博士論文

ケイ素 traceless 保護による
カルボン酸選択的触媒的不斉アルドール反応

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略語表

本論文中では便宜上、以下の略語を用いた。

Ac	acetyl
aq.	aqueous solution
Ar	aryl
Bn	benzyl
Boc	tert-butoxycarbonyl
Bu	(normal-)butyl
Bus	tert-butylsulfonyl
cat.	catalyst or catalytic amount
Cbz	carbobenzoxy or benzyloxycarbonyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	N,N-dimethyl-4-aminopyridine
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESI	electrospray ionization
eq	equivalent(s)
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
^{i}Pr	isopropyl
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
LRMS	low-resolution mass spectroscopy
M	molar
Me	methyl
Mes	mesityl
min	minute(s)
MS	mass spectrometry or molecular sieves
Ms	methanesulfonyl

MTBE	methyl tert-butyl ether
NMR	nuclear magnetic resonance
Ph	phenyl
phth	phthaloyl
PTC	phase-transfer catalyst
quant.	quantitative
rt	room temperature
TBS	tert-butyldimethylsilyl
^{t}Bu	tert-butyl
temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	p-toluenesulfonyl
Xyl	xylyl

1. 序論

　近時の感染症禍を例にとらずとも、現代に生きる我々の生活において医薬品が不可欠であることは論を待たない。特に、低分子医薬品は身近な有機化学の知識と技術の結晶でありこれまで医薬品の主流であった。近年では、ペプチドに代表される中分子医薬や抗体に代表される高分子医薬に注目が集まっているが、元をたどればいずれも化学結合から構成される巨大な有機分子にすぎない。しかし複雑な構造を有する中・高分子へも適用可能な化学反応・修飾反応は少なく、その開発は課題である。また、低分子医薬品であっても数多くの候補化合物を合成する必要があり、その効率的な合成法は依然として高い需要がある。

　種類を問わず医薬品となる有機分子は、生体内における溶解性や、受容体を初めとする生体高分子との相互作用に必要な極性官能基を幾つも有することが多い。従って、多官能基存在下、狙った官能基だけを特異的に活性化、修飾できるような反応は低分子から高分子まで適用可能な優れた反応となる。即ち、医薬品合成反応において要求される性質とは、似た反応性を有する官能基の中から化学選択的に活性化できること、また反応性の高い極性官能基の影響を受けずに活性化できる官能基許容性の高さである。更に、反応が不斉点を構築するような場合、合成初期段階ではエナンチオ選択的、既にほかの不斉点を有しているような合成終盤ではジアステレオ選択的である必要も多い。このように自由に立体を制御できるような立体選択性も重要であるといえる。

　このような**官能基許容性の高い、化学選択的かつ立体選択的な反応**は、革新的な医薬品創出及び新規合成ルート開発、後期誘導体化による迅速なライブラリー構築などを実現し医薬品開発に貢献することが期待される。さらにこのような性質を有する反応は、ペプチド、タンパク質修飾へと応用することで新たな性質や新奇構造を創出し構造生物学にも貢献しうると期待できる。

　以上のような背景から、当研究室では官能基許容性の高い化学選択的かつ立体選択的な反応の開発に取り組んできた。

2. ジアステレオ・エナンチオ選択的触媒的アルドール反応

2-1. カルボン酸に対する化学、位置選択的な修飾反応の現状

　カルボン酸は、有機分子に幅広く含まれる重要な官能基であり、特に非ステロイド性抗炎症薬（NSAIDs）や抗生物質などの生物学的に活性な天然物や医薬品にも多く含まれている。従って、複数の官能基を有するカルボン酸の化学選択的、官能基許容的かつ立体選択的な炭素炭素結合形成反応は、複雑分子の合成や、医薬品リード化合物群最適化のための後期誘導体化における有効な手法となる。

