855, 1695 cm^{-1}. HRMS (MALDI) Calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$: 191.1179, found 191.1180.



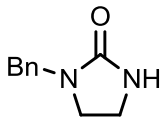
S9

1-Allyl-2-imidazolidone (S9): A solution of 2-imidazolidinone (0.40 g, 4.7 mmol) in 47 ml of 1,4-dioxane was prepared in a 100 ml 3-neck flask. 60% NaH (0.22 g, 5.6 mmol) was added slowly under an atmosphere of Ar with vigorous stirring. The milky solution was heated to 65 °C and stirred at this temperature for 2 h and then cooled to 0 °C. Allylbromide (0.47 mL, 5.6 mmol) was added slowly via syringe and the resulting mixture was stirred at room temperature for 14 h. The reaction was quenched by adding 1N HCl aq. and the mixture was concentrated under reduced pressure. The residue was purified twice by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to provide the titled compound **S9** as a colorless solid (0.21 g, 36%). Mp: 55–57 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.36–3.44 (4 H, m), 3.79 (2 H, d, *J* = 6.0 Hz), 4.81 (NH, brs), 5.16–5.22 (2 H, m), 5.76 (1 H, tdd, *J* = 6.0, 10.0, 17.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.1, 44.7, 46.4, 117.5, 133.3, 162.6. IR (neat): 3296, 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_{11}N_2O$ $[M+H]^+$: 127.0866, found 127.0864.



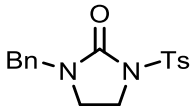
56J

1-Allyl-3-tosyl-2-imidazolidone (56J) (Table 12, entry 2): To a solution of **S9** (0.86 g, 6.8 mmol) in THF (34 mL, 0.20 M) were added *n*-BuLi (2.7 mL, 7.2 mmol, 2.65 M) at –78 °C. After stirring for 10 min, a solution of TsCl (1.7 g, 8.9 mmol) in THF (17 mL, 0.4 M) was added to the flask through a cannula. The mixture was stirred at room temperature for 30 min. The reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **56J** as a colorless solid (1.5 g, 77%). Mp: 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (3 H, s), 3.29–3.33 (2 H, m), 3.73 (2 H, dt, *J* = 6.5, 1.5 Hz), 3.79–3.83 (2 H, m), 5.11–5.18 (2 H, m), 5.64 (1 H, tdd, *J* = 6.5, 10.0, 16.5 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 7.90 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 41.1, 41.8, 46.4, 119.0, 128.0, 129.6, 131.5, 134.7, 144.7, 153.7. IR (neat): 1786 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{17}N_2O_3S$ $[M+H]^+$: 281.0954, found 281.0951.



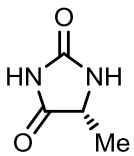
S10

1-Benzyl-2-imidazolidone (S10):[60] A solution of 2-imidazolidinone (0.40 g, 4.7 mmol) in 47 ml of 1,4-dioxane was prepared in a 100 ml 3-neck flask. 60% NaH (0.22 g, 5.6 mmol) was added slowly under an atmosphere of Ar with vigorous stirring. The milky solution was heated to 65 °C and stirred at this temperature for 2 h and then cooled to 0 °C. BnBr (0.67 ml, 5.6 mmol) was added slowly via syringe and the resulting mixture was stirred at room temperature for 14 h. The reaction was quenched by adding 1N HCl aq. and the mixture was concentrated under reduced pressure. The residue was purified twice by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to provide the titled compound **S10** as a colorless solid (0.28 g, 34%). Mp: 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.29–3.62 (4 H, m), 4.39 (2 H, s), 7.27–7.41 (5 H, m).



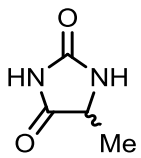
56K

1-Benzyl-3-tosyl-2-imidazolidone (56K) (Table 12, entry 3): To a solution of **S10** (0.20 g, 1.1 mmol) in THF (6.0 mL, 0.20 M) were added 60% NaH (0.23 g, 5.7 mmol) at 0 °C. After stirring for 10 min, TsCl (0.26 g, 1.4 mmol) was added. The mixture was stirred at room temperature for 18 h. The reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **56K** as a colorless solid (0.29 g, 78%). Mp: 119–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (3 H, s), 3.22 (2 H, dd, J = 6.5, 7.5 Hz), 3.81 (2 H, dd, J = 6.5, 7.5 Hz), 7.15–7.20 (2 H, m), 7.27–7.32 (3 H, m), 7.35 (2 H, d, J = 8.0 Hz), 7.95 (2 H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 41.0, 41.8, 47.9, 128.0, 128.2, 128.3, 128.8, 130.0, 134.8, 135.3, 144.8, 154.0. IR (neat): 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{18}N_2O_3NaS$ $[M+Na]^+$: 353.0930, found 353.0929.



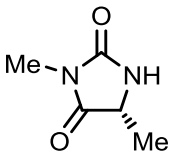
(*R*)-**S11**

(5*R*)-5-Methylimidazolidine-2,4-dione ((*R*)-S11): A round bottomed flask equipped with a reflux condenser was loaded with *D*-alanine (0.29 g, 3.3 mmol) and potassium cyanate (0.36 g, 4.4 mmol). Water was added (20 mL, 0.16 M) and the mixture stirred at 90 °C for 2 h. After the solution was cooled to room temperature, conc. HCl (20 mL) was added and heating continued at 90 °C for 1 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:5) to provide the titled compound (*R*)-**S11** as a colorless solid (0.33 g, 88%). Mp: 140–142 °C. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.36 (3 H, d, *J* = 7.0 Hz), 4.10 (1 H, q, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.4, 56.4, 160.6, 180.0. IR (neat): 3458, 3401, 1695 cm^{-1}. HRMS (MALDI) Calcd for $C_4H_7N_2O_2$ $[M+H]^+$: 115.0502, found 115.0503. The absolute configuration was assigned on the basis of that of *D*-alanine.



(±)-**S11**

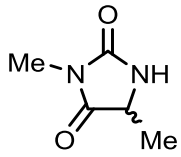
(±)-5-Methylimidazolidine-2,4-dione ((±)-S11): A round bottomed flask equipped with a reflux condenser was loaded with *DL*-alanine (0.29 g, 3.3 mmol) and potassium cyanate (0.36 g, 4.4 mmol). Water was added (20 mL, 0.16 M) and the mixture stirred at 90 °C for 2 h. After the solution was cooled to room temperature, conc. HCl (20 mL) was added and heating continued at 90 °C for 1 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:5) to provide the titled compound (±)-**S11** as a colorless solid (0.33 g, 88%). Mp: 141–143 °C. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.36 (3 H, d, *J* = 7.5 Hz), 4.10 (1 H, q, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.4, 56.4, 160.6, 180.0. IR (neat): 3458, 3410, 1695 cm^{-1}. HRMS (MALDI) Calcd for $C_4H_7N_2O_2$ $[M+H]^+$: 115.0502, found 115.0508.



(*R*)-**S12**

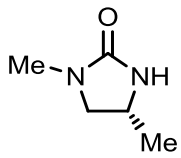
(5*R*)-3,5-Dimethylimidazolidine-2,4-dione ((*R*)-S12): To a solution of (5*R*)-5-methylimidazolidine-2,4-dione ((*R*)-**S11**) (0.30 g, 2.6 mmol) in DMF (13 mL, 0.20 M) were added 60% NaH (0.11 g, 2.6 mmol) and MeI (0.17 mL, 2.8 mmol) at 0 °C. After stirring for 11 h at room temperature, the reaction was quenched by adding 1N HCl and the mixture was evaporated

under reduced pressure until a white solid appeared. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:15) to provide the titled compound (*R*)-**S5** as a colorless solid (0.31 g, 91%). Mp: 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (3 H, d, *J* = 7.0 Hz), 2.92 (3 H, s), 3.93 (1 H, q, *J* = 7.0 Hz), 8.78 (NH, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 27.1, 58.4, 155.9, 174.1. IR (neat): 3277, 1699 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_9N_2O_2$ $[M+H]^+$: 129.0659, found 129.0660. The absolute configuration was assigned on the basis of that of (*R*)-**S12**, which was synthesized from *D*-alanine.



(±)-**S12**

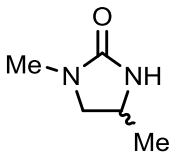
(±)-3,5-Dimethylimidazolidine-2,4-dione ((±)-S12):[61] To a solution of (±)-5-methylimidazolidine-2,4-dione ((±)-**S11**) (0.67 g, 5.8 mmol) in DMF (14 mL, 0.41 M) were added 60% NaH (0.26 g, 5.8 mmol) and MeI (0.40 mL, 6.4 mmol) at 0 °C. After stirring for 13 h at room temperature, the reaction was quenched by adding 1N HCl and the mixture was evaporated under reduced pressure until a white solid appeared. The residue was purified by flash column chromatography on silica gel (EtOAc only) to provide the titled compound (±)-**S12** as a colorless solid (0.35 g, 47%). Mp: 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 (3 H, d, *J* = 7.0 Hz), 3.00 (3 H, s), 4.09 (1 H, q, *J* = 7.0 Hz), 6.64 (NH, brs). IR (neat): 3277, 1699 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_9N_2O_2$ $[M+H]^+$: 129.0659, found 129.0663.



(*R*)-**S13**

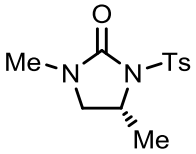
(4*R*)-1,4-Dimethylimidazolidin-2-one ((*R*)-S13): To a solution of $NaBH_4$ (0.18 g, 4.7 mmol) in THF (6.0 mL, 0.40 M) were added $BF_3{\cdot}OEt_2$ (0.71 mL, 5.7 mmol) at 0 °C. After stirring for 0.25 h, A solution of (5*R*)-3,5-dimethylimidazolidine-2,4-dione ((*R*)-**S12**) (0.30 g, 2.4 mmol) in anhydrous THF (6.0 mL, 0.40 M) was added to the flask through a cannula and washed with THF (12 mL, 0.20 M). After stirring for 11 h, the reaction was quenched by adding MeOH and 1N HCl. The mixture was evaporated under reduced pressure until a white solid appeared. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:15) to provide the titled compound (*R*)-**S13** as a colorless solid (0.17 g, 64%). Mp: 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (3 H, d, *J* =

5.5 Hz), 2.76 (3 H, s), 2.95 (1 H, dd, J = 7.0, 8.5 Hz), 3.51 (1 H, dd J = 8.5, 8.5 Hz), 3.73–3.80 (1 H, m), 4.65 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 30.5, 45.4, 54.7, 162.2. IR (neat): 3422, 1655 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_{11}N_2O$ $[M+H]^+$: 115.0866, found 115.0869. The absolute configuration was assigned on the basis of that of (*R*)-**S13**, which was synthesized from *D*-alanine.



(±)-**S13**

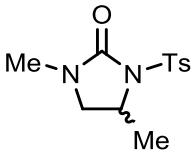
(±)-1,4-Dimethylimidazolidin-2-one ((±)-S13): To a solution of $NaBH_4$ (0.20 g, 5.3 mmol) in THF (7.0 mL) were added $BF_3{\cdot}OEt_2$ (0.80 mL, 6.4 mmol) at 0 °C. After stirring for 5 min, a solution of 3,5-dimethylimidazolidine-2,4-dione ((±)-**S12**) (0.34 g, 2.7 mmol) in anhydrous THF (7 mL, 0.39 M) was added to the flask through a cannula. After stirring for 3 h, the reaction was quenched by adding MeOH and 1N HCl. The mixture was evaporated under reduced pressure until a white solid appeared. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:12) to provide the titled compound (±)-**S13** as a colorless solid (0.23 g, 75%). Mp: 105–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (3 H, d, J = 6.5 Hz), 2.76 (3 H, s), 2.95 (1 H, dd, J = 6.5, 8.5 Hz), 3.51 (1 H, dd J = 8.5, 8.5 Hz), 3.73–3.80 (1 H, m), 4.73 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 30.5, 45.4, 54.7, 162.3. IR (neat): 3422, 1655 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_{11}N_2O$ $[M+H]^+$: 115.0866, found 115.0862.



(*R*)-**56L**

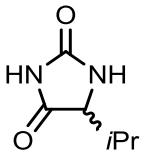
(4*R*)-1,4-Dimethyl-3-tosyl-imidazolidin-2-one ((*R*)-56L) (Table 12, entry 4): To a solution of (4*R*)-1,4-dimethylimidazolidin-2-one ((*R*)-**S13**) (0.17 g, 1.5 mmol) in THF (8.0 mL, 0.20 M) were added 60% NaH (0.30 g, 7.6 mmol) and TsCl (0.35 g, 1.8 mmol) at 0 °C. After stirring for 10 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:20) to provide the titled compound (*R*)-**56L** as a colorless solid (0.32 g, 79%). Mp: 83–85 °C. $[\alpha]_D^{20}$ = +7.4 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (3 H, d, J = 6.0 Hz), 2.40 (3 H, s), 2.73 (3 H, s), 2.92 (1 H, dd, J = 4.0, 8.5 Hz), 3.55 (1 H, dd J = 8.5, 8.5 Hz),

4.31–4.39 (1 H, m), 7.29 (2 H, d, J = 8.0 Hz), 7.92 (2 H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 21.7, 30.5, 50.2, 51.9, 128.1, 129.4, 136.4, 144.4, 153.9. IR (neat): 2924, 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{17}N_2O_3S$ $[M+H]^+$: 269.0954, found 269.0956. The enantiomeric excess of the product (*R*)-**56L** was determined to be 89% by HPLC with CHIRALCEL® AD-3 (Eluent: hexane/2-PrOH = 90/10, Flow rate: 1.0 mL/min, Retention time: t_R of (*S*)-isomer = 35.0 min, t_R of (*R*)-isomer = 38.2 min). The absolute configuration was assigned on the basis of that of (*R*)-**S13**, which was synthesized from *D*-alanine.



(±)-**56L**

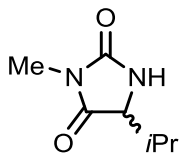
(±)-1,4-Dimethyl-3-tosyl-imidazolidin-2-one ((±)-56L): To a solution of (±)-1,4-dimethylimidazolidin-2-one ((±)-**S13**) (0.22 g, 2.2 mmol) in THF (11 mL, 0.20 M) were added 60% NaH (0.13 g, 3.3 mmol) and TsCl (0.52 g, 2.7 mmol) at 0 °C. After stirring for 10 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound (±)-**56L** as a colorless solid (0.45 g, 75%). Mp: 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (3 H, d, J = 6.0 Hz), 2.40 (3 H, s), 2.73 (3 H, s), 2.92 (1 H, dd, J = 4.5, 9.0 Hz), 3.54 (1 H, dd, J = 9.0, 9.0 Hz), 4.31–4.39 (1 H, m), 7.29 (2 H, d, J = 8.0 Hz), 7.92 (2 H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 21.7, 30.5, 50.2, 51.9, 128.0, 129.4, 136.3, 144.4, 153.9. IR (neat): 1734 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{16}N_2O_3NaS$ $[M+Na]^+$: 291.0774, found 291.0771.



(±)-**S14**

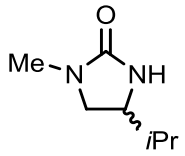
(±)-5-Isopropylimidazolidine-2,4-dione ((±)-S14):[62] A round bottomed flask equipped with a reflux condenser was loaded with *DL*-valine (1.1 g, 9.8 mmol) and potassium cyanate (1.1 g, 13 mmol). Water was added (60 mL, 0.16 M) and the mixture stirred at 90 °C for 2 h. After the solution was cooled to room temperature, conc. HCl (60 mL) was added and heating continued at 90 °C for 1 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was

purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:15) to provide the titled compound (±)-**S14** as a colorless solid (1.3 g, 94%). Mp: 140–142 °C.



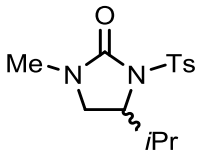
(±)-**S15**

(±)-5-Isopropyl-3-methylimidazolidine-2,4-dione ((±)-S15): To a solution of (±)-**S14** (2.0 g, 14 mmol) in DMF (47 mL, 0.30 M) were added 60% NaH (0.56 g, 14 mmol) and MeI (0.92 mL, 15 mmol) at 0 °C. After stirring for 12 h at room temperature, the reaction was quenched by adding 1N HCl and the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to provide the titled compound (±)-**S15** as a colorless solid (1.8 g, 80%). Mp: 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (3 H, d, *J* = 7.5 Hz), 1.03 (3 H, d, *J* = 7.5 Hz), 2.15–2.25 (1 H, m), 2.96 (3 H, s), 3.92 (1 H, dd, *J* = 1.0, 3.5 Hz), 7.16 (NH, brs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 18.7, 24.2, 30.1, 62.6, 158.8, 173.8. IR (neat): 3227, 2957, 1702 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_9N_2O_2$ $[M+H]^+$: 129.0659, found 129.0660.