　カルボン酸は酸性度の高い高反応性の OH 基を官能基内に有している為、通常は合成初期にエステルなどの保護を行い、終盤で脱保護されることでカルボキシ基として導入することが多い。一方で、反応形式に限定はあるもののカルボン酸をそのままの形で修飾、変換する反応が報告されている。複雑分子であっても、カルボン酸の保護脱保護という本来必要のない工程を使用することなく直截的に変換することが出来れば高効率な合成経路を実現しうる。先駆的な研究として、山本らはボランによるカルボン酸の触媒的な活性化を見出し不飽和カルボン酸とジエンの触媒的 Diels-Alder 反応[1]を報告した(Figure 2-1-1)。ホウ素とカルボン酸酸素原子間の可逆な共有結合を利用することで、カルボン酸活性化と触媒回転を同時に実現し、更に酒石酸から誘導した配位子を用いることで不斉化にも成功している。本報告以来、カルボン酸活性化の触媒としてホウ素原子が注目されるようになりアミド化[2]、マイケル付加[3]など様々な形式の反応が報告されてきた。特に Hall らは前述の山本らと同じ Diels-Alder 反応ながら、独自に開発したボロン酸触媒が不飽和カルボン酸を特異的に活性化し、不飽和エステル存在下でもカルボン酸選択的な Diels-Alder 反応が進行する[4]ことを見出している。これはカルボン酸が本質的に高反応性であることを利用して、カルボン酸が化学選択的に活性化できることを示した興味深い報告である。

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[1] Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110,* 6254.

[2] For selected example see: (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61,* 4196. (catalytic) (b) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876. (Mild condition) (c) Noda, H.; Furutachi, M.; Asada, Y.; Shibasaki, M.; Kumagai, N. *Nat. Chem.* **2017**, *9,* 571. (Recent advances)

[3] For selected example see: (a) Hayama, N.; Kuramoto, R.; Földes, T.; Nishibayashi, K.; Kobayashi, Y.; Pápai, I.; Takemoto, Y. *J. Am. Chem. Soc.* **2018**, *140*, 12216. (b) Horibe, T.; Hazeyama, T.; Nakata, Y.; Takeda, K.; Ishihara, K. *Angew. Chem.* **2020,** *132*, 17409.

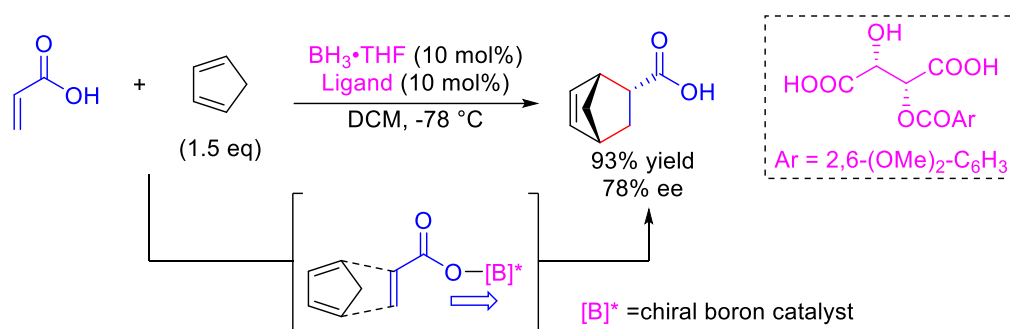[4] Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876.

Figure 2-1-1　ホウ素触媒を用いた不飽和カルボン酸に対する不斉 Diels-Alder 反応

　　カルボン酸が本質的に高反応性であることを利用することで、化学選択性以外にも位置選択性を実現する反応が報告されている。Yu らは、パラジウム触媒が多官能基存在下でもカルボキシ基に選択的に認識されて可逆な共有結合を形成することで、位置選択的な C-H 結合活性化を達成しこれを鍵反応とする複雑化合物の全合成[5]を達成している(Figure 2-1-2)。
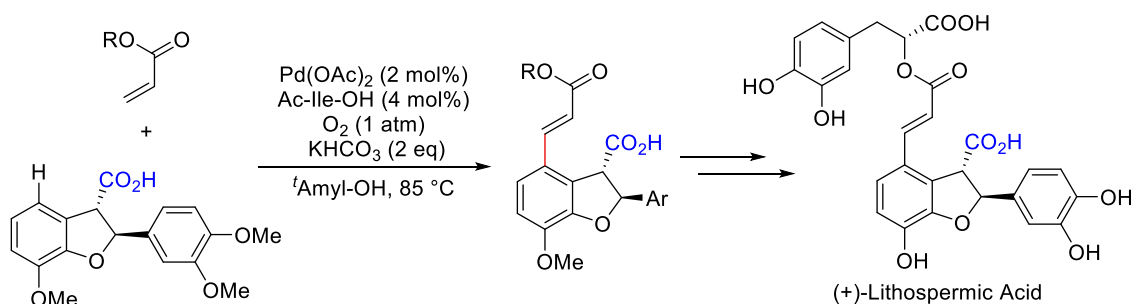