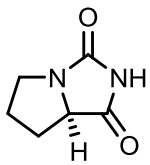
(±)-**S16**

(±)-4-Isopropyl-1-methylimidazolidin-2-one ((±)-S16): To a solution of $NaBH_4$ (0.77 g, 4.9 mmol) in THF (12 mL, 0.40 M) were added $BF_3{\cdot}OEt_2$ (1.5 mL, 12 mmol) at 0 °C. After stirring for 0.25 h, A solution of (±)-**S15** (0.30 g, 2.4 mmol) in anhydrous THF (24 mL, 0.2 M) was added to the flask through a cannula. After stirring for 11 h, the reaction was quenched by adding MeOH and 1N HCl. The mixture was evaporated under reduced pressure until a white solid appeared. The residue was purified by flash column chromatography on silica gel (EtOAc) to provide the titled compound (±)-**S16** as a colorless solid (0.43 g, 61%). Mp: 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (3 H, d, *J* = 7.0 Hz), 0.91 (3 H, d, *J* = 7.0 Hz), 1.58–1.68 (1 H, m), 2.75 (3 H, s), 3.04 (1 H, dd, *J* = 7.0, 9.0 Hz), 3.35 (1 H, dt, *J* = 9.0, 7.0 Hz), 3.44 (1 H, dd, *J* = 9.0, 9.0 Hz), 4.97 (NH, brs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 18.4, 30.4, 33.0, 51.3, 55.7, 162.4. IR (neat): 3220, 2965, 1696 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_{11}N_2O$ $[M+H]^+$: 115.0866, found 115.0869.



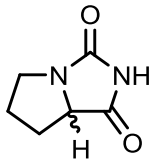
(±)-**56M**

(±)-4-Isopropyl-1-methyl-3-tosylimidazolidin-2-one ((±)-56M) (Table 12, entry 5): To a solution of (±)-**S16** (0.43 g, 3.0 mmol) in THF (15 mL, 0.20 M) were added 60% NaH (0.60 g, 15 mmol) and TsCl (0.69 g, 3.6 mmol) at 0 °C. After stirring for 7 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound (±)-**56M** as a colorless solid (0.71 g, 79%). Mp: 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.72 (3 H, d, *J* = 7.0 Hz), 0.90 (3 H, d, *J* = 7.0 Hz), 2.41 (3 H, s), 2.43–2.51 (1 H, m), 2.74 (3 H, s), 3.08 (1 H, dd, *J* = 3.5, 9.5 Hz), 3.37 (1 H, dd *J* = 9.5, 9.5 Hz), 4.27 (1 H, dt, *J* = 9.5, 3.5 Hz), 7.30 (2 H, d, *J* = 8.5 Hz), 7.94 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 17.7, 21.6, 30.3, 30.3, 44.7, 58.3, 128.0, 129.4, 136.5, 144.3, 154.2. IR (neat): 2966, 1724 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{17}N_2O_3S$ $[M+H]^+$: 269.0954, found 269.0956.



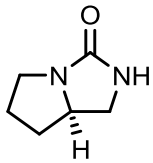
(*R*)-**S17**

(*R*)-Tetrahydro-1H-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione ((*R*)-S17): A round bottomed flask equipped with a reflux condenser was loaded with *D*-proline (2.0 g, 17 mmol) and potassium cyanate (1.9 g, 24 mmol). Water (0.11 L, 0.15 M) was added and the mixture stirred at 100 °C for 13 h. After the solution was cooled to room temperature, HCl (0.11 L, 6 N) was added and heating continued at 100 °C for 2 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:20) to provide the titled compound (*R*)-**S17** as a colorless solid (1.3 g, 55%). Mp: 156–159 °C. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.72 (1 H, tt, *J* = 8.0, 11.5 Hz), 2.01–2.22 (3 H, m), 3.23 (1 H, ddd, *J* = 4.5, 8.0, 11.0 Hz), 3.59 (1 H, ddd, *J* = 8.0, 8.0, 11.0 Hz), 4.17 (1 H, dd, *J* = 8.0, 8.0 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 29.0, 29.1, 47.1, 67.0, 164.1, 178.6. IR (neat): 3188, 1759 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_9N_2O_2$ $[M+H]^+$: 141.0659, found 141.0658. The absolute configuration was assigned on the basis of that of *D*-proline.



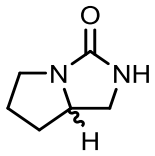
(±)-**S17**

(±)-Hexahydropyrrolo[1,2-*c*]imidazol-1,3-dione ((±)-S17): A round bottomed flask was loaded with *DL*-proline (5.0 g, 43 mmol) and potassium cyanate (4.3 g, 52 mmol). Water (0.26 L, 0.17 M) was added and the mixture stirred at 95 °C for 10 h. After the solution was cooled to room temperature, HCl (0.26 L, 1 N) was added and heating continued at 95 °C for 1 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15) to provide the titled compound (±)-**S17** as a colorless solid (3.7 g, 60%). Mp: 158–160 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 1.66–1.78 (1 H, m), 1.98–2.24 (3 H, m), 3.14–3.22 (1 H, m), 3.59 (1 H, ddd, *J* = 7.5, 7.5, 10.5 Hz), 4.17 (1 H, dd, *J* = 7.0, 9.5 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 29.0, 29.1, 47.1, 67.0, 164.1, 178.6. IR (neat): 3188, 1755 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_9N_2O_2$ $[M+H]^+$: 141.0659, found 141.0662.



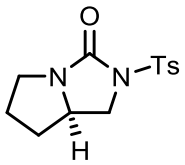
(*R*)-**S18**

(*R*)-Hexahydropyrrolo[1,2-*c*]imidazol-3-one ((*R*)-S18): To a solution of $NaBH_4$ (0.65 g, 17 mmol) in THF (21 mL, 0.81 M) was added $BF_3{\cdot}OEt_2$ (2.6 mL, 21 mmol) at 0 °C. After stirring for 20 min, a solution of (*S*)-**S17** (1.2 g, 8.6 mmol) in THF (42 mL, 0.20 M) was added to the flask through a cannula. The mixture was stirred at room temperature for 2 days. The reaction was quenched by adding MeOH and the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15) to provide the titled compound (*R*)-**S18** as a colorless solid (0.82 g, 76%). Mp: 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (1 H, tt, *J* = 8.5, 11.5 Hz), 1.74–1.97 (3 H, m), 2.98–3.06 (1 H, m), 3.28 (1 H, dd, *J* = 1.5, 8.5 Hz), 3.55–3.64 (2 H, m), 3.69–3.77 (1 H, m), 5.70 (NH, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.2, 30.4, 42.9, 45.1, 59.4, 165.9. IR (neat): 3265, 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_{11}N_2O$ $[M+H]^+$: 127.0866, found 127.0865. The absolute configuration was assigned on the basis of that of (*R*)-**S10**, which was synthesized from *D*-proline.



(±)-**S18**

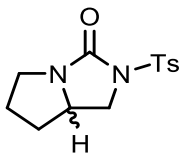
(±)-Hexahydropyrrolo[1,2-*c*]imidazol-3-one ((±)-S18): To a solution of $NaBH_4$ (1.6 g, 43 mmol) in THF (70 mL, 0.30 M) was added $BF_3{\cdot}OEt_2$ (6.5 mL, 51 mmol) at 0 °C. After stirring for 20 min, a solution of (±)-**S17** (3.0 g, 21 mmol) in THF (143 mL, 0.15 M) was added to the flask through a cannula. The mixture was stirred at room temperature for 19 h. The reaction was quenched by adding MeOH and the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15) to provide the titled compound (±)-**S18** as a colorless solid (2.2 g, 80%). Mp: 171–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39–1.47 (1 H, m), 1.78–1.86 (1 H, m), 1.92–1.99 (2 H, m), 3.04 (1 H, ddd, *J* = 4.0, 9.0, 13.5 Hz), 3.29 (1 H, dd, *J* = 2.0, 9.0 Hz), 3.59–3.65 (2 H, m), 3.73–3.78 (1 H, m), 5.09 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.2, 30.5, 42.9, 45.1, 59.4, 165.8. IR (neat): 3266, 1705 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_{11}N_2O$ $[M+H]^+$: 127.0866, found 127.0866.



(*R*)-**56N**

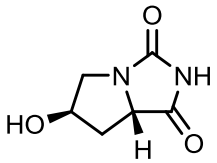
(*R*)-2-Tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one ((*R*)-56N) (Table 12, entry 6): To a solution of (*S*)-hexahydropyrrolo[1,2-*c*]imidazol-3-one ((*R*)-**S18**) (0.81 g, 6.4 mmol) in THF (32 mL, 0.20 M) were added 60% NaH (1.3 g, 32 mmol) and TsCl (1.5 g, 7.7 mmol) at 0 °C. After stirring for 12 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:2) to provide the titled compound (*R*)-**56N** as a colorless solid (1.6 g, 91%). Mp: 111–113 °C. $[\alpha]_D^{20}$ = +9.4 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29–1.40 (1 H, m), 1.80–1.88 (1 H, m), 1.94–2.05 (2 H, m), 2.42 (3 H, s), 2.99–3.07 (1 H, m), 3.51–3.71 (2 H, m), 3.76 (1 H, dd, *J* = 3.5, 9.5 Hz), 3.98 (1 H, dd, *J* = 8.5, 9.5 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.91 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 25.0, 30.7, 44.7, 47.0, 55.6, 127.9, 129.6, 135.0, 144.8, 156.5. IR (neat): 1748 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{16}N_2O_3NaS$ $[M+Na]^+$: 303.0774, found 303.0775. The enantiomeric excess of the product (*R*)-**56N** was determined to be 88% by HPLC with CHIRALCEL® OD-3 (Eluent: hexane/2-PrOH = 90/10, Flow rate: 1.0

mL/min, Retention time: t_R of (*S*)-isomer = 44.5 min, t_R of (*R*)-isomer = 48.5 min). The absolute configuration was assigned on the basis of that of (*R*)-**S18**, which was synthesized from *D*-proline.



(±)-**56N**

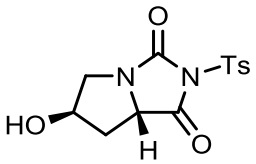
(±)-2-Tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one ((±)-56N): To a solution of hexahydropyrrolo[1,2-*c*]imidazol-3-one ((±)-**S18**) (2.0 g, 16 mmol) in THF (80 mL, 0.20 M) were added 60% NaH (2.5 g, 64 mmol) and TsCl (3.9 g, 21 mmol) at 0 °C. After stirring for 12 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound (±)-**56N** as a colorless solid (3.1 g, 70%). Mp: 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30–1.38 (1 H, m), 1.81–2.01 (3 H, m), 2.42 (3 H, s), 3.03 (1 H, ddd, *J* = 4.0, 9.5, 11.0 Hz), 3.55 (1 H, ddd, *J* = 8.0, 8.0, 12.0 Hz), 3.64–3.70 (1 H, m), 3.76 (1 H, dd, *J* = 3.5, 10.0 Hz), 3.98 (1 H, dd, *J* = 8.0, 10.0 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.91 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 25.0, 30.7, 44.7, 47.0, 55.6, 127.9, 129.6, 135.0, 144.8, 156.5. IR (neat): 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{16}N_2O_3NaS$ $[M+Na]^+$: 303.0774, found 303.0769.



S19

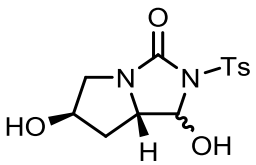
(6*R*,7a*S*)-6-Hydroxytetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (S19): A round bottomed flask was loaded with *trans*-4-hydroxy-*L*-proline (0.13 g, 1.0 mmol) and potassium cyanate (0.11 g, 1.4 mmol). Water was added (6.0 mL, 0.16 M) and the mixture stirred at 90 °C for 10 h. After the solution was cooled to room temperature, 1N HCl (6.0 mL) was added and heating continued at 90 °C for 1 h. The solvent was evaporated under reduced pressure until a white solid appeared. The crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:7) to provide the titled compound **S19** as a colorless solid (0.12 g, 74%). Mp: 171–173 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.77 (1 H, ddd, *J* = 5.0, 11.5, 12.5 Hz), 1.93 (1 H, dd, *J* = 7.0, 12.5 Hz), 2.89 (1 H, d, *J* = 11.5 Hz), 3.62 (1 H, dd, *J* = 5.0, 11.5 Hz), 4.26 (1 H, dd, *J* = 7.0, 11.5 Hz), 4.44 (1 H, s), 5.20 (OH,

brs), 10.7 (NH, brs). ^{13}C NMR (125 MHz, CD_3OD) δ: 38.3, 55.9, 65.8, 75.4, 163.8, 178.4. IR (neat): 3503, 1717 cm^{-1}. HRMS (MALDI) Calcd for $C_6H_9N_2O_3$ $[M+H]^+$: 157.0608, found 157.0608. The absolute configuration was assigned on the basis of that of *trans*-4-hydroxy-*L*-proline.



S20

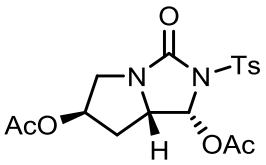
(6*R*,7a*S*)-6-Hydroxy-2-tosyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (S20): To a solution of **S19** (1.2 g, 7.7 mmol) in CH_2Cl_2 (80 mL, 0.10 M) were added Et_3N (2.0 mL, 15 mmol), TsCl (1.5 g, 7.7 mmol) and DMAP (96 mg, 0.77 mmol) at room temperature. After stirring for 80 min, the reaction was quenched by adding H_2O and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 5:1) to provide the titled compound **S20** as a colorless solid (0.66 g, 28%). Mp: 153–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (1 H, ddd, *J* = 5.0, 11.0, 14.5 Hz), 2.26 (1 H, dd, *J* = 6.0, 14.5 Hz), 2.45 (3 H, s), 3.21 (1 H, d, *J* = 12.5 Hz), 3.87 (1 H, dd, *J* = 5.0, 12.5 Hz), 4.45 (1 H, dd, *J* = 6.0, 11.0 Hz), 4.68 (1 H, t, *J* = 5.0 Hz), 7.36 (2 H, d, *J* = 8.0 Hz), 8.02 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 37.3, 54.5, 61.6, 72.8, 128.6, 130.0, 134.7, 146.4, 153.6, 168.4. IR (neat): 3516, 1734 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{14}N_2O_5NaS$ $[M+Na]^+$: 333.0516, found 333.0519. The absolute configuration was assigned on the basis of that of **S19**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



S21

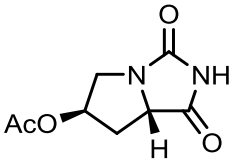
(6*R*,7a*S*)-1,6-Dihydroxy-2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one (S21): To a solution of $NaBH_4$ (0.23 g, 6.1 mmol) in THF (5.0 mL, 1.2 M) were added $BF_3{\cdot}OEt_2$ (0.92 mL, 7.3 mmol) at 0 °C. After stirring for 10 min, a solution of **S20** (0.63 g, 2.0 mmol) in THF (5.0 mL, 0.40 M) was added to the flask through a cannula. The mixture was stirred at room temperature for 8 h. The reaction was quenched by adding MeOH and the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to provide the titled compound **S21** as a colorless solid (0.57 g, 90%). Mp: 157–160 °C. ^{1}H NMR (400 MHz, CD_3OD) δ:

1.28–1.36 (0.5 H, m), 1.73–1.78 (0.5 H, m), 1.98–2.09 (1 H, m), 2.42 (3 H, d, *J* = 3.5 Hz), 2.89 (0.5 H, d, *J* = 12.0 Hz), 2.98 (0.5 H, d, *J* = 12.0 Hz), 3.51 (0.5 H, dd, *J* = 4.5, 12.0 Hz), 3.70–3.77 (1 H, m), 4.28–4.34 (0.5 H, m), 4.41 (0.5 H, dd, *J* = 5.0, 5.0 Hz), 4.48–4.50 (0.5 H, m), 5.72 (0.5 H, s), 5.90 (0.5 H, d, *J* = 6.0 Hz), 7.35–7.39 (2 H, m), 7.91–7.96 (2 H, m). ^{13}C NMR (125 MHz, CD_3OD) δ: 21.5, 21.6, 34.1, 38.8, 53.7, 55.8, 61.5, 66.0, 72.1, 73.9, 82.0, 83.2, 129.4, 129.7, 130.3, 130.5, 137.7, 138.4, 145.9, 146.4, 155.5, 158.4. IR (neat): 3474, 3335, 1713 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{16}N_2O_5NaS$ [M+Na]$^+$: 335.0672, found 335.0673. The absolute configuration was assigned on the basis of that of **S20**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



56O

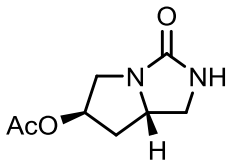
(1*R*,6*R*,7a*S*)-3-Oxo-2-tosylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,6-diyl diacetate (56O) (Table 12, entry 7): To a solution of **S21** (0.90 g, 2.9 mmol) in CH_2Cl_2 (30 mL, 0.10 M) were added Et_3N (2.0 mL, 14 mmol), Ac_2O (1.4 mL, 14 mmol) and DMAP (35 mg, 0.29 mmol) at room temperature. After stirring for 3 h, the reaction was quenched by adding H_2O and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **56O** as a colorless solid (0.59 g, 52%). Mp: 145–147 °C. $[\alpha]_D^{20}$ = –24.3 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72–1.82 (1 H, m), 1.94 (1 H, dd, *J* = 6.0, 14.0 Hz), 2.02 (3 H, s), 2.06 (3 H, s), 2.42 (3 H, s), 3.15 (1 H, d, *J* = 12.5 Hz), 3.74 (1 H, dd, *J* = 5.0, 12.5 Hz), 4.36–4.43 (1 H, m), 5.36 (1 H, brs), 6.69 (1 H, d, *J* = 6.5 Hz), 7.32 (2 H, d, *J* = 8.0 Hz), 7.92 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.3, 20.8, 21.6, 31.7, 50.2, 58.8, 74.9, 79.9, 128.4, 129.4, 135.8, 145.1, 152.3, 168.9, 170.0. IR (neat): 1744 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{20}N_2O_7NaS$ [M+Na]$^+$: 419.0883, found 419.0883. The absolute configuration was assigned on the basis of that of **S21**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