Figure 2-1-2　カルボン酸を配向基にした Pd 触媒による位置選択的 C-H 活性化反応

[5] (a) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767. (b) Rosen, B. R.; Sim-ke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J.-Q.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7317. (c) Meng, G.; Lam, N. Y. S. Lucas, E. L. Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. *J. Am. Chem. Soc.* **2020**, *142*, 10571.

2-2.　カルボン酸エノラートを経由するα位修飾反応の現状

　さて、カルボニル化合物においてそのエノラートを経由した求核反応は多様な求電子剤が導入可能なことや、官能基周辺の光学活性部位を容易に構築できるため非常に重要である。特に、α位プロトンの酸性度が高いケトンやアルデヒドのエノラート形成は比較的容易であるためこれまで数多くの反応が報告されており、金属触媒や有機分子触媒による活性化も盛んである。その一方で、エステルやアミド、カルボン酸といった高酸化度基質においては、そのα位プロトンの脱プロトン化が困難なことから配向基や特殊な基質を用いたエノラート形成が一般的であった。とくにカルボン酸は、より酸性度の高いカルボキシ基のOHを分子内に有している為に、そのエンジオラート形成はジアニオンを経由する必要があり最も困難な反応のひとつであった。

　そのためこれまでは、LDA を初めとする過剰量の強塩基を用いることで、ヒドロキシ基とカルボン酸のαプロトンを脱プロトン化し求核反応を行うことが一般的であった。近年Zakarian らは、当量のキラルアミンを用いることで立体選択的なカルボン酸α位修飾反応[6],を達成しアルキル化、アリル化、マイケル付加反応、アルドール反応に成功している(Figure 2-2-1. アルドール反応については後述)。一連の報告は、高反応性故制御の難しいエンジオラート種を制御して高い立体選択性にてα位修飾を実現した点で優れているが、過剰量の強塩基を必要とするために複雑基質への適用や、化学選択性発現が困難な点、当量のキラルアミンを必要とする点や、反応によっては基質としてカルボン酸α位にアリール基やメトキシ基を必要とする点において改善の余地が残る。
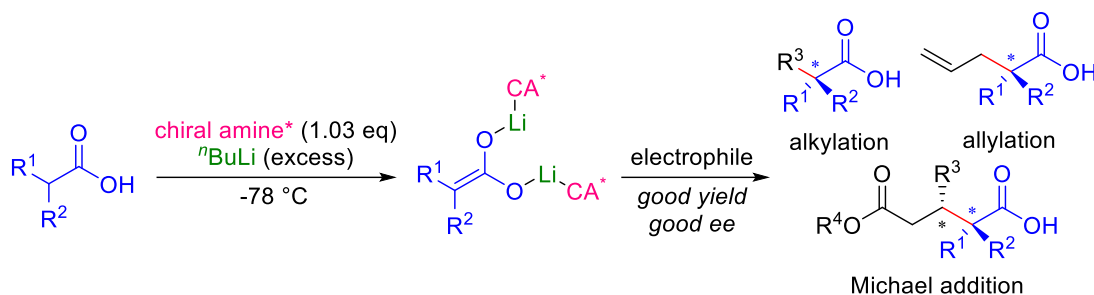

Figure 2-2-1　キラルアミンを利用したカルボン酸に対するα位不斉求核反応

　上述の強塩基を用いる手法に比べてあまり一般的ではないものの、強力なルイス酸活性化剤と弱塩基の組み合わせによってエノラート形成が可能になることも知られている。先

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[6] (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011** *133*, 11936. (b) Ma, Y.; Stivala, C. E.; Wright, A. M.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 16853. (c) Lu, P.; Jackson, J. J.; Eickhoff, J. A.; Zakarian, A. *J. Am. Chem. Soc.* **2015***, 137,* 656. (d) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T. A. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian. *J. Am. Chem. Soc.* **2017**, *139*, 527. (e) Yu, K.; Miao, B.; Wang, W.; Zakarian, A. *Org. Lett.* **2019**, *21*, 1930.