S22

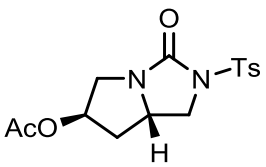
(6*R*,7a*S*)-1,3-Dioxohexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-6-yl acetate (S22): To a solution of **S19** (2.0 g, 13 mmol) in CH_2Cl_2 (0.13 L, 0.10 M) were added Et_3N (3.5 mL, 25 mmol) and Ac_2O (1.3 mL,

14 mmol) at room temperature. After stirring for 22 h, the reaction was quenched by adding H_2O and the mixture was extracted with CH_2Cl_2 twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:20) to provide the titled compound **S15** as a colorless solid (2.4 g, 95%). Mp: 148–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95 (1 H, ddd, *J* = 5.5, 11.0, 14.0 Hz), 2.09 (3 H, s), 2.37 (1 H, dd, *J* = 6.5, 14.0 Hz), 3.25 (1 H, d, *J* = 13.0 Hz), 4.02 (1 H, dd, *J* = 6.5, 13.0 Hz), 4.38 (1 H, dd, *J* = 6.5, 11.0 Hz), 5.50 (1 H, dd, *J* = 5.5, 5.5 Hz), 8.30 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.9, 34.2, 51.6, 63.3, 75.6, 159.4, 170.1, 173.1. IR (neat): 3210, 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_8H_{11}N_2O_4$ $[M+H]^+$: 199.0713, found 199.0712. The absolute configuration was assigned on the basis of that of **S19**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



S23

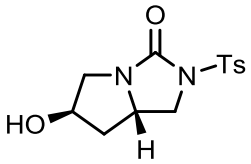
(6*R*,7a*S*)-3-Oxohexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-6-yl acetate (S23): To a solution of **S22** (0.98 g, 5.0 mmol) in THF (33 mL, 0.15 M) were added $BH_3{\cdot}SMe_2$ (0.94 g, 9.9 mmol) at room temperature. After stirring for 12 h at 60 °C, the reaction was quenched by adding MeOH and the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15) to provide the titled compound **S23** as a colorless oil (0.72 g, 78%). ^{1}H NMR (500 MHz, CD_3OD) δ: 1.66–1.72 (1 H, m), 2.03 (3 H, s), 2.07 (1 H, dd, *J* = 5.0, 13.5 Hz), 2.98 (1 H, dd, *J* = 1.0, 13.5 Hz), 3.28–3.31 (1 H, m), 3.63 (1 H, dd, *J* = 8.5, 8.5 Hz), 3.93 (1 H, dd, *J* = 6.5, 13.0 Hz), 3.99–4.04 (1 H, m), 5.28 (1 H, dd, *J* = 5.5, 5.5 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 21.0, 37.8, 43.0, 53.6, 59.3, 76.2, 167.4, 172.2. IR (neat): 3265, 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_8H_{13}N_2O_3$ $[M+H]^+$: 185.0921, found 185.0921. The absolute configuration was assigned on the basis of that of **S22**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



56P

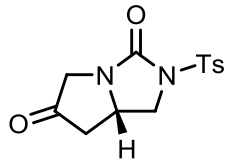
(6*R*,7a*S*)-3-Oxo-2-tosylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-6-yl-acetate (56P) (Table 12, entry

8): To a solution of **S23** (22 mg, 0.12 mmol) in THF (1.2 mL, 0.10 M) were added 60% NaH (12 mg, 0.30 mmol) and TsCl (31 mg, 0.16 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **56P** as a colorless solid (27 mg, 68%). Mp: 124–127 °C. $[\alpha]_D^{20}$ = –17.1 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.60 (1 H, m), 2.02 (3 H, s), 2.12 (1 H, dd, *J* = 5.0, 8.0 Hz), 2.42 (3 H, s), 3.00 (1 H, dd, *J* = 1.5, 13.5 Hz), 3.80 (1 H, dd, *J* = 2.5, 9.5 Hz), 3.90–4.04 (3 H, m), 5.28 (1 H, dd, *J* = 5.5, 5.5 Hz), 7.32 (2 H, d, *J* = 8.0 Hz), 7.90 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.9, 21.6, 37.5, 46.2, 52.3, 54.0, 74.1, 127.9, 129.7, 134.8, 145.1, 156.3, 170.1. IR (neat): 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{15}H_{18}N_2O_5NaS$ $[M+Na]^+$: 361.0829, found 361.0834. The absolute configuration was assigned on the basis of that of **S23**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



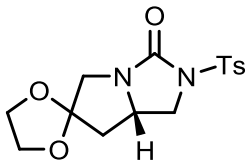
S24

(6*R*,7a*S*)-6-Hydroxy-2-tosylhexahydro-3*H*-pyrrolo[1,2-c]imidazol-3-one (S24): A round bottomed flask equipped with a reflux condenser was loaded with **56P** (0.15 g, 0.45 mmol) and ZnTAC[43] (8.0 mg, 5 wt%), MeOH (9.0 mL, 0.05 M) at room temperature. After stirring for 22 h at reflux, the mixture was concentrated under reduced pressure. The residue was filtered through Celite pad (washed with CH_2Cl_2) and concentrated under reduced pressure as a colorless solid (0.12 g, 93%). This compound **S24** was used for next reaction without purification due to the instability on silica gel column chromatography. Mp: 95–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.52 (1 H, m), 2.03 (1 H, dd, *J* = 4.5, 13.5 Hz), 2.43 (1 H, s), 2.96 (1 H, d, *J* = 13.0 Hz), 3.75–3.81 (1 H, m), 3.86 (1 H, dd, *J* = 5.5, 13.0 Hz), 4.00–4.06 (2 H, m), 4.55 (1 H, dd, *J* = 5.5, 5.5 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.89 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 40.6, 46.5, 53.8, 54.9, 71.8, 127.9, 129.7, 134.9, 145.0, 156.5. IR (neat): 3476, 1726 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{16}N_2O_4NaS$ $[M+Na]^+$: 319.0723, found 319.0721. The absolute configuration was assigned on the basis of that of **56P**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



(*S*)-**S25**

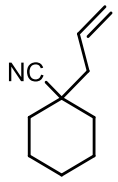
(*S*)-2-Tosyltetrahydro-3*H*-pyrrolo[1,2-c]imidazole-3,6(5*H*)-dione ((*S*)-S25): To a solution of **S24** (0.72 g, 2.4 mmol) in CH_2Cl_2 (24 mL, 0.10 M) were added Celite (4.2 g, 600 wt%) and PCC (1.0 g, 4.7 mmol) at room temperature. After stirring for 25 h at room temperature, the reaction mixture was directly applied on silica gel of flash column chromatography and purified (EtOAc/hexane = 3:2) to provide the titled compound (*S*)-**S25** as a colorless solid (0.71 g, 100%). Mp: 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (1 H, dd, *J* = 9.5, 18.0 Hz), 2.34 (3 H, s), 2.63 (1 H, dd, *J* = 5.5, 18.0 Hz), 3.29 (1 H, d, *J* = 19.0 Hz), 3.93 (1 H, d, *J* = 7.5 Hz), 4.00 (1 H, d, *J* = 19.0 Hz), 4.14–4.22 (2 H, m), 7.34 (2 H, d, *J* = 8.0 Hz), 7.91 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7, 42.8, 47.6, 52.2, 52.5, 128.0, 129.8, 134.5, 145.4, 155.7, 209.6. IR (neat): 2922, 1734 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{14}N_2O_4NaS$ $[M+Na]^+$: 317.0566, found 317.0557. The absolute configuration was assigned on the basis of that of **S24**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



(*S*)-**56S**

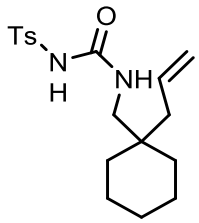
(*S*)-2-Tosyltetrahydro-3*H*,5*H*-spiro[pyrrolo[1,2-*c*]imidazole-6,2′ -[1,3]dioxolan]-3-one ((*S*)-56S) (Table 12, entry 9): A round bottomed flask equipped with a reflux condenser was loaded with (*S*)-**S25** (0.71 g, 2.4 mmol) and TsOH·H_2O (46 mg, 0.24 mmol), toluene (6.0 mL, 0.40 M) and ethylene glycol (6.0 mL, 0.40 M) at room temperature. After stirring for 11 h at reflux, the reaction was quenched by adding $NaHCO_3$ aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:2) to provide the titled compound (*S*)-**56S** as a colorless solid (0.76 g, 92%). Mp: 108–109 °C. $[\alpha]_D^{20}$ = +202.5 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.71 (1 H, dd, *J* = 9.0, 13.0 Hz), 2.15 (1 H, dd, *J* = 6.0, 13.0 Hz), 2.42 (3 H, s), 3.02 (1 H, d, *J* = 12.5 Hz), 3.63 (1 H, d, *J* = 12.5 Hz), 3.71 (1 H, dd, *J* = 3.5, 9.0 Hz), 3.76–4.06 (6 H, m), 7.31 (2 H, d, *J* = 8.0 Hz), 7.89 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 41.4, 47.7, 53.5, 54.0, 64.8, 64.9, 115.8, 127.9, 129.6, 134.8, 144.8, 156.1. IR (neat): 2924, 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{15}H_{19}N_2O_5S$ $[M+H]^+$: 339.1009, found 339.1011. The absolute configuration was assigned on the basis of that of **S25**, which was synthesized

from *trans*-4-hydroxy-*L*-proline.



S26

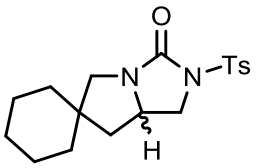
(±)-1-Allylcyclohexane-1-carbonitrile (S26):[63] To a solution of LHMDS in THF (11 mL, 1.0 M) was added cyclohexane carbonitrile (1.2 mL, 9.9 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 30 min. Allyl bromide (1.2 mL, 14.0 mmol) was added to the reaction mixture dropwise before allowing the reaction mixture to warm up to room temperature. After stirring for overnight, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:15) to provide the titled compound **S26** as a colorless oil (1.5 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.27 (3 H, m), 1.56–1.77 (5 H, m), 1.96 (2 H, d, *J* = 12.5 Hz), 2.28 (2 H, d, *J* = 7.5 Hz), 5.14–5.22 (2 H, m), 5.83 (1 H, tdd, *J* = 7.5, 10.0, 17.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.0, 25.3, 35.4, 38.8, 44.6, 119.6, 123.4, 132.0. IR (neat): 2934 cm^{-1}. HRMS (MALDI) Calcd for $C_{10}H_{15}NNa$ $[M+Na]^+$: 172.1097, found 172.1100.



S28

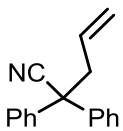
(±)-*N*-(((1-Allylcyclohexyl)methyl)carbamoyl)-4-methylbenzenesulfonamide (S28):[63] To a solution of $LiAlH_4$ (2.5 g, 66 mmol) in Et_2O (28 mL, 2.4 M) was added a solution of **S26** (2.5 g, 16 mmol) in Et_2O (56 mL, 0.30 M) through a cannula at 0 °C and then warmed slowly to room temperature and stirred overnight. The resulting suspension was cooled to 0 °C and quenched by slow addition of 6M NaOH (54 mL). The resulting mixture was extracted with ether (3×80 mL) and the combined ether extracts were dried ($MgSO_4$) and concentrated to give (1-allylcyclohexyl)methanamine (**S27**) (2.0 g) as a pale yellow. This compound **S27** was used for next reaction without purification. A round bottomed flask was loaded with **S27** (2.0 g, 13.0 mmol) and TsNCO (2.1 mL, 13.7 mmol) and CH_2Cl_2 (43 mL, 0.30 M) at room temperature. After stirring for 20 h, the reaction was quenched by adding H_2O and the mixture was extracted with CH_2Cl_2 twice. The combined organic extracts were washed

with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **S28** as a colorless solid (3.2 g, 56%, 2 steps). Mp: 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.16–1.44 (10 H, m), 1.98 (2 H, d, *J* = 7.5 Hz), 2.44 (3 H, s), 3.12 (2 H, d, *J* = 6.5 Hz), 5.06–5.10 (2 H, m), 5.76 (1 H, tdd, *J* = 7.5, 9.5, 18.0 Hz), 6.59 (1 H, t, *J* = 5.5 Hz), 7.32 (2 H, d, *J* = 8.0 Hz), 7.77 (2 H, d, *J* = 8.0 Hz), 8.24 (NH, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 21.6, 26.0, 33.2, 36.8, 40.6, 46.4, 117.9, 126.8, 129.9, 134.0, 136.7, 144.8, 151.6. IR (neat): 3362, 2926, 1667 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{26}N_2O_3NaS$ $[M+Na]^+$: 373.1556, found 373.1555.



(±)-**56R**

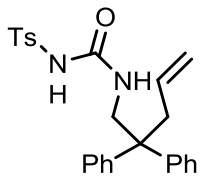
(±)-2'-Tosyltetrahydro-3'*H*,5'*H*-spiro[cyclohexane-1,6'-pyrrolo[1,2-*c*]imidazol]-3'-one ((±)-56R) (Table 12, entry 10):[63] A suspension of **S28** (2.3 g, 6.5 mol), NIS (2.9 g, 13 mmol), and $NaHCO_3$ (0.57 g, 6.8 mmol) in toluene (65 mL) was stirred at room temperature for 3 h. The reaction was quenched by adding Na_2SO_3 aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound (±)-**56R** as a colorless solid (1.4 g, 60%). Mp: 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16–1.50 (11 H, m), 1.90 (1 H, dd, *J* = 6.5, 12.5 Hz), 2.42 (3 H, s), 2.79 (1 H, d, *J* = 12.0 Hz), 3.39 (1 H, d, *J* = 12.0 Hz), 3.65 (1 H, dd, *J* = 4.0, 9.5 Hz), 3.82–3.87 (1 H, m), 4.00 (1 H, dd, *J* = 9.5, 9.5 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 7.91 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 23.1, 23.7, 25.5, 36.3, 37.7, 43.9, 44.7, 48.0, 54.1, 56.4, 128.0, 129.6, 134.9, 144.7, 156.3. IR (neat): 2924, 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{24}N_2O_3NaS$ $[M+Na]^+$: 371.1400, found 371.1397.



S29

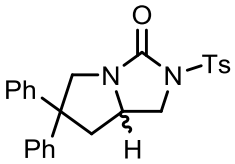
2,2-Diphenylpent-4-enenitrile (S29):[63] To a solution of LHMDS in THF (7.2 mL, 1.0 M) was added diphenylacetonitrile (1.3 g, 6.6 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 30 min. Allyl bromide (1.2 mL, 14 mmol) was added to the reaction mixture

dropwise before allowing the reaction mixture to warm up to room temperature. After stirring for overnight, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:15) to provide the titled compound **S29** as a colorless oil (1.6 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.14 (2 H, dt, *J* = 7.0, 1.0 Hz), 5.16–5.24 (2 H, m), 5.71 (1 H, tdd, *J* = 7.0, 10.0, 17.0 Hz), 7.28–7.41 (10 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 51.7, 120.4, 121.9, 127.0, 127.9, 128.8, 131.7, 139.7. IR (neat): 3061, 1493 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{15}NNa$ $[M+Na]^+$: 256.1097, found 256.1093.



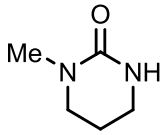
S31

***N*-((2,2-Diphenylpent-4-en-1-yl)carbamoyl)-4-methylbenzenesulfonamide (S31) (Table 4):**[63] To a solution of $LiAlH_4$ (0.13 g, 3.3 mmol) in Et_2O (1.4 mL, 2.4 M) was added a solution of **S29** (0.19 g, 0.81 mmol) in Et_2O (2.8 mL, 0.30 M) through a cannula at 0 °C and then warmed slowly to room temperature and stirred overnight. The resulting suspension was cooled to 0 °C and quenched by slow addition of 6 M NaOH (5 mL). The resulting mixture was extracted with ether (3 × 30 mL) and the combined ether extracts were dried ($MgSO_4$) and concentrated to give 2,2-diphenylpent-4-en-1-amine (**S30**) (0.18 g) as a pale yellow. This compound **S30** was used for next reaction without purification. A round bottomed flask was loaded with **S30** (0.18 g, 0.75 mmol) and TsNCO (0.17 mL, 1.1 mmol) and CH_2Cl_2 (4 mL, 0.20 M) at room temperature. After stirring for 2 h, the reaction was quenched by adding H_2O and the mixture was extracted with CH_2Cl_2 twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **S31** as a colorless solid (0.24 g, 67%, 2 steps). Mp: 117–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (3 H, s), 2.80 (2 H, d, *J* = 7.0 Hz), 3.89 (2 H, d, *J* = 5.5 Hz), 4.88–4.95 (2 H, m), 5.33 (1 H, tdd, *J* = 6.5, 10.0, 16.5 Hz), 6.27 (1 H, t, *J* = 5.0 Hz), 7.13–7.39 (14 H, m), 8.82 (NH, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 41.7, 46.9, 49.5, 118.7, 126.6, 126.8, 127.8, 128.4, 129.7, 133.3, 136.5, 144.5, 144.8, 151.7. IR (neat): 3370, 3059, 1684, 1541 cm^{-1}. HRMS (MALDI) Calcd for $C_{25}H_{26}N_2O_3NaS$ $[M+Na]^+$: 457.1556, found 457.1558.