駆的な研究として、Evans らはジアルキルボロントリフラートを活性化剤、ジイソプロピルエチルアミンを塩基として用いることで系内でジボラエンジオラート種が生成し、アルデヒドを加えることでアルドール反応[7]が良い収率で進行することを見出した(Figure 2-2-2)。ジアステレオ選択性は基質や用いるボロントリフラート類に依存しており選択的な反応は実現できていないものの、金属強塩基を用いることなくカルボン酸のエンジオラート種が形成できることを見出した点で革新的である。その一方で、同様の条件でケトンやエステル類もエノラート形成することから化学選択性の観点からは改善の余地が残る。
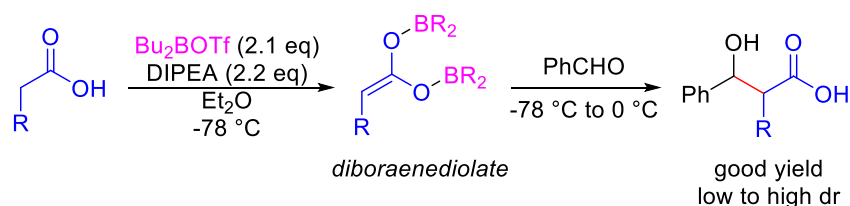

diboraenediolate

good yield
low to high dr

Figure 2-2-2　ホウ素試薬によるカルボン酸直截的アルドール反応

　本報告以来、報告数は多くないもののホウ素活性化剤と三級アミンを用いることでエノラート形成と引き続くアルドール反応[8]が報告されている。また同様に報告例は少ないもののケイ素トリフラートと ^{i}Pr$_2$NEt によって、シリルケテンアセタールを形成しアルドール反応[9]を行う例も報告されている(Figure 2-2-2)。本手法は one-pot に全ての試薬を混ぜることで反応が進行し、室温化高い収率にて目的物を得ることが可能である。
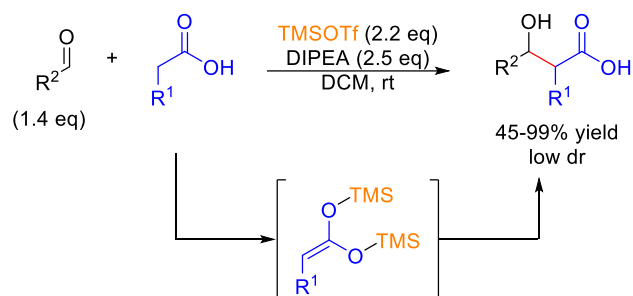

(1.4 eq)

45-99% yield
low dr

Figure 2-2-3　ケイ素試薬によるカルボン酸直截的アルドール反応

　最近 Hartwig らは、カルボン酸に対して強塩基とケイ素化合物を組み合わせることでシリルケテンアセタールを形成し、更に one-pot でパラジウム触媒を作用させることでカルボン酸 α 位アリール化反応[10]を達成している(Figure 2-2-4)。カルボン酸に対して二当量以上の

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[7] Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981***, 103,* 3099.

[8] (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499-504. (b) Ramachandran, P. V.; Chanda, P. M.; Otoo, B. *Tetrahedron Lett.* **2019**, *60*, 151102.

[9] Downey, C. W.; Johnson, M. W.; Lawrence, D. H.; Fleisher, A. S.; Tracy, K. J. *J. Org. Chem.* **2010***, 75,* 5351.

[10] He, Z-T.; Hartwig, J. F. *J. Am. Chem. Soc*. **2019**, *141*, 11749.

TMSCl 及び塩基として過剰量の LHMDS を用いることで系内にてジシラエンジオラート種を生成させ、アリールハライドとのカップリングパートナーとして用いている。本手法は操作の容易性に加え、二級アミドにも適用可能であり優れた研究である。
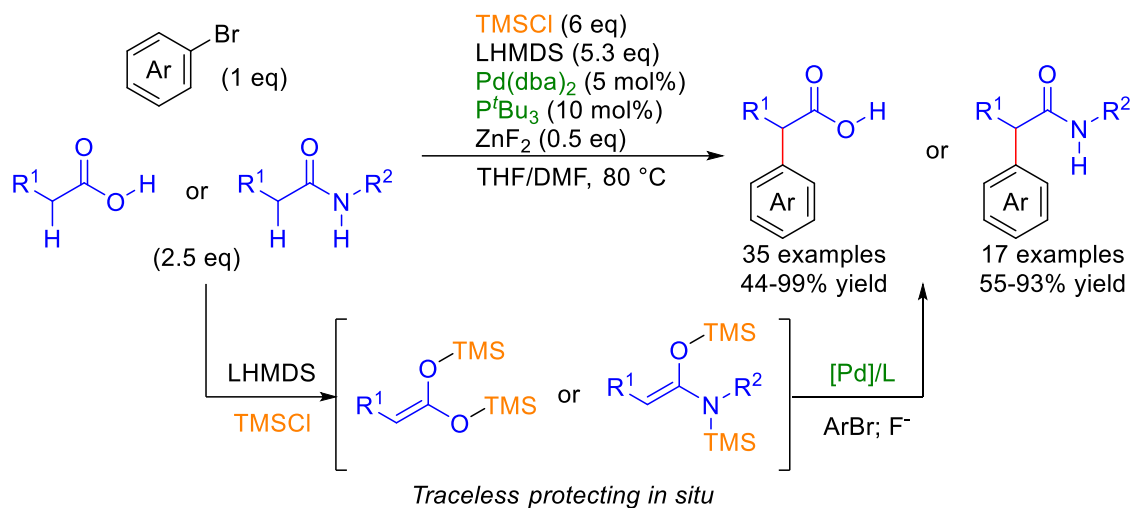

Figure 2-2-4 ケイ素を traceless 保護基として用いる α 位アリール化反応

　しかしながらこれらの例は、いずれも当量以上の強力な活性化剤あるいは強塩基を必要としており Evans らと同様の問題点がある。また触媒化や不斉化は困難であり、多官能性基質に対する立体選択的後期誘導体化に関する適用例は存在しなかった。

　そのような背景のもと、当研究室では最近、温和な DBU 塩基性条件下、カルボン酸がホウ素触媒によって化学選択的に活性化できることをみいだし、Mannich 型反応[11]やアリル基転位反応[12]等を報告した(Figure 2-2-4)。これらの反応においては、ホウ素触媒上に適切な配位子を用いることで触媒の活性や立体選択性をコントロールすることが可能であり、BINOL 型配位子やアミノ酸型の配位子を用いることで高い収率と立体選択性を実現している。反応中間体については Evans らと同様にジボラエンジオラート種を想定しているものの、興味深いことに本手法では、よりエノラート形成しやすいケトンやエステル、アミド類に関しては反応が進行せず、同一基質中にこれらの官能基を有していてもカルボン酸 α 位選択的に反応が進行する。また温和な塩基性、室温という条件や化学選択的であることを活用し、ペプチドや低分子医薬品の後期誘導体化を実現している点も特筆すべき点である。

[11] Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075.
[12] Fujita, T.; Yamamoto, T.; Morita, Y.; Cheng, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2018**, *140*, 5899.