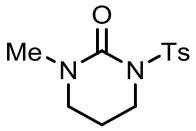
(±)-**56S**

(±)-6,6-Diphenyl-2-tosylhexahydro-3H-pyrrolo[1,2-*c*]imidazol-3-one ((±)-56S) (Table 12, entry 11):[63] A suspension of **S31** (1.4 g, 3.2 mol), NIS (1.5 g, 6.4 mmol), and $NaHCO_3$ (0.27 g, 3.2 mmol) in toluene (20 mL) was stirred at room temperature for 3 h. The reaction was quenched by adding Na_2SO_3 aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound (±)-**56S** as a colorless solid (0.57 g, 41%). Mp: 183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.23 (1 H, dd, *J* = 9.5, 11.5 Hz), 2.44 (3 H, s), 2.54 (1 H, dd, *J* = 5.0, 11.5 Hz), 3.63 (1 H, dd, *J* = 5.5, 9.5 Hz), 3.84 (1 H, d, *J* = 11.5 Hz), 3.86–3.95 (1 H, m), 3.06 (1 H, t, *J* = 9.0 Hz), 3.06 (1 H, d, *J* = 11.5 Hz), 7.08–7.33 (12 H, m), 7.89 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 43.6, 48.0, 54.0, 56.1, 56.8, 126.4, 126.70, 126.73 128.0, 128.5, 129.6, 134.9, 144.8, 145.2, 145.4, 156.2. IR (neat): 1732 cm^{-1}. HRMS (MALDI) Calcd for $C_{25}H_{24}N_2O_3NaS$ $[M+Na]^+$: 455.1400, found 455.1403.



S32

1-Methyltetrahydropyrimidin-2(1*H*)-one (S32): A round bottomed flask equipped with a reflux condenser was loaded with urea (1.57 g, 26 mmol) and N-Methyl-1,3-propanediamine (2.9 mL, 26 mmol), Pyridine (10 mL, 2.6 M) at room temperature. After stirring for 24 h at reflux, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to provide the titled compound **S32** as a colorless solid (0.97 g, 33%). Mp: 87–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (2 H, quint, *J* = 6.0 Hz), 2.84 (3 H, s), 3.17 (2 H, t, *J* = 6.0 Hz), 3.19–3.24 (2 H, m), 5.68 (NH, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 34.8, 40.2, 47.3, 156.9. IR (neat): 3383, 1643 cm^{-1}. HRMS (MALDI) Calcd for $C_5H_{11}N_2O$ $[M+H]^+$: 115.0866, found 115.0865.

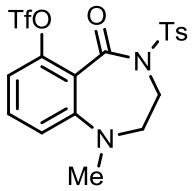


56T

1-Methyl-3-tosyltetrahydropyrimidin-2(1*H*)-one (56T): To a solution of **S32** (0.82 g, 7.2 mmol) in THF (24 mL, 0.30 M) were added NaH (0.86 g, 22 mmol) and TsCl (1.6 g, 8.6 mmol) at 0 °C. After stirring for 13 h at room temperature, the reaction was quenched by adding NH_4Cl aq. and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (only EtOAc) to provide the titled compound **56T** as a colorless solid (1.4 g, 74%). Mp: 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (2 H, quint, *J* = 6.0 Hz), 2.41 (3 H, s), 2.87 (3 H, s), 3.26 (2 H, t, *J* = 6.0 Hz), 3.97 (2 H, t, *J* = 6.0 Hz), 7.29 (2 H, d, *J* = 8.0 Hz), 7.87 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 22.6, 35.4, 44.8, 47.9, 128.2, 129.2, 137.4, 143.9, 151.5. IR (neat): 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{16}N_2O_3NaS$ $[M+Na]^+$: 291.0774, found 291.0779.

General Procedure for the synthesis of 1,4-benzodiazepines 4 by the reaction between benzynes 3 and cyclic ureas 2 (Tables 1–3 and Scheme 2)

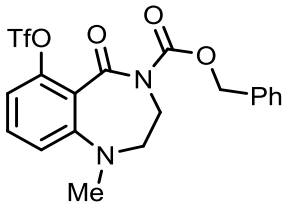
General Procedure: CsF (3.0 equiv) was flame-dried under reduced pressure in a flask equipped with a three-way stopcock, and back-filled with Ar. Cyclic urea **56** (3.0 equiv) with a magnetic stir bar was loaded into the flask and evacuated and backfilled with Ar (This process was repeated three times). Dioxane (One-fifth of its total volume) was added into the flask via a syringe. A solution of precursor **5a**, **5c**, **5lB**, **5o**, **5u** (1.0 equiv) in anhydrous dioxane (one-fifth of its total volume) was added to the flask through a cannula and washed with dioxane (three-fifth of its total volume). The mixture was stirred at 80 ºC for 30–60 min. After completion of the benzyne reaction by monitoring TLC, the reaction was quenched by the addition of H_2O. EtOAc was added to the reaction mixture, and the aqueous phase was extracted three times. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (a mixture of hexane and EtOAc) to afford **57**.



57lAα

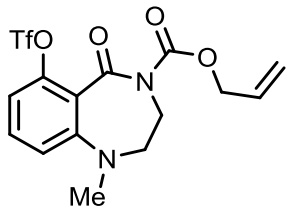
1-Methyl-4-tosyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lAα) (Table 9, entry 6): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol),

1-methyl-3-tosyl-2-imidazolidone (**56A**) (76 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **57lAα** as a colorless solid (33 mg, 69%) and its regiochemistry was determined by NOE experiments. Mp: 47–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (3 H, s), 2.87 (3 H, s), 3.36 (2 H, t, *J* = 5.5 Hz), 4.11 (2 H, t, *J* = 5.5 Hz), 6.84 (1 H, d, *J* = 8.0 Hz), 6.96 (1 H, d, *J* = 8.0 Hz), 7.33 (2 H, d, *J* = 8.5 Hz), 7.42 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.97 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 40.5, 44.1, 58.6, 115.6, 118.4 (q, *J* = 319 Hz), 118.6, 122.7, 128.8, 129.3, 133.1, 135.3, 145.1, 147.3, 149.4, 164.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.0. IR (neat): 1697 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{17}N_2O_6F_3NaS_2$ $[M+Na]^+$: 501.0372, found 501.0371.



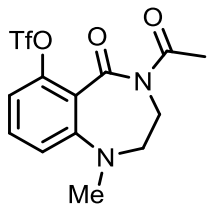
57lBα

1-Methyl-4-benzyloxycarbonyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lBα) (Table 10, entry 1): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-benzyloxycarbonyl-2-imidazolidone (**56B**) (70 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 1 h at 80 °C . The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **57lBα** as a yellow oil (10 mg, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (3 H, s), 3.19 (2 H, t, *J* = 6.0 Hz), 4.01 (2 H, t, *J* = 6.0 Hz), 5.39 (2 H, s), 6.93 (1 H, d, *J* = 5.0 Hz), 6.96 (1 H, d, *J* = 5.0 Hz), 7.30–7.50 (6 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.1, 43.7, 56.7, 68.8, 115.7, 118.1, 118.5 (q, *J* = 319 Hz), 123.8, 127.7, 128.2, 128.5, 132.8, 135.2, 147.3, 148.7, 152.9, 164.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.0. IR (neat): 1715 cm^{-1}. HRMS (MALDI) Calcd for $C_{19}H_{17}N_2O_6F_3NaS$ $[M+Na]^+$: 481.0652, found 481.0651.



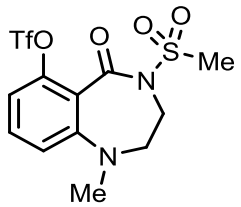
57lCα

1-Methyl-4-allyloxycarbonyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzo diazepin-5-one (57lCα) (Table 10, entry 2): Following General Procedure B, a mixture of CsF (46 mg, 0.30 mmol), urea **56C** (55 mg, 0.30 mmol) and **5lB** (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **57lCα** as a colorless solid (14 mg, 34%). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.1, 43.7, 56.7, 67.8, 115.7, 118.1, 118.5 (q, *J* = 318 Hz), 118.6, 123.9, 131.2, 132.8, 147.3, 148.7, 152.8, 164.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.0. HRMS (MALDI) Calcd for $C_{15}H_{15}N_2O_6F_3NaS$ $[M+H]^+$: 431.0495, found 431.0489.



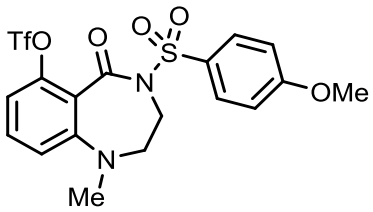
57lDα

1-Methyl-4-acetyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lDα) (Table 10, entry 3): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-acetyl-2-imidazolidone (**56D**) (43 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 45 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **57lDα** as a colorless oil (15 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.69 (3 H, s), 2.83 (3 H, s), 3.18 (2 H, t, *J* = 6.0 Hz), 4.05 (2 H, t, *J* = 6.0 Hz), 6.94 (1 H, d, *J* = 8.5 Hz), 6.97 (1 H, dd, *J* = 1.0, 8.5 Hz), 7.46 (1 H, dd, *J* = 8.5, 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.7, 40.2, 41.0, 56.8, 115.5, 118.1, 118.6 (q, *J* = 318 Hz), 123.8, 132.9, 147.3, 148.8, 166.8, 172.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.1. IR (neat): 1699 cm^{-1}. HRMS (MALDI) Calcd for $C_{13}H_{13}N_2O_5F_3NaS$ $[M+Na]^+$: 389.0389, found 389.0389.



57lEα

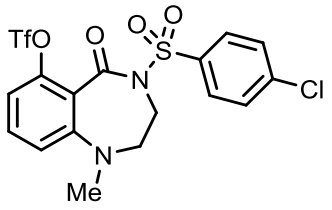
1-Methyl-4-(methanesulfonyl)-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lEα) (Table 10, entry 4): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-(methanesulfonyl)-2-imidazolidone (**56E**) (53 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **57lEα** as a colorless solid (17 mg, 43%). Mp: 94–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.88 (3 H, s), 3.30 (2 H, t, *J* = 5.5 Hz), 3.45 (3 H, s), 4.03 (2 H, t, *J* = 5.5 Hz), 6.92 (1 H, d, *J* = 8.0 Hz), 7.00 (1 H, d, *J* = 8.0 Hz), 7.48 (1 H, dd, *J* = 8.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.4, 42.1, 43.5, 58.7, 115.6, 118.6 (q, *J* = 320 Hz), 118.8, 122.3, 133.5, 147.5, 149.5, 166.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.8. IR (neat): 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{13}N_2O_6F_3NaS_2$ $[M+Na]^+$: 425.0059, found 425.0056.



57lFα

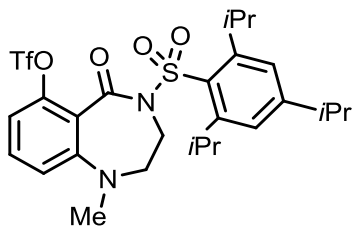
1-Methyl-4-(*p*-methoxy-benzenesulfonyl)-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lFα) (Table 10, entry 5): Following General Procedure A, a mixture of CsF (46 mg, 0.30 mmol), 1-Methyl-3-(*p*-methoxybenzenesulfonyl)-2-imidazolidone **56F** (81 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **57lFα** as a colorless solid (28 mg, 56%) and its regiochemistry was determined by NOESY spectra. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.86 (3 H, s), 3.35 (2 H, t, *J* = 5.5 Hz), 3.87 (3 H, s), 4.10 (2 H, t, *J* = 5.5 Hz), 6.83 (1 H, d, 8.5 Hz), 6.95 (1 H, d, *J* = 8.5 Hz), 6.99 (2 H, d, *J* = 9.0 Hz), 7.41 (1 H, t, *J* = 8.5 Hz), 8.03 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.4, 44.0, 55.7, 58.7, 113.9, 115.6, 118.4 (q, *J* = 319 Hz), 118.5, 122.8, 129.6, 131.2, 133.0, 147.3, 149.3, 164.0, 164.3. ^{19}F NMR

(283 MHz, $CDCl_3$) δ: –73.0. HRMS (MALDI) Calcd for $C_{18}H_{17}N_2O_7F_3NaS_2$ $[M+Na]^+$: 517.0321, found 517.0325.



57lGα

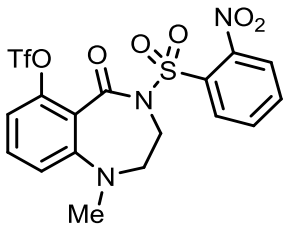
1-Methyl-4-(*p*-chloro-benzenesulfonyl)-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lGα) (Table 10, entry 7): Following General Procedure A, a mixture of CsF (46 mg, 0.30 mmol), 1-Methyl-3-(*p*-chloro-benzenesulfonyl)-2-imidazolidone **56G** (82 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **57lGα** as a colorless solid (34 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.88 (3 H, s), 3.36 (2 H, t, *J* = 6.0 Hz), 4.11 (2 H, t, *J* = 6.0 Hz), 6.85 (1 H, d, *J* = 8.0 Hz), 6.97 (1 H, d, *J* = 8.0 Hz), 7.44 (1 H, t, *J* = 8.0 Hz), 7.51 (2 H, d, *J* = 8.5 Hz), 8.03 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.5, 44.2, 58.6, 115.7, 118.4 (q, *J* = 316 Hz), 118.7, 122.5, 129.0, 130.3, 133.3, 136.7, 140.7, 147.3, 149.4, 164.5. ^{19}F NMR (283 MHz, $CDCl_3$) δ: –72.9. HRMS (MALDI) Calcd for $C_{17}H_{14}N_2O_6F_3NaS_2Cl$ $[M+Na]^+$: 520.9826, found 520.9815.



57lHα

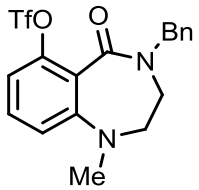
1-Methyl-4-(2,4,6-triisopropyl-benzenesulfonyl)-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lHα) (Table 10, entry 8): Following General Procedure A, a mixture of CsF (46 mg, 0.30 mmol), 1-Methyl-3-(2,4,6-triisopropylbenzenesulfonyl)-2-imidazolidone **56H** (0.11 g, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene **5lB** (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 1 h at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled

compound **57lHα** as a colorless solid (33 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (6 H, d, *J* = 7.0 Hz), 1.29 (12 H, d, *J* = 7.0 Hz), 2.87 (3 H, s), 2.84–2.95 (1 H, m), 3.41 (2 H, t, *J* = 5.5 Hz), 4.03–4.20 (4 H, m), 6.90 (1 H, d, *J* = 8.0 Hz), 6.94 (1 H, d, *J* = 8.0 Hz), 7.18 (2 H, s), 7.42 (1 H, t, *J* = 8.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.6. HRMS (MALDI) Calcd for $C_{26}H_{33}N_2O_6NaS_2$ $[M+Na]^+$: 613.1624, found 613.1635.



57lIα

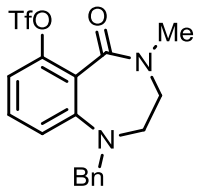
1-Methyl-4-(2-nitro-benzenesulfonyl)-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lIα) (Table 10, entry 9): Following General Procedure A, a mixture of CsF (46 mg, 0.30 mmol), urea **56I** (90 mg, 0.30 mmol) and **5lB** (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 1 h at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **57lIα** as a colorless solid (18 mg, 34%) and its regiochemistry was determined by NOESY spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.91 (3 H, s), 3.41 (2 H, t, *J* = 6.0 Hz), 4.23 (2 H, t, *J* = 5.5 Hz), 6.83 (1 H, d, *J* = 8.5 Hz), 6.99 (1 H, d, *J* = 8.5 Hz), 7.46 (1 H, t, *J* = 8.5 Hz), 7.78–7.86 (3 H, m), 8.61–8.67 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.5, 45.1, 58.8, 115.4, 118.3 (q, *J* = 319 Hz), 118.7, 121.9, 124.5, 131.8, 132.1, 133.6, 134.9, 135.6, 147.6, 147.8, 149.8, 164.9. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –73.3. HRMS (MALDI) Calcd for $C_{17}H_{14}N_3O_8F_3NaS_2$ $[M+H]^+$: 532.0067, found 532.0067.



14lBα

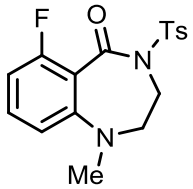
1-Methyl-4-benzyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (14lBα) (Scheme 28): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-benzyl-2-imidazolidone (**13B**) (57 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in MeCN (1.0 mL) for 3 h at room temperature. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:3) to provide the titled compound **14lBα** as a

colorless solid (18 mg, 43%) and its regiochemistry was determined by NOE experiments. Mp: 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77 (3 H, s), 3.01 (2 H, t, *J* = 6.0 Hz), 3.40 (2 H, t, *J* = 6.0 Hz), 4.84 (2 H, s), 6.91 (2 H, d, *J* = 8.5 Hz), 7.28–7.44 (6 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.2, 44.7, 49.3, 57.8, 115.1, 117.9, 118.6 (q, *J* = 319 Hz), 123.7, 127.7, 128.4, 128.6, 131.8, 136.9, 147.6, 148.6, 165.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.3. IR (neat): 1651 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{17}N_2O_4F_3NaS$ $[M+Na]^+$: 437.0753, found 437.0754.



14lBβ

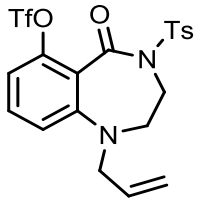
1-Benzyl-4-methyl-6-(trifluoromethanesulfonyloxy)-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (14lBβ) (Scheme 28) was obtained from the above-mentioned reaction mixture as a colorless solid (4.4 mg, 11%). Mp: 69–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (3 H, s), 3.16 (2 H, t, *J* = 6.0 Hz), 3.46 (2 H, t, *J* = 6.0 Hz), 4.30 (2 H, s), 6.91 (1 H, d, *J* = 8.0 Hz), 6.96 (1 H, d, *J* = 8.0 Hz), 7.22–7.25 (1 H, m) , 7.26–7.35 (5 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.6, 47.4, 54.5, 56.7, 115.7, 118.6 (q, *J* = 318 Hz), 119.2, 124.7, 127.5, 127.9, 128.7, 131.6, 137.0, 147.3, 148.1, 165.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.4. IR (neat): 1653 cm^{-1}. HRMS (MALDI) Calcd for $C_{18}H_{17}N_2O_4F_3NaS$ $[M+Na]^+$: 437.0753, found 437.0755.



57lOα

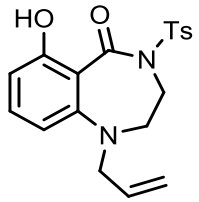
1-Methyl-4-tosyl-6-fluoro-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57lOα) (Table 11, entry 4): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-tosyl-2-imidazolidone (**56A**) (76 mg, 0.30 mmol), and 2-fluoro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (**5o**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **57oAα** as a colorless solid (19 mg, 34%). Mp: 47–50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.42 (3 H, s), 2.80 (3 H, s), 3.30 (2 H, t, *J* = 5.5 Hz), 4.10 (2 H, t, *J* = 5.5 Hz),

6.68 (1 H, d, J = 8.5 Hz), 6.71 (1 H, d, J = 8.5 Hz), 7.30–7.34 (3 H, m), 7.97 (2 H, d, J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 40.4, 44.1, 58.2, 110.1 (d, J = 21.5 Hz), 114.1 (d, J = 3.5 Hz), 116.6 (d, J = 13.0 Hz), 128.7, 129.3, 133.5 (d, J = 10.5 Hz), 135.7, 144.8, 149.1 (d, J = 3.5 Hz), 161.2 (d, J = 255 Hz), 164.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –112.29–(–112.26) (m). IR (neat): 1695, 1612 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{17}N_2O_3FNaS$ $[M+Na]^+$: 371.0836, found 371.0829.



57lJα

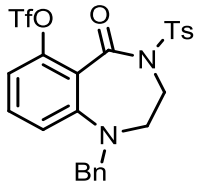
1-Allyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-6-yl trifluoromethanesulfonate (57lJα) (Table 12, entry 2): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-allyl-3-tosyl-2-imidazolidone (**56J**), (84 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 50 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:7) to provide the titled compound **57lJα** as a colorless solid (22 mg, 43%). Mp: 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (3 H, s), 3.33 (2 H, t, J = 6.0 Hz), 3.76 (2 H, d, J = 6.0 Hz), 4.12 (2 H, t, J = 6.0 Hz), 5.23–5.31 (2 H, m), 5.75 (1 H, tdd, J = 6.0, 10.5, 17.0 Hz), 6.87 (1 H, d, J = 8.0 Hz), 6.97 (1 H, d, J = 8.0 Hz), 7.33 (2 H, d, J = 8.5 Hz), 7.40 (1 H, dd, J = 8.0, 8.0 Hz), 7.97 (2 H, d, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 44.0, 55.6, 55.7, 116.2, 118.4 (q, J = 322 Hz), 119.0, 119.9, 123.7, 128.9, 129.2, 132.9, 133.5, 135.4, 145.0, 147.1, 148.7, 164.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –73.0. IR (neat): 1697 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{19}N_2O_6F_3NaS_2$ $[M+Na]^+$: 527.0529, found 527.0533.



57lJα'

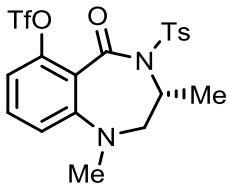
1-Allyl-6-hydroxy-4-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (57lJα') (Table 12, entry 2) was obtained from the above-mentioned reaction mixture as a colorless solid (4.2 mg, 11%). Mp: 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (3 H, s), 3.36 (2 H, t, J = 5.5 Hz), 3.75 (2 H, d, J = 6.5 Hz), 4.03 (2 H, t, J = 5.5 Hz), 5.24 (1 H, dd, J = 1.5, 10.0 Hz), 5.28 (1 H, dd, J = 1.5, 17.5 Hz),

5.80 (1 H, tdd, J = 6.5, 10.0, 17.0 Hz), 6.46 (1 H, d, J = 8.5 Hz), 6.57 (1 H, d, J = 8.5 Hz), 7.26 (1 H, dd, J = 8.5, 8.5 Hz), 7.34 (2 H, d, J = 8.0 Hz), 7.96 (2 H, d, J = 8.0 Hz), 9.57 (OH, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7, 44.8, 56.0, 56.5, 111.8, 111.9, 112.5, 118.5, 128.7, 129.5, 134.3, 134.8, 135.6, 145.1, 149.4, 160.6, 171.9. IR (neat): 2359 cm^{-1}. HRMS (MALDI) Calcd for $C_{19}H_{20}N_2O_4NaS$ $[M+Na]^+$: 395.1036, found 395.1032.



57lKα

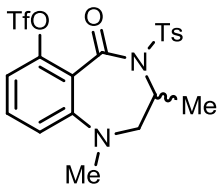
1-Benzyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1H-benzo[*e*][1,4]diazepin-6-yl trifluoromethanesulfonate (57lKα) (Table 12, entry 3): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-benzyl-3-tosyl-2-imidazolidone (**56K**) (99 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:3) to provide the titled compound **57lKα** as a colorless oil (17 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (3 H, s), 3.29 (2 H, t, J = 5.0 Hz), 4.12 (2 H, t, J = 5.0 Hz), 4.31 (2 H, s), 6.89 (1 H, d, J = 8.5 Hz), 7.02 (1 H, d, J = 8.5 Hz), 7.21–7.30 (5 H, m) , 7.32 (2 H, d, J = 8.5 Hz) , 7.38 (1 H, t, J = 8.5 Hz) , 7.95 (2 H, d, J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 43.9, 56.0, 56.7, 116.5, 118.4 (q, J = 319 Hz), 120.0, 124.1, 127.7, 128.0, 128.7, 128.9, 129.3, 132.9, 135.5, 136.2, 145.0, 147.0, 148.6, 164.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.0. IR (neat): 1695 cm^{-1}. HRMS (MALDI) Calcd for $C_{24}H_{21}N_2O_6F_3NaS_2$ $[M+Na]^+$: 577.0685, found 577.0691.



(*R*)-**57lLα**

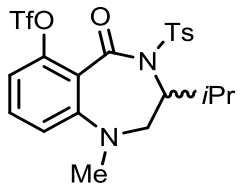
(*R*)-1,3-Dimethyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-6-yl trifluoromethansulfonate ((*R*)-57lLα) (Table 12, entry 4): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (4*R*)-1,4-dimethyl-3-tosyl-imidazolidin-2-one ((*R*)-**56L**) (80 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg,

0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound (*R*)-**57lLα** as a colorless oil (22 mg, 44%). $[\alpha]_D^{20}$ = +5.5 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (3 H, d, *J* = 7.0 Hz), 2.43 (3 H, s), 2.90 (3 H, s), 3.33 (1 H, dd, *J* = 5.5, 12 Hz), 3.51 (1 H, dd, *J* = 5.5, 12 Hz), 4.84–4.94 (1 H, m), 6.82 (1 H, d, *J* = 8.0 Hz) , 6.91 (1 H, d, *J* = 8.0 Hz) , 7.32 (2 H, d, *J* = 8.5 Hz) , 7.39 (1 H, dd, *J* = 8.0, 8.0 Hz) , 7.98 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4, 21.6, 41.0, 51.3, 63.2, 114.9, 117.7, 118.3 (q, *J* = 318 Hz), 121.5, 128.7, 129.2, 132.8, 136.2, 144.8, 147.9, 149.6, 164.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –73.4. IR (neat): 1688 cm^{-1}. HRMS (MALDI) Calcd for $C_{19}H_{19}N_2O_6F_3NaS_2$ $[M+Na]^+$: 515.0529, found 515.0537. The enantiomeric excess of the product (*R*)-**57lLα** was determined to be 89% by HPLC with CHIRALCEL® AD-3 (Eluent: hexane/2-PrOH = 90/10, Flow rate: 1.0 mL/min, Retention time: t_R of (*R*)-isomer = 26.5 min, t_R of (*S*)-isomer = 31.3 min). The absolute configuration was assigned on the basis of that of (*R*)-**56L**, which was synthesized from *D*-alanine.



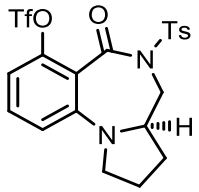
(±)-**57lLα**

(±)-1,3-Dimethyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-6-yl trifluoromethansulfonate ((±)-57lLα): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (±)-1,4-dimethyl-3-tosyl-imidazolidin-2-one ((±)-**56L**) (80 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound (±)-**57lLα** as a colorless oil (22 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (3 H, d, *J* = 7.5 Hz), 2.43 (3 H, s), 2.90 (3 H, s), 3.33 (1 H, dd, *J* = 5.5, 11.0 Hz), 3.50 (1 H, dd, *J* = 5.5, 11.0 Hz), 4.87–4.91 (1 H, m), 6.82 (1 H, d, *J* = 8.0 Hz), 6.90 (1 H, d, *J* = 8.0 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.38 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.98 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.3, 21.4, 40.9, 51.1, 63.0, 114.8, 117.5, 118.2 (q, *J* = 318 Hz), 121.3, 128.5, 129.1, 132.7, 136.1, 144.6, 147.8, 149.4, 164.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.4. IR (neat): 1688 cm^{-1}. HRMS (MALDI) Calcd for $C_{19}H_{19}N_2O_6F_3NaS_2$ $[M+Na]^+$: 515.0529, found 515.0521.



(±)-**57lMα**

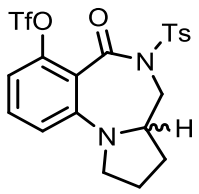
(±)-3-Isopropyl-1-methyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-6-yl trifluoromethanesulfonate ((±)-57lMα) (Table 12, entry 5): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (±)-4-isopropyl-1-methyl-3-tosylimidazolidin-2-one ((±)-**56M**) (89 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound (±)-**57lMα** as a colorless solid (13 mg, 24%). Mp: 72–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3 H, d, *J* = 6.5 Hz), 0.96 (3 H, d, *J* = 6.5 Hz), 2.42 (3 H, s), 2.91 (3 H, s), 3.47–3.77 (2 H, m), 4.31–4.52 (1 H, m), 6.76 (1 H, d, *J* = 8.0 Hz), 6.80 (1 H, d, *J* = 8.0 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 7.32 (1 H, dd, *J* = 8.0, 8.0 Hz), 8.00 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4, 20.6, 21.6, 29.4, 41.2, 59.1, 113.1, 116.1, 118.3 (q, *J* = 319 Hz), 127.0, 129.1, 129.5, 132.6, 135.6, 144.9, 148.1, 148.9, 164.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.6. IR (neat): 2928, 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{21}H_{23}N_2O_6F_3NaS_2$ $[M+Na]^+$: 543.0847, found 543.0844.



(*R*)-**57lNα**

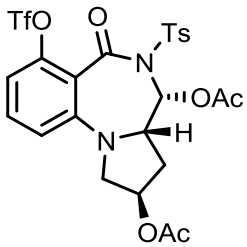
(*R*)-6-Oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate ((*R*)-57lNα) (Table 12, entry 6): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (*R*)-2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one ((*R*)-**56N**) (84 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound (*R*)-**57lNα** as a yellow solid (35 mg, 70%). $[\alpha]_D^{20}$ = +5.5 (*c* 0.15, $CHCl_3$). Mp: 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86–1.98 (2 H, m), 2.05–2.16 (2 H, m), 2.43 (3 H, s), 3.24–3.35 (2 H, m), 3.48–3.52 (1 H, m), 4.07 (1 H, dd, *J* = 4.5, 16 Hz), 4.24 (1 H, dd, *J* = 3.0, 16 Hz), 6.67 (1 H, d, *J* = 8.0 Hz), 6.75 (1 H, d, *J* = 8.5 Hz), 7.29–7.34 (3 H, m), 7.95 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 21.6, 22.1, 29.5, 45.1, 48.9, 65.8, 112.6, 116.0, 117.3, 118.4 (q, *J* = 319 Hz), 129.1, 129.2, 132.7, 135.2, 145.0, 146.4, 148.6, 164.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.1. IR (neat): 1699, 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{19}N_2O_6F_3NaS_2$ $[M+Na]^+$: 527.0529, found 527.0519. The enantiomeric excess of the product (*R*)-**57lNα** was determined to be 88% by HPLC with CHIRALCEL® AD-3 (Eluent: hexane/2-PrOH = 90/10, Flow rate: 1.0 mL/min, Retention time: t_R of (*R*)-isomer = 30.0 min, t_R of (*S*)-isomer = 33.0 min). The absolute configuration was assigned on the basis of that of (*R*)-**56N**, which was synthesized from *D*-proline.



(±)-**57lNα**

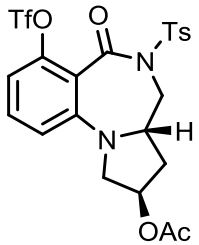
(±)-6-Oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate ((±)-57lNα): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one ((±)-**56N**) (84 mg , 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 35 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound (±)-**57lNα** as a yellow solid (35 mg, 70%). Mp: 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.86–2.05 (2 H, m), 2.09–2.18 (2 H, m), 2.44 (3 H, s), 3.24–3.37 (2 H, m), 3.48–3.54 (1 H, m), 4.07 (1 H, dd, *J* = 4.5, 16 Hz), 4.25 (1 H, dd, *J* = 3.0, 16 Hz), 6.67 (1 H, d, *J* = 8.5 Hz), 6.75 (1 H, d, *J* = 8.5 Hz), 7.30 (1 H, dd, *J* = 8.5, 8.5 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.96 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 22.1, 29.5, 45.1, 48.9, 65.8, 112.6, 116.0, 117.3, 118.4 (q, *J* = 319 Hz), 129.1, 129.2, 132.7, 135.2, 145.1, 146.4, 148.6, 164.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.1. IR (neat): 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{19}N_2O_6F_3NaS_2$ $[M+Na]^+$: 527.0529, found 527.0516.



57lOα

(2*R*,3a*S*,4*R*)-6-Oxo-5-tosyl-7-(((trifluoromethyl)sulfonyl)oxy)-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*

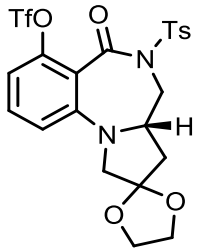
]pyrrolo[1,2-*a*][1,4]diazepine-2,4-diyl diacetate (57lOα) (Table 12, entry 7): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (1*R*,6*R*,7a*S*)-3-oxo-2-tosylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,6-diyl diacetate (**56O**) (0.12 g, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **57lOα** as a colorless solid (39 mg, 63%). $[\alpha]_D^{20}$ = +69.5 (*c* 0.15, $CHCl_3$). Mp: 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84 (3 H, s), 1.95–2.05 (1 H, m), 2.11 (3 H, s), 2.43 (3 H, s), 2.46 (1 H, dd, *J* = 5.5, 14.0 Hz), 3.53 (1 H, d, *J* = 11.5 Hz), 3.78 (1 H, dd, *J* = 4.5, 11.5 Hz), 4.41 (1 H, dd, *J* = 4.5, 11.5 Hz), 5.41 (1 H, t, *J* = 3.6 Hz), 6.56 (2 H, t, *J* = 7.5 Hz), 7.25–7.29 (2 H, m), 7.32 (2 H, d, *J* = 8.0 Hz), 8.04 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3, 21.1, 21.7, 36.2, 56.9, 65.1, 70.3, 72.6, 110.7, 113.1, 113.3, 118.3 (q, *J* = 319 Hz), 129.1, 130.1, 132.3, 134.4, 145.3, 145.5, 149.2, 163.9, 168.9, 170.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.0. IR (neat): 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{24}H_{23}N_2O_{10}F_3NaS_2$ $[M+Na]^+$: 643.0638, found 643.0643. The absolute configuration was assigned on the basis of that of **56O**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



57lPα

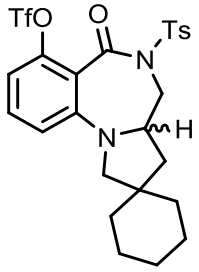
(2*R*,3a*S*)-6-Oxo-5-tosyl-7-(((trifluoromethyl)sulfonyl)oxy)-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl acetate (57lPα) (Table 12, entry 7): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (6*R*,7a*S*)-3-oxo-2-tosylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-6-yl acetate (**56P**) (102 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 50 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **57lPα** as a yellow solid (41 mg, 73%). Mp: 163–166 °C. $[\alpha]_D^{20}$ = –43.3 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (3 H, s), 2.17–2.30 (2 H, m), 2.44 (3 H, s), 3.24 (1 H, dd, *J* = 2.0, 11.0 Hz), 3.71–3.76 (1 H, m), 3.79 (1 H, dd, *J* = 6.0, 11.0 Hz), 4.16 (1 H, dd, *J* = 3.5, 17.0 Hz), 4.20 (1 H, dd, *J* = 3.5, 17.0 Hz), 5.36 (1 H, t, *J* = 6.0 Hz), 6.74 (1 H, d, *J* = 9.0 Hz), 6.76 (1 H, d, *J* = 9.0 Hz), 7.33 (2 H, d, *J* = 8.5 Hz), 7.36 (1 H, dd, *J* = 9.0, 9.0 Hz), 7.95 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 21.6, 35.9, 44.7, 55.4, 63.8, 71.1, 114.0, 116.6, 118.3 (q, *J* = 319 Hz), 118.8, 129.1, 129.2, 133.0, 134.9, 145.2,