(a)

up to 97% yield
up to 11/1 dr
up to 98% ee

(b)

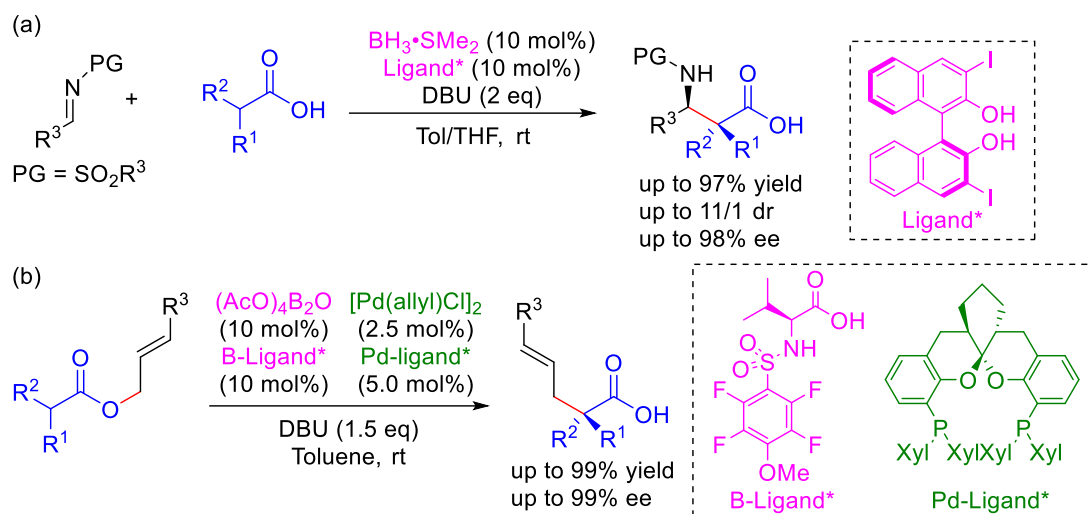

up to 99% yield
up to 99% ee

Figure 2-2-4　ホウ素触媒によるカルボン酸選択的 α 位変換反応

　当研究室の一連の報告以来、触媒的なカルボン酸のエノラート形成反応が報告されるようになった。大嶋らは鉄触媒とアルカリ金属を用いることで、カルボン酸エノラートを形成し TEMPO でエノラートを一電子酸化することによって α 位ラジカルを生成させ、オキシムとのラジカル反応[13]へと応用した(Figure 2-2-5)。本手法は、触媒量のアセテート程度でカルボン酸がエノラート形成し、化学選択的に一電子酸化できることを見出した点において優れている。しかし、適用可能な基質は α 位にアリールまたはアリル基を有する基質に限定されることや立体制御が困難な点において改善の余地が残る[14]。
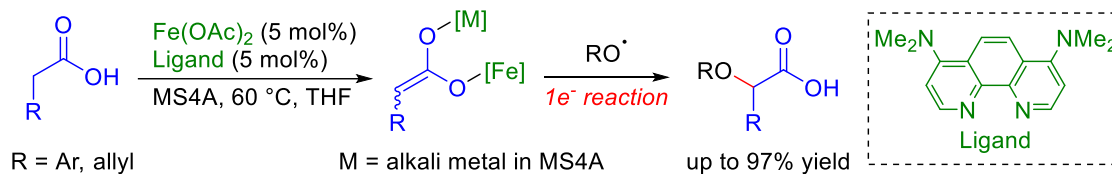

Figure 2-2-5　ヘテロバイメタリック触媒によるカルボン酸 α 位ラジカル反応

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[13] Tanaka, T.; Yazaki, R.; Oshima, T. *J. Am. Chem. Soc.* **2020**, *142*, 4517.

[14] ごく最近、π 共役系を伸ばすようチューニングされたホウ素触媒と DBU を用いてエノラート形成を行った後、可視光照射下エノラートからカップリングパートナーへの一電子移動によって、カルボン酸の α ラジカルを生成しラジカルカップリングを行う反応が清水らによって報告されたが立体制御や基質の適用範囲に問題が残る。Sun, K.; Ueno, M.; Imaeda, K.; Ueno, K.; Sawamura, M., Shimizu, Y. *ACS Catal.* **2021**, *11*, 9722.