145.5, 148.5, 164.6, 170.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.0. IR (neat): 2922, 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{22}H_{21}N_2O_8F_3NaS_2$ $[M+Na]^+$: 585.0584, found 585.0591. The absolute configuration was assigned on the basis of that of **56P**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



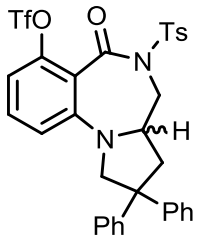
(*S*)-**57lQα**

(*S*)-6-Oxo-5-tosyl-3a,4,5,6-tetrahydro-1*H*,3*H*-spiro[benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-2,2′-[1,3]dioxolan]-7-yl trifluoromethanesulfonate ((*S*)-57lQα) (Table 12, entry 9): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (*S*)-2-tosyltetrahydro-3*H*,5*H*-spiro[pyrrolo[1,2-*c*]imidazole-6,2′-[1,3]dioxolan]-3-one ((*S*)-**56Q**) (102 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound (*S*)-**57lQα** as a colorless solid (43 mg, 77%). Mp: 69–73 °C. $[\alpha]_D^{20}$ = –4.0 (*c* 0.30, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00 (1 H, dd, *J* = 5.5, 12.5 Hz), 2.36 (1 H, dd, *J* = 12.5, 12.5 Hz), 2.43 (3 H, s), 3.36 (1 H, d, *J* = 10.5 Hz), 3.46 (1 H, d, *J* = 10.5 Hz), 3.59–3.65 (1 H, m), 3.89–4.07 (5 H, m), 4.29 (1 H, dd, *J* = 3.0, 16.0 Hz), 6.77 (1 H, d, *J* = 8.0 Hz), 6.78 (1 H, d, *J* = 8.0 Hz), 7.33 (2 H, d, *J* = 8.0 Hz), 7.36 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.96 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 40.6, 44.9, 58.1, 64.6, 64.9, 65.2, 112.9, 114.9, 117.2, 118.4 (q, *J* = 319 Hz), 120.4, 129.1, 129.2, 133.1, 135.1, 145.1, 146.1, 148.2, 164.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.0. IR (neat): 2924, 1694 cm^{-1}. HRMS (MALDI) Calcd for $C_{22}H_{21}N_2O_8F_3NaS_2$ $[M+Na]^+$: 585.0584, found 585.0592. The absolute configuration was assigned on the basis of that of (*S*)-**56Q**, which was synthesized from *trans*-4-hydroxy-*L*-proline.



(±)-**57lRα**

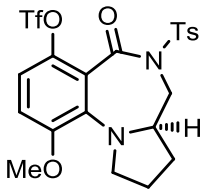
(±)-6-Oxo-5-tosyl-3a,4,5,6-tetrahydro-1*H*,3*H*-spiro[benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-2,1'-cyclohexan]-7-yl trifluoromethanesulfonate ((±)-57lRα) (Table 12, entry 10): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), (±)-2'-tosyltetrahydro-3'*H*,5'*H*-spiro[cyclohexane-1,6'-pyrrolo[1,2-*c*]imidazol]-3'-one ((±)-**56R**) (105 mg, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to provide the titled compound (±)-**57lRα** as a colorless solid (43 mg, 75%). Mp: 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.63 (10 H, m), 1.72 (1 H, dd, *J* = 12.0, 12.0 Hz), 1.99 (1 H, dd, *J* = 6.0, 12.0 Hz), 2.43 (3 H, s), 3.04 (1 H, d, *J* = 9.0 Hz), 3.08 (1 H, d, *J* = 9.0 Hz), 3.54–3.60 (1 H, m), 4.07 (1 H, dd, *J* = 3.5, 16.0 Hz), 4.16 (1 H, dd, *J* = 3.5, 16.0 Hz), 6.67 (1 H, d, *J* = 8.0 Hz), 6.73 (1 H, d, *J* = 8.0 Hz), 7.29–7.33 (3 H, m), 7.96 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 23.0, 23.6, 25.8, 36.1, 38.2, 39.8, 41.7, 45.4, 60.9, 64.7, 112.7, 116.0, 117.6, 118.4 (q, *J* = 319 Hz), 129.1, 129.2, 132.7, 135.2, 145.0, 146.5, 148.6, 164.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.1. IR (neat): 2924, 1684 cm^{-1}. HRMS (MALDI) Calcd for $C_{25}H_{27}N_2O_6F_3NaS_2$ $[M+Na]^+$: 595.1155, found 595.1156.



(±)-**57lSα**

(±)-6-Oxo-2,2-diphenyl-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate ((±)-57lSα) (Table 12, entry 11): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 6,6-diphenyl-2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one ((±)-**56S**) (0.13 g, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL) for 45 min at 80 °C. The crude product was purified by column

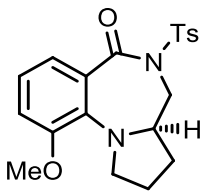
chromatography on silica gel (EtOAc/hexane = 2:7) to provide the titled compound (±)-**57lSα** as a colorless solid (32 mg, 49%). Mp: 108–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.39 (3 H, s), 2.53 (1 H, dd, *J* = 11.5, 11.5 Hz), 2.66 (1 H, dd, *J* = 4.0, 11.5 Hz), 3.59 (1 H, d, *J* = 10.0 Hz), 3.60–3.65 (1 H, m), 3.83 (1 H, dd, *J* = 8.0, 16.0 Hz), 4.25 (1 H, d, *J* = 10.0 Hz), 4.65 (1 H, d, *J* = 15.0 Hz), 6.66 (1 H, d, *J* = 8.0 Hz), 6.73 (1 H, d, *J* = 8.0 Hz), 7.13–7.17 (4 H, m), 7.22–7.29 (4 H, m), 7.31–7.36 (5 H, m), 7.82 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 42.4, 45.0, 51.6, 60.7, 63.7, 111.0, 113.6, 114.2, 118.4 (q, *J* = 318 Hz), 126.5, 126.7, 126.8, 127.0, 128.6, 128.7, 129.0, 129.2, 132.6, 134.6, 144.4, 144.7, 145.1, 145.3, 149.2, 164.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.1. IR (neat): 1684, 1612 cm^{-1}. HRMS (MALDI) Calcd for $C_{32}H_{27}N_2O_6F_3NaS_2$ $[M+Na]^+$: 679.1155, found 679.1158.



(*R*)-**57uNα**

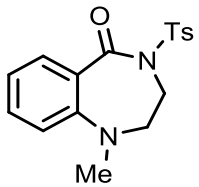
(*R*)-10-Methoxy-6-oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate ((*R*)-57uNα) (Scheme 29): Following General Procedure, a mixture of CsF (48 mg, 0.32 mmol), (*R*)-2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one ((*R*)-**56N**) (88 mg, 0.32 mmol) and 1,2-bis(trifluoromethanesulfonyloxy)-3-(trimethylsilyl)-4-methoxybenzene (**5u**) (50 mg, 0.11 mmol) was stirred in dioxane (1.1 mL) for 30 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound (*R*)-**57uNα** as a colorless solid (23 mg, 41%) and its regiochemistry was determined by NOE experiments. Mp: 204–206 °C. $[\alpha]_D^{20}$ = +193.3 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88–2.05 (3 H, m), 2.10–2.17 (1 H, m), 2.43 (3 H, s), 3.14–3.19 (1 H, m), 3.58–3.63 (1 H, m), 3.71 (1 H, dd, *J* = 3.5, 15.5 Hz), 3.78–3.84 (1 H, m), 3.82 (3 H, s), 4.49 (1 H, d, *J* = 15.5 Hz), 6.83 (1 H, d, *J* = 9.0 Hz), 6.86 (1 H, d, *J* = 9.0 Hz), 7.32 (2 H, d, *J* = 8.0 Hz), 7.93 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 23.3, 27.7, 47.1, 49.3, 55.9, 64.4, 113.8, 117.4, 118.4 (q, *J* = 320 Hz), 127.2, 129.1, 129.1, 135.2, 135.7, 139.8, 145.0, 155.7, 164.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.8. IR (neat): 2924, 1697 cm^{-1}. HRMS (MALDI) Calcd for $C_{21}H_{21}N_2O_7F_3NaS_2$ $[M+Na]^+$: 557.0634, found 557.0629. The absolute configuration was assigned on the basis of that of (*R*)-**56N**, which was synthesized from *D*-proline.

Functional group transformation of benzodiazepines 4e, 4q, and 4u (Schemes 28, 30, 31)



58

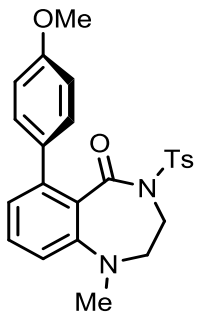
(*R*)-10-Methoxy-5-tosyl-1,2,3,3a,4,5-hexahydro-6*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-6-one (58) (Scheme 29): An oven dried Schlenk tube was charged with (*R*)-**57nNv** (50 mg, 94 µmol), $Pd(OAc)_2$ (2.1 mg, 9.4 µmol), PPh_3 (5.0 mg, 19 µmol) and evacuated and back-filled with argon. Anhydrous DMF (0.22 mL, 0.42 M), Et_3N (39 µL, 0.28 mmol) and HCO_2H (7.2 µL, 0.19 mmol) were added via syringes, and the reaction mixture was stirred at 60 °C for 10 h. The mixture was filtered through a pad of silica gel cake using EtOAc and the eluent was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **58** as a colorless solid (36 mg, quant). Mp: 163–165 °C. $[\alpha]_D^{20}$ = +206.0 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–2.02 (3 H, m), 2.10–2.18 (1 H, m), 2.43 (3 H, s), 3.09–3.15 (1 H, m), 3.61–3.74 (3 H, m), 3.80 (3 H, s), 4.44 (1 H, d, *J* = 15.0 Hz), 6.95–7.00 (2 H, m), 7.10 (1 H, dd, *J* = 3.0, 7.0 Hz), 7.32 (2 H, d, *J* = 8.5 Hz), 7.96 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 23.5, 28.1, 47.7, 50.3, 55.9, 64.2, 115.9, 123.2, 123.8, 128.8, 129.2, 132.3, 135.2, 136.4, 144.5, 155.6, 169.8. IR (neat): 2926, 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{23}N_2O_4S$ $[M+H]^+$: 387.1373, found 387.1370.



57aA.

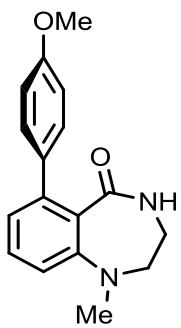
1-Methyl-4-tosyl-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (57aAα) (Scheme 31): An oven dried Schlenk tube was charged with **57lAo** (50 mg, 0.10 mmol), $Pd(OAc)_2$ (2.5 mg, 11 µmol), PPh_3 (5.8 mg, 22 µmol) and evacuated and back-filled with argon. Anhydrous DMF (0.25 mL, 0.42 M), Et_3N (44 µL, 0.31 mmol) and HCO_2H (8.0 µL, 0.21 mmol) were added via syringes, and the reaction mixture was stirred at 60 °C for 10 h. The mixture was filtered through a pad of silica gel cake using EtOAc and the eluent was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:5) to provide the titled compound **57aAl** as a

colorless solid (35 mg, quant). Mp: 107–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (3 H, s), 2.85 (3 H, s), 3.39 (2 H, t, *J* = 5.5 Hz), 4.06 (2 H, t, *J* = 5.5 Hz), 6.89 (1 H, d, *J* = 7.5 Hz), 6.95 (1 H, ddd, *J* = 1.5, 7.5, 7.5 Hz), 7.33 (2 H, d, *J* = 8.5 Hz), 7.41 (1 H, ddd, *J* = 1.5, 7.5, 7.5 Hz), 7.53 (1 H, dd, *J* = 1.5, 7.5 Hz), 7.97 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 40.3, 44.5, 58.6, 118.4, 121.6, 127.7, 128.6, 129.4, 130.9, 133.7, 135.9, 144.7, 147.7, 169.3. IR (neat): 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{19}N_2O_3S$ $[M+H]^+$: 331.1111, found 331.1106.



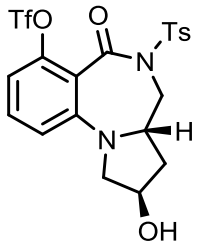
64

6-(4-Methoxyphenyl)-1-methyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (64) (Scheme 31): An oven dried Schlenk tube was charged with **57lAo** (10 mg, 21 μmol), $Pd(PPh_3)_4$ (1.2 mg, 1.1 μmol), 4-MeO-$C_6H_4B(OH)_2$ **52B** (4.8 mg, 31 μmol), K_2CO_3 (4.3 mg, 31 μmol) and evacuated and back-filled with argon. Anhydrous DMF (0.10 mL, 0.20 M) was added via syringes, and the reaction mixture was stirred at 80 °C for 15 h. The mixture was filtered through a pad of silica gel cake using EtOAc and the eluent was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **6** as a colorless solid (9.1 mg, quant). Mp: 224–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (3 H, s), 2.78 (3 H, s), 3.26 (2 H, s), 3.79 (3 H, s), 4.29 (2 H, s), 6.69 (2 H, d, *J* = 8.5 Hz), 6.87 (1 H, d, *J* = 8.0 Hz), 7.01–7.03 (3 H, m), 7.26 (2 H, d, *J* = 8.5 Hz), 7.38 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.90 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 40.3, 44.7, 55.1, 58.0, 113.9, 116.6, 124.7, 128.3, 128.7, 129.1, 131.8, 132.2, 136.0, 142.2, 144.5, 147.6, 159.0, 168.6. IR (neat): 1694 cm^{-1}. HRMS (MALDI) Calcd for $C_{24}H_{24}N_2O_4NaS$ $[M+Na]^+$: 459.1349, found 459.1350.



65

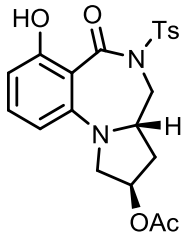
6-(4-Methoxyphenyl)-1-methyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (65) (Scheme 31): Sodium naphthalenide in dry THF (0.3 M) was prepared in the flask by the treatment of naphthalene (0.12 g, 0.92 mmol) in THF (3.0 mL) with metallic sodium (25 mg, 1.1 mmol) at room temperature for 1 h. A solution of **64** (40 mg, 92 μmol) in anhydrous THF (2.0 mL) was added to the solution of sodium naphthalenide in the flask through a cannula and washed with THF (1.0 mL). The mixture was stirred for 10 min. Then saturated NH_4Cl solution and EtOAc were added to the reaction mixture, and the aqueous phase was extracted three times with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1 ~ 1:0) to provide the titled compound **65** as a white solid (16 mg, 63%) with **64** (12 mg, 29%) recovered. Mp: 178–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.84 (3 H, s), 3.15 (2 H, t, *J* = 6.0 Hz), 3.48 (2 H, dt, *J* = 6.0, 6.0 Hz), 3.82 (3 H, s), 6.55 (NH, brs), 6.90–6.92 (3 H, m), 6.91 (2 H, d, *J* = 9.0 Hz), 7.05 (1 H, dd, *J* = 1.0, 7.5 Hz), 7.32 (2 H, d, *J* = 9.0 Hz), 7.38 (1 H, dd, *J* = 7.5, 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.0, 40.5, 55.2, 59.4, 113.8, 116.7, 124.3, 128.4, 129.3, 130.9, 133.5, 141.8, 147.8, 159.0, 172.9. IR (neat): 3420, 1651 cm^{-1}. HRMS (MALDI) Calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283.1441, found 283.1445.



66

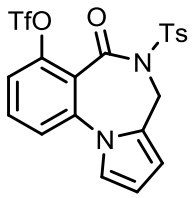
(2*R*,3a*S*)-2-Hydroxy-6-oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate (66) (Scheme 32): A round bottomed flask equipped with a reflux condenser was loaded with **57lPα** (0.12 g, 0.21 mmol) and ZnTAC[43] (15 mg, 16 μmol), MeOH (2.0 mL, 0.10 M) at room temperature. After stirring for 9 h at reflux, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to provide the titled compound **66** as a colorless solid (0.11 g, 96%). Mp: 158–160 °C. $[\alpha]_D^{20}$ = –87.5 (*c* 0.10, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (1 H, dd, *J* = 5.5, 13.0 Hz), 2.19 (1 H, dt, *J* = 6.5, 13.0 Hz), 2.44 (3 H, s), 3.22 (1 H, dd, *J* = 2.5, 10.0 Hz), 3.65 (1 H, dd, *J* = 5.5, 10.0 Hz), 3.76–3.84 (1 H, m), 4.18 (2 H, d, *J* = 3.0 Hz), 4.65 (1 H, brs), 6.73 (1 H, d, *J* = 8.5 Hz), 6.77 (1 H, d, *J* = 8.5 Hz), 7.33 (2 H, d, *J* = 8.5 Hz), 7.33 (1 H, dd, *J* = 8.5, 8.5 Hz), 7.95 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 39.4, 45.0, 57.7, 63.4, 68.4, 113.6, 116.7, 118.4 (q, *J* = 320 Hz),

118.7, 129.1, 129.3, 132.9, 135.1, 145.2, 146.0, 148.5, 164.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.1. IR (neat): 2924, 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{19}N_2O_7F_3NaS_2$ $[M+Na]^+$: 543.0478, found 543.0480. The absolute configuration was assigned on the basis of that of **57lPα**, which was synthesized by the reaction between **56P** and 3-(triflyloxy)benzyne (**1l**).



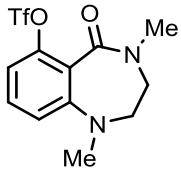
67

(2*R*,3a*S*)-7-Hydroxy-6-oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl acetate (67) (Scheme 32): A round bottomed flask was loaded with **57lPα** (32 mg, 57 μmol) and CsF (26 mg, 0.17 mmol), dioxane (3.0 mL, 20 mM) at room temperature. The mixture was stirred for 13 h at 80 °C. Then H_2O and EtOAc were added to the reaction mixture, and the aqueous phase was extracted twice with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 2:3) to provide the titled compound **67** as a yellow solid (19 mg, 79%). Mp: 199–201 °C. $[\alpha]_D^{20}$ = +180.0 (*c* 0.10, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.09 (3 H, s), 2.18 (1 H, ddd, *J* = 5.5, 11.0, 14.0 Hz), 2.34 (1 H, dd, *J* = 6.0, 14.0 Hz), 2.45 (3 H, s), 3.32 (1 H, d, *J* = 12.5 Hz), 3.76 (1 H, dd, *J* = 6.0, 15.5 Hz), 3.81 (1 H, dd, *J* = 5.0, 10.5 Hz), 3.86–3.90 (1 H, m), 4.44 (1 H, dd, *J* = 1.5, 15 Hz), 5.38 (1 H, t, *J* = 5.0 Hz), 6.13 (1 H, d, *J* = 8.0 Hz), 6.38 (1 H, d, *J* = 8.0 Hz), 7.21 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.34 (2 H, d, *J* = 8.0 Hz), 7.92 (2 H, d, *J* = 8.0 Hz), 10.9 (OH, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 21.7, 36.5, 46.4, 56.6, 62.9, 71.0, 105.6, 106.8, 108.1, 128.8, 129.4, 135.3, 136.0, 145.1, 145.8, 163.3, 170.6, 172.2. IR (neat): 1742, 1594 cm^{-1}. HRMS (MALDI) Calcd for $C_{21}H_{22}N_2O_6NaS$ $[M+Na]^+$: 453.1091, found 453.1088. The absolute configuration was assigned on the basis of that of **57lPα**, which was synthesized by the reaction between **56P** and 3-(triflyloxy)benzyne (**1l**).



68

6-Oxo-5-tosyl-5,6-dihydro-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl trifluoromethanesulfonate (68) (Scheme 32): To a solution of **57lPα** (9.7 mg, 17 μmol) in MeCN (2.0 mL, 0.01 M) were added DDQ (39 mg, 0.17 mmol) and TsOH·H_2O (33 mg, 0.17 mmol) at room temperature. The mixture was stirred for 36 h at room temperature. Then H_2O and EtOAc were added to the reaction mixture, and the aqueous phase was extracted twice with EtOAc. The combined organic phase was washed with a saturated aqueous NaCl solution (brine). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:2) to provide the titled compound **68** as a colorless solid (5.7 mg, 66%). Mp: 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (3 H, s), 4.47 (1 H, d, *J* = 16.0 Hz), 5.59 (1 H, d, *J* = 16.0 Hz), 6.35 (1 H, dd, *J* = 2.5, 3.0 Hz), 6.48 (1 H, d, *J* = 2.5 Hz), 7.03 (1 H, dd, *J* = 2.5, 3.0 Hz), 7.21–7.23 (3 H, m), 7.36 (1 H, dd, *J* = 1.0, 8.0 Hz), 7.60 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.78 (2 H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 40.7, 109.7, 111.5, 118.5 (q, *J* = 320 Hz), 120.1, 120.6, 122.1, 122.7, 129.0, 129.2, 130.2, 133.3, 134.9, 138.2, 145.2, 148.1, 161.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –72.7. IR (neat): 2922, 1682 cm^{-1}. HRMS (MALDI) Calcd for $C_{20}H_{15}N_2O_6F_3NaS_2$ $[M+Na]^+$: 523.0216, found 523.0220.



14lA

1,4-Dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-6-yl trifluoromethanesulfonate (14lA) (Scheme 36): Following General Procedure, a mixture of CsF (46 mg, 0.30 mmol), 1,3-dimethyl-2-imidazolidinone (**13A**) (33 μL, 0.30 mmol) and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**5lB**) (50 mg, 0.10 mmol) was stirred in dioxane (1.0 mL, 0.10 M) for 40 min at 80 °C. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 2:1) to provide the titled compound **14lA** as a colorless oil (16 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.83 (3 H, s), 3.20 (3 H, s), 3.27 (2 H, t, *J* = 6.0 Hz), 3.47 (2 H, t, *J* = 6.0 Hz), 6.88 (1 H, d, *J* = 8.0 Hz), 6.90 (1 H, d, *J* = 8.0 Hz), 7.37 (1 H, dd, *J* = 8.0, 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.8, 40.3, 47.4, 57.4, 115.0, 117.8, 118.6 (q, *J* = 319

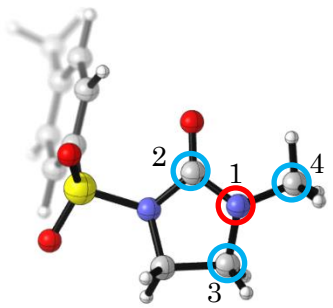
Hz), 123.6, 131.7, 147.5, 148.5, 165.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –73.5. IR (neat): 1655 cm^{-1}. HRMS (MALDI) Calcd for $C_{12}H_{13}N_2O_4F_3NaS$ $[M+Na]^+$: 361.0440, found 361.0446.

***s*-Character of the orbitals for lone pair electrons on nitrogen atoms of imidazolidinones 56A and 56N** optimized by B3LYP/6-31G(d) and their orbitals were characterized by natural localized molecular orbitals (NLMO)[41]

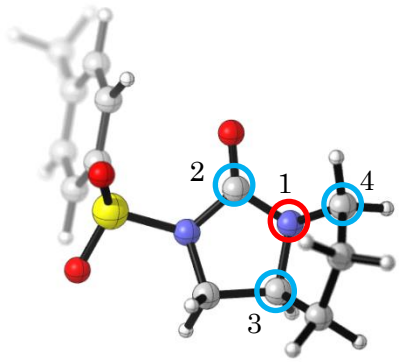
Table 15. Dihedral agle showing pyramidal geometry (N1, C2, C3, C4) and s-character of the orbitals for lone pair electrons on nitrogen atoms of imidazolidinones **56A** and **56N**.

	dihedral angle*	*s* character	*p* character	*d* character
N-tosyl-*N*-methyl imidazolidinone **56A**	27.1 °	3.55%	96.41%	0.03%
N-tosyl-bicyclic imidazolidinone **56N**	40.6 °	6.62%	93.32%	0.06%

*Dihedral angles were defined as following two sets of three atoms (N1,C2,C3) and (N1,C3,C4) shown below.



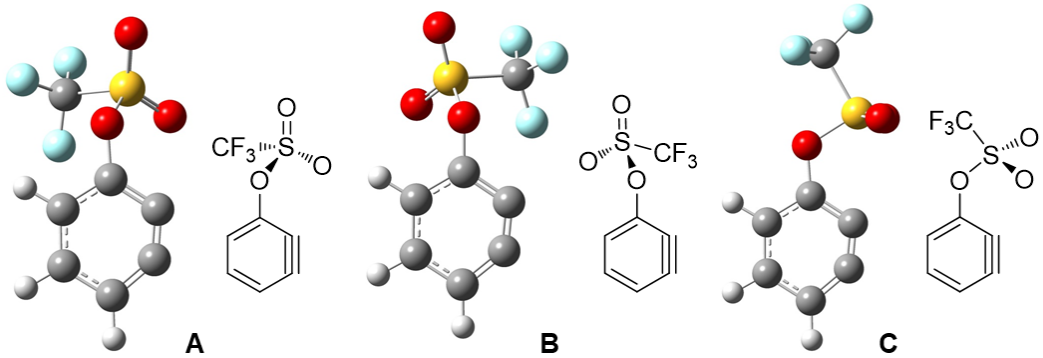
56A



56N

Conformation analysis of 3-(triflyloxy)benzyne 1l: The structures were optimized by B3LYP-D3/6-31G(d) using Gaussian09.

The conformations A and B showed very similar free energies (The difference was just 0.10 kcal/mol). On the other hand, the conformation C showed higher free energy and the difference between A and C was 2.375 kcal/mol. This number is high enough to regard that this conformer is ignorable (<5% of population). Among these three conformations, a transitions state structure made of A was found, while those having different conformations B and C had not been obtained so far.

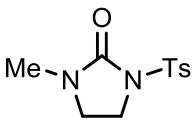


G = –1191.669474 (0.000 kcal/mol)

G = –1191.669626 (–0.095 kcal/mol)

G = –1191.665689 (2.375 kcal/mol)

Cartesian coordinates



56A

C	3.44211200	0.17180200	-1.26530000
C	2.57502300	-1.05205900	-0.92354600
C	1.82277200	0.84443600	0.28532400
H	3.19579700	0.57457000	-2.26079700
H	3.09753900	-1.73120900	-0.23990000
H	4.51210900	-0.05800100	-1.24002600
H	2.24542800	-1.61217400	-1.79832100
N	3.07653700	1.11430400	-0.21893600
N	1.43373200	-0.40509800	-0.25436400

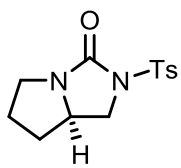
O	1.16271500	1.54559600	1.02993100
C	3.62172300	2.45433400	-0.17858000
H	3.44460800	2.99062800	-1.12297400
H	3.13278000	2.99431400	0.63418300
H	4.70044700	2.41602400	0.00714300
S	0.26360600	-1.39400400	0.52498200
O	0.30805000	-2.63516400	-0.25478100
O	0.50148700	-1.39865100	1.96709100
C	-1.26775100	-0.54352400	0.18750000
C	-2.02912900	-0.94499500	-0.91056800
C	-1.69288200	0.47657400	1.04063000
C	-3.23842900	-0.29987000	-1.16013800
H	-1.68398300	-1.75746400	-1.54087800
C	-2.90347300	1.10792000	0.76988400
H	-1.07628300	0.77066500	1.88051100
C	-3.69046200	0.73537500	-0.33014600
H	-3.84346600	-0.60976700	-2.00847500
H	-3.24575500	1.90358500	1.42682500
C	-4.98594100	1.45297600	-0.62369000
H	-4.79993400	2.37746100	-1.18617600
H	-5.66268100	0.83497800	-1.22244600
H	-5.50559400	1.73394300	0.29858400

SCF energy = -1160.95433521

Zero-point electronic energy = -1160.706988

Enthalpy = -1160.689595

Free energy = -1160.752774



(*R*)-**56N**

C	-2.9945320	0.0554440	-1.2399630
C	-2.0739590	1.2073140	-0.7701180
H	-2.8955810	-0.0752690	-2.3237840
H	-2.5519110	1.8164970	0.0083480

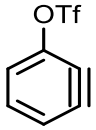
H	-1.7638680	1.8646940	-1.5827350
C	-1.3054720	-0.8413100	0.1563100
N	-0.9182650	0.4675990	-0.2254280
O	-0.7153170	-1.5724080	0.9283110
N	-2.4613070	-1.1291160	-0.5433640
C	-3.5326700	-1.9249800	0.0572610
H	-3.8861070	-2.6795680	-0.6567830
H	-3.1466900	-2.4378930	0.9409120
S	0.2886890	1.3398300	0.6330030
O	0.2818970	2.6476790	-0.0303320
O	0.0580240	1.2352520	2.0727920
C	1.7985250	0.4821880	0.2160160
C	2.5511140	0.9416290	-0.8664090
C	2.2247970	-0.5950700	0.9947390
C	3.7477600	0.2994970	-1.1748950
H	2.2054020	1.7923530	-1.4434520
C	3.4239990	-1.2227040	0.6664690
H	1.6169890	-0.9394970	1.8221790
C	4.2029890	-0.7880510	-0.4156420
H	4.3398730	0.6514830	-2.0160710
H	3.7607890	-2.0670210	1.2627440
C	5.5173550	-1.4580060	-0.7376980
H	6.3422500	-0.9893730	-0.1846420
H	5.5038240	-2.5180930	-0.4644160
H	5.7561570	-1.3828170	-1.8035380
C	-4.6203910	-0.8739610	0.3486230
H	-5.6234790	-1.3047780	0.4249220
C	-4.4900670	0.1206470	-0.8291200
H	-5.1169720	-0.1985920	-1.6687330
H	-4.3969030	-0.3744490	1.2986020
H	-4.7993050	1.1356380	-0.5596640

SCF energy = -1238.33871951

Zero-point electronic energy = -1238.055192

Enthalpy = -1238.036882

Free energy = -1238.103136



1l

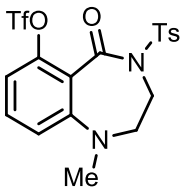
C	3.22268400	-0.90613800	0.58804900
C	2.08925000	-1.28383400	0.20913200
C	3.94369000	0.25419300	0.44442400
C	1.30285100	-0.39778000	-0.50444700
C	1.87187400	0.86649200	-0.74699200
C	3.16072600	1.17912000	-0.28752500
H	4.93770800	0.47644000	0.81284200
H	1.29159900	1.59862600	-1.29980700
H	3.57180900	2.16462300	-0.49179500
O	0.04501000	-0.67360300	-1.05807800
S	-1.24754900	-0.90338100	-0.05788800
O	-2.27897800	-1.48824400	-0.88972800
O	-0.82846000	-1.45387000	1.21876200
C	-1.69929700	0.89523800	0.23135800
F	-0.73649900	1.48144600	0.94564900
F	-2.84952700	0.94432600	0.89728000
F	-1.82415000	1.51827200	-0.93922500

SCF energy = -1191.72199502

Zero-point electronic energy = -1191.627743

Enthalpy = -1191.614427

Free energy = -1191.669474



57lA

C	1.13194000	1.58201700	2.26159600
C	0.37237600	0.25965300	2.24912500
C	-0.11667900	2.26364500	0.25316100
C	-0.63095200	1.03093500	-0.22593500

C	0.19007300	-0.23228500	-0.16971800
H	2.18228600	1.38870100	2.50590300
H	-0.71046600	0.40246100	2.23324600
H	0.71740600	2.22332600	3.06086900
H	0.61588400	-0.31210500	3.14413600
C	-0.81173700	3.44791100	-0.04665700
C	-1.84824500	1.04151500	-0.90910100
C	-2.55143700	2.20759600	-1.18412300
C	-2.00476400	3.41862200	-0.76640700
H	-0.42496900	4.39944000	0.29994400
H	-3.49535400	2.14699000	-1.71324200
H	-2.52690400	4.34689700	-0.97867300
N	1.10325900	2.26543400	0.96041200
N	0.71842800	-0.54355200	1.07236700
O	0.40187800	-0.89070800	-1.17333800
C	1.88232100	3.49326100	0.96412900
H	1.92897900	3.90652900	-0.04688500
H	1.48793700	4.26697200	1.64641700
H	2.90280500	3.25453200	1.28234500
S	1.98760400	-1.73294900	1.19207200
O	2.46407700	-1.58315100	2.57178700
O	1.49998100	-3.01001200	0.69072100
C	3.24344700	-1.09399800	0.09377400
C	4.17079500	-0.17927000	0.59650700
C	3.27806900	-1.51227200	-1.23641000
C	5.14168500	0.33286900	-0.25928300
H	4.14286300	0.10205300	1.64377100
C	4.26035700	-0.98906200	-2.07426500
H	2.54322400	-2.22073100	-1.59721200
C	5.19755700	-0.05797600	-1.60555500
H	5.87415300	1.03867200	0.12461200
H	4.29752900	-1.30940100	-3.11226400
C	6.23107000	0.52854700	-2.53659900
H	5.83184600	1.41101200	-3.05394600
H	7.12851300	0.84458900	-1.99483900
H	6.53154500	-0.19036100	-3.30587100

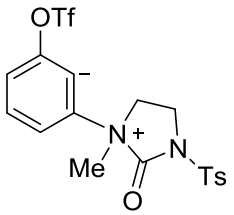
O	-2.39652600	-0.15594300	-1.40510300
S	-3.06379700	-1.22658600	-0.35203100
O	-2.42652400	-1.13060500	0.95304000
O	-3.22694200	-2.46337100	-1.08449200
C	-4.76282500	-0.44652200	-0.17707000
F	-4.66219900	0.67847300	0.53502900
F	-5.56375600	-1.30457100	0.44872500
F	-5.25469700	-0.16290300	-1.38290600

SCF energy = -2352.80763642

Zero-point electronic energy = -2352.460224

Enthalpy = -2352.430794

Free energy = -2352.522853



72lA

C	0.22760800	0.07089900	1.84898300
C	0.58667300	-0.94176300	0.76299700
C	-0.76773200	1.77685400	0.25641400
C	1.65676700	1.12526000	0.27208600
H	0.89599200	0.00744100	2.71110200
H	-0.26930000	-1.14727500	0.11637500
H	-0.83591200	0.03379000	2.10498600
H	0.98680400	-1.87228700	1.16637900
C	-0.56325000	2.79494000	-0.68144200
C	-2.92838100	1.42772300	-0.35658000
C	-2.86929700	2.41606300	-1.33329300
C	-1.66217400	3.11341700	-1.48075500
H	0.38521400	3.30567000	-0.81387500
H	-3.72326700	2.63129600	-1.96891800
H	-1.57459200	3.89107900	-2.23353400
N	0.47626700	1.39713500	1.17808000
N	1.64143400	-0.21167300	0.03052400

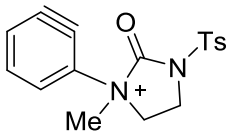
O	2.41186700	1.98962100	-0.09337000
C	0.75155600	2.50453100	2.13730500
H	0.99345800	3.40028000	1.56824400
H	-0.15753700	2.65702800	2.71986600
H	1.59140100	2.23472000	2.78223600
O	-4.17772300	0.73987700	-0.26858000
S	-4.14920500	-0.70969000	0.49833300
O	-4.27120400	-0.58320000	1.94484900
O	-3.22099200	-1.64855800	-0.12439100
C	-5.85178000	-1.16456000	-0.12972900
F	-6.75360800	-0.26851300	0.27221800
F	-5.85572100	-1.23627500	-1.46070800
F	-6.16111500	-2.36167200	0.37832600
C	-1.90263400	1.06186900	0.49799000
S	2.61941900	-0.95674000	-1.21617200
O	2.49282300	-0.13679700	-2.41165500
O	2.19749800	-2.35266800	-1.15545200
C	4.26385900	-0.79802900	-0.55366700
C	4.98698700	0.37344600	-0.78974500
C	4.79554700	-1.85448000	0.18923100
C	6.26878600	0.48009500	-0.25714500
H	4.54579400	1.17821100	-1.36523100
C	6.08066600	-1.72428400	0.70853100
H	4.21660300	-2.75938400	0.34024000
C	6.83472500	-0.56071800	0.49434200
H	6.84165900	1.38720000	-0.43067300
H	6.50776200	-2.54089800	1.28471800
C	8.23983200	-0.44440400	1.03235600
H	8.96691400	-0.80793800	0.29450700
H	8.49799300	0.59492000	1.25960900
H	8.37298500	-1.03841400	1.94218000

SCF energy = -2352.70627842

Zero-point electronic energy = -2352.360922

Enthalpy = -2352.330902

Free energy = -2352.425672



73A

C	-1.81211700	1.08599600	1.95026400
C	-1.02670400	-0.22622200	1.95999500
C	-3.14888000	0.54946300	-0.07008100
C	-0.65541300	0.82373200	-0.13316500
H	-1.22319100	1.90748900	2.36448900
H	-1.67441300	-1.10285200	1.86842300
H	-2.78679500	1.03630000	2.43531400
H	-0.40433100	-0.33434600	2.84836800
C	-2.96142900	-0.51154900	-0.97487100
C	-5.32487100	0.09189300	-0.15935900
C	-5.39237300	-0.96369800	-1.02360600
C	-4.06765800	-1.24772700	-1.43585000
H	-1.97686300	-0.79173300	-1.33548500
H	-6.26105200	-1.51269800	-1.36408600
H	-3.90546000	-2.06363300	-2.13478100
N	-1.99452200	1.35958700	0.47288900
N	-0.18861700	-0.06996600	0.76068800
O	-0.26204700	1.20959200	-1.19511500
C	-2.17371300	2.81231400	0.13670800
H	-2.17857900	2.90199600	-0.94910200
H	-3.12305000	3.14168500	0.55937600
H	-1.33954300	3.37540500	0.55766100
C	-4.44261300	0.83164200	0.34572200
S	0.89363600	-1.41759300	0.22767200
O	0.31529100	-1.84352700	-1.04099800
O	0.90171000	-2.25112600	1.42190400
C	2.44849500	-0.62675600	-0.01891700
C	2.71738600	-0.02323400	-1.25240400
C	3.37903300	-0.63584100	1.02647000
C	3.95360500	0.58884700	-1.42788400
H	1.97721500	-0.03296000	-2.04374500
C	4.60767600	-0.01910500	0.81952100

H	3.14927700	-1.12940800	1.96468700
C	4.91534200	0.59907700	-0.40416400
H	4.18032800	1.06146300	-2.37922300
H	5.34503000	-0.02329000	1.61723500
C	6.26608800	1.22959300	-0.62454600
H	6.97902100	0.47974000	-0.99118800
H	6.22114200	2.03012600	-1.36885500
H	6.67430800	1.64077700	0.30378900

SCF energy = -1391.03063644

Zero-point electronic energy = -1390.714969

Enthalpy = -1390.693059

Free energy = -1390.766580

TfO$^-$

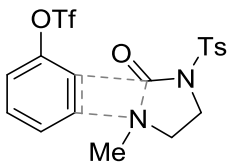
O	-1.24376600	-1.17022800	0.85135100
S	-0.92747600	-0.00001600	0.00008900
O	-1.24359700	1.32239700	0.58785100
O	-1.24411200	-0.15215800	-1.43890900
C	0.94233100	-0.00002800	-0.00003800
F	1.44609500	0.12894800	1.24862400
F	1.44586000	-1.14590200	-0.51283000
F	1.44553700	1.01699200	-0.73618600

SCF energy = -961.50343652

Zero-point electronic energy = -961.476227

Enthalpy = -961.468098

Free energy = -961.508780



TS-I

C	0.64577400	2.58112700	1.90598800
C	0.55522900	1.04444700	1.94436300
C	-1.13725700	2.50948600	-0.38579200
C	-1.30149300	1.28639600	-0.72202100

C	1.50285600	1.74625000	-0.11894000
H	1.49848500	2.95123000	2.49304100
H	-0.46902800	0.68276200	1.83391800
H	-0.26892300	3.06279900	2.26004900
H	0.99900100	0.61406600	2.84263400
C	-1.96877200	3.59426600	-0.24131000
C	-2.61309200	0.94706700	-0.98589000
C	-3.62726100	1.91022100	-0.89350100
C	-3.29853400	3.22865900	-0.54192200
H	-1.69598900	4.60243600	0.05044500
H	-4.65865900	1.62850900	-1.07953800
H	-4.08158500	3.97984500	-0.48094800
N	0.85708200	2.86862400	0.47823600
N	1.34989300	0.69167100	0.75829400
O	2.05630000	1.75908700	-1.19601600
C	1.34766500	4.18755900	0.09575700
H	1.51497900	4.18892200	-0.98185600
H	0.59914600	4.93975700	0.35563200
H	2.28810400	4.42660500	0.61100500
S	1.58796700	-0.96738600	0.30662600
O	1.27721600	-1.67872200	1.54622600
O	0.89995800	-1.23630800	-0.94818700
C	3.34983400	-1.02473500	0.02192100
C	4.18856600	-1.39728500	1.07325400
C	3.85322100	-0.71376100	-1.24241100
C	5.56201700	-1.45164400	0.84827500
H	3.76613400	-1.65094400	2.03970900
C	5.22965200	-0.77305500	-1.44297100
H	3.17803200	-0.41794300	-2.03570200
C	6.10184000	-1.14238600	-0.40836300
H	6.22472700	-1.74374800	1.65902800
H	5.63450200	-0.52887300	-2.42181800
C	7.58837700	-1.23680700	-0.65437600
H	8.15944100	-1.09842300	0.26941800
H	7.85327500	-2.22244600	-1.05914500
H	7.92286400	-0.48738800	-1.37949100

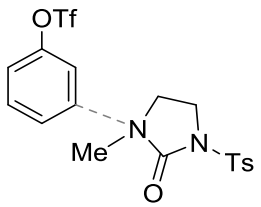
O	-2.99737700	-0.36679800	-1.36537200
S	-2.81599100	-1.57570100	-0.27175600
O	-2.05465400	-1.14564400	0.89129400
O	-2.53630700	-2.78862500	-1.01270900
C	-4.60278900	-1.66175600	0.28059800
F	-4.96680600	-0.47526600	0.78221800
F	-4.72087600	-2.59589300	1.22397800
F	-5.38798900	-1.96306800	-0.75151300

SCF energy = -961.50343652

Zero-point electronic energy = -2352.345174

Enthalpy = -2352.314902

Free energy = -2352.409634



TS-II

C	-0.00835500	1.06407900	-2.07919600
C	-0.39944600	-0.27598200	-1.44081100
C	1.13995600	1.88900900	0.32368200
C	-1.53275700	1.49991900	-0.34654800
H	-0.54138200	1.25355800	-3.01852300
H	0.41934000	-0.67958800	-0.83954500
H	1.07658900	1.14583200	-2.22310700
H	-0.72037700	-1.02345000	-2.16612900
C	0.72227000	1.92097500	1.63331600
C	3.26403800	1.30420400	0.59736300
C	3.05609600	1.27485500	1.98233900
C	1.79182100	1.60192100	2.49348100
H	-0.28116700	2.12214200	1.98793800
H	3.86232900	0.97456000	2.64354500
H	1.61865300	1.57340900	3.56543700
N	-0.42888400	2.03925300	-1.06418300
N	-1.53110400	0.13433700	-0.58385700

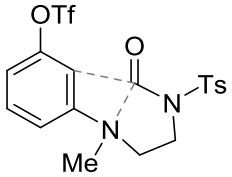
O	-2.28349900	2.14119500	0.35821300
C	-0.48408000	3.45068700	-1.44713100
H	-0.87979100	4.01968800	-0.60540700
H	0.53244300	3.77781500	-1.67597500
H	-1.12923200	3.59136000	-2.32290700
O	4.57468700	0.92627100	0.16031600
S	4.72156100	-0.36918000	-0.81804300
O	6.14975400	-0.58114600	-0.96139300
O	3.82032600	-0.31934000	-1.95894100
C	4.05584900	-1.71973900	0.31056300
F	4.55661600	-1.57570300	1.53839300
F	2.72261800	-1.65784700	0.36593200
F	4.42435000	-2.89843400	-0.18897100
C	2.25411800	1.64477100	-0.28277300
O	-1.75414500	-2.27558600	0.06858300
O	-1.89862000	-0.50026700	1.90321100
C	-3.96391200	-0.81550700	0.27022600
C	-4.67420600	0.20751900	0.90200900
C	-4.58956100	-1.72770300	-0.58108300
C	-6.04092000	0.31335200	0.66008300
H	-4.15830500	0.90812700	1.54697100
C	-5.95859200	-1.60313800	-0.80409700
H	-4.01313900	-2.52035900	-1.04583100
C	-6.70279500	-0.58582500	-0.18972300
H	-6.60518800	1.10858400	1.14038400
H	-6.45772600	-2.30873400	-1.46321600
C	-8.19170900	-0.47737100	-0.41245900
H	-8.74085400	-1.01934200	0.36861500
H	-8.52649100	0.56471700	-0.38198800
H	-8.48672500	-0.90447700	-1.37626700
S	-2.21382500	-0.97683800	0.55984000

SCF energy = -2352.69970664

Zero-point electronic energy = -2352.355845

Enthalpy = -2352.325848

Free energy = -2352.420729



TS-III

C	0.40078400	1.79471300	2.10199300
C	0.46176700	0.27418600	1.90550600
C	-0.87691000	2.56388100	0.08194100
C	1.20411400	1.26796900	-0.12108600
H	1.25197400	2.15176600	2.68728700
H	-0.52930600	-0.15111100	1.74266000
H	-0.53693800	2.12798500	2.54264100
H	0.98293300	-0.22424500	2.72431300
C	-1.33912500	3.83047000	-0.28708300
C	-2.81612900	1.51794900	-0.52734200
C	-3.40308100	2.71641900	-0.92351500
C	-2.63680900	3.88220300	-0.80590400
H	-0.76270600	4.74587300	-0.19775400
H	-4.41825200	2.74890400	-1.30851700
H	-3.05517800	4.83655900	-1.11162000
N	0.52128200	2.38780300	0.70984100
N	1.26254700	0.17573500	0.67796200
O	1.67399500	1.50043500	-1.20042400
C	1.38674200	3.60134500	0.67309100
H	1.47595300	3.92122800	-0.36397100
H	0.92341500	4.37780800	1.28237100
H	2.37186600	3.34829000	1.06948600
O	-3.64223800	0.36315200	-0.65586400
S	-3.09969100	-0.99064600	0.10419700
O	-3.00971200	-0.81457200	1.55290100
O	-2.08292200	-1.70561900	-0.65317600
C	-4.71184600	-1.89042200	-0.19955200
F	-5.72207800	-1.25929200	0.40178000
F	-4.95884600	-1.98341800	-1.50633600
F	-4.58954900	-3.11746900	0.31632100
C	-1.53824800	1.36453500	-0.02444700

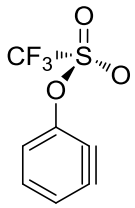
S	1.77767500	-1.38856800	0.05200700
O	1.17634300	-1.58659800	-1.25434500
O	1.54585400	-2.27024200	1.19220700
C	3.52893600	-1.11040100	-0.14206100
C	4.00446700	-0.56861500	-1.33839700
C	4.38938400	-1.45512200	0.90162100
C	5.37450600	-0.36188000	-1.47526200
H	3.31192300	-0.31545000	-2.13221900
C	5.75615200	-1.24242100	0.73921200
H	3.99242600	-1.89922700	1.80838100
C	6.26778600	-0.69057700	-0.44450900
H	5.75822500	0.05518100	-2.40277000
H	6.43752400	-1.51778900	1.54008300
C	7.74735800	-0.43613700	-0.60167800
H	8.33989100	-1.09514700	0.04064100
H	8.07117600	-0.58567100	-1.63687100
H	7.99513900	0.59829300	-0.32945700

SCF energy = -2352.69938003

Zero-point electronic energy = -2352.353777

Enthalpy = -2352.324725

Free energy = -2352.416083



A

C	3.2221170	-0.9060690	0.5888740
C	2.0887710	-1.2839230	0.2099030
C	3.9430130	0.2542710	0.4444780
C	1.3024020	-0.3985520	-0.5045070
C	1.8714350	0.8655700	-0.7478360
C	3.1601670	1.1785990	-0.2883030
H	4.9369360	0.4768680	0.8129510
H	1.2912170	1.5972640	-1.3012950

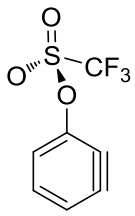
H	3.5712260	2.1639780	-0.4932030
O	0.0446900	-0.6747910	-1.0581530
S	-1.2480940	-0.9033390	-0.0580030
O	-0.8296030	-1.4544910	1.2185700
O	-2.2800640	-1.4871070	-0.8899560
C	-1.6981010	0.8957350	0.2315770
F	-0.7354530	1.4804830	0.94719600
F	-2.8490370	0.9458880	0.8962020
F	-1.8209420	1.5194780	-0.9388660

SCF energy = -1191.72199504

Zero-point electronic energy = -1191.627742

Enthalpy = -1191.614426

Free energy = -1191.669474



B

C	-2.9467810	1.3722970	-0.3041590
C	-1.7899700	1.1218640	-0.7180690
C	-3.9301570	0.6429020	0.3166400
C	-1.3146720	-0.1716010	-0.5787180
C	-2.1887960	-1.0844780	0.0405040
C	-3.4605240	-0.6829930	0.4777750
H	-4.9085000	0.9731740	0.6432100
H	-1.8586800	-2.1077430	0.1831190
H	-4.1118120	-1.4118300	0.9536090
O	-0.0718080	-0.5962530	-1.0715970
S	1.16039400	-0.9036570	-0.0171270
O	2.13585000	-1.6641200	-0.7718170
O	0.63597100	-1.3239270	1.2721280
C	1.82648800	0.8378450	0.1882710
F	2.14927000	1.3341150	-1.0011020
F	2.90476900	0.7831570	0.9672130

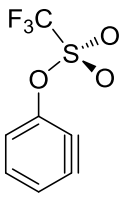
F	0.89474600	1.6009820	0.7595460

SCF energy = -1191.72261925

Zero-point electronic energy = -1191.628374

Enthalpy = -1191.615074

Free energy = -1191.669626



C

C	-2.3510950	2.6010950	0.0000000
C	-1.3030350	1.9127300	0.0000000
C	-3.6958710	2.3305430	0.0000000
C	-1.4395360	0.5359640	0.0000000
C	-2.7577390	0.0436030	0.0000000
C	-3.8515180	0.9226650	0.0000000
H	-4.5252590	3.0262030	0.0000000
H	-2.9177370	-1.0299420	0.0000000
H	-4.8578770	0.5109640	0.0000000
O	-0.4138400	-0.4119060	0.0000000
S	1.1493860	0.1324740	0.0000000
O	1.4643520	0.7557990	1.2741650
O	1.4643520	0.7557990	-1.2741650
C	1.8593380	-1.6028760	0.0000000
F	1.4643520	-2.2535910	1.0894270
F	3.1855760	-1.4802270	0.0000000
F	1.4643520	-2.2535910	-1.0894270

SCF energy = -1191.71979733

Zero-point electronic energy = -1191.625820

Enthalpy = -1191.613222

Free energy = -1191.665689

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