2-3. ホウ素触媒によるシロキシエステル活性化を経由したカルボン酸α位求核付加反応の反応設計

　上述のように、ホウ素-DBU を用いたカルボン酸求核付加反応はケトンやエステル、アミドのような他のカルボニル官能基存在下でもカルボン酸を化学選択的にエノラート形成できる点や温和な条件のために他の官能基を侵さない点、共有結合を介した配座固定に由来すると考えられる高い立体選択性の観点から、他のカルボン酸活性化法と比較して優れている。しかしその一方で、水酸基やアミノ基といった求核性の高い配位性高い官能基の存在下においては、ホウ素触媒と配位性官能基が不可逆的に結合して触媒が不活性化されるため適用できないという問題点があった(Figure 2-3-1)。
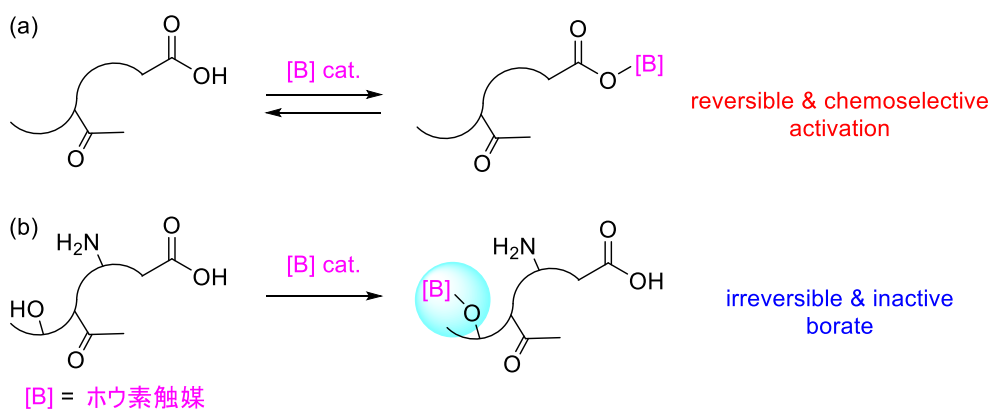
Figure 2-3-1　ホウ素触媒によるカルボン酸活性化における問題点

　実際、我々の手法を用いた場合、反応の進行とともにヒドロキシ基が生成するようなアルドール反応[15,16]においてはホウ素が不活性なボレート種を形成する為に触媒回転せず、ホウ素が当量必要である。この時エナンチオ選択性も低く改善の余地を残す(Figure 2-3-2)。

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[15] Nagai, H.; Morita, Y.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2016**, *18*, 2276.

[16] 非常に限定された基質では触媒的なアルドール反応が進行する。Ishizawa, K.; Nagai, H.; Shimizu, Y.; Kanai, M. *Chem. Pharm. Bull.* **2018**, *66*, 231.
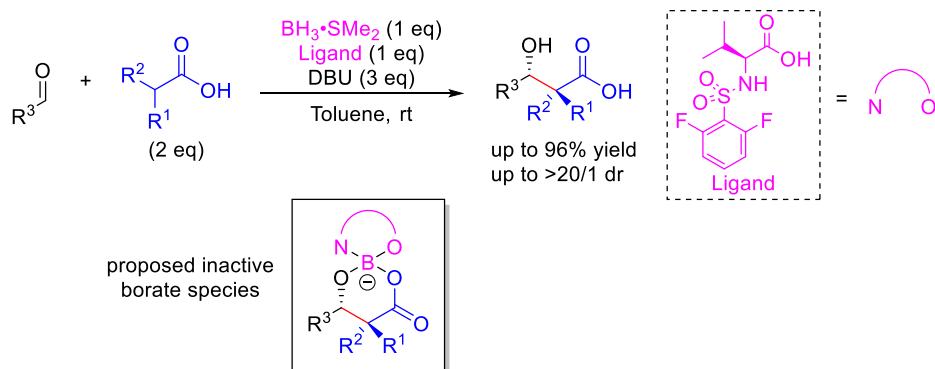
Figure 2-3-2　当量のホウ素試薬を用いるカルボン酸選択的アルドール反応

　水酸基やアミノ基は生体内高分子との相互作用や酵素による変換の足掛かりであること
から、医薬品や天然物に普遍的にみられる基本骨格であり、この問題点の解決はより幅広
い基質への適用と高い実用性獲得のためには必須である。即ち、ホウ素触媒-DBU 系の

温和な反応条件

カルボン酸選択性

高い立体選択性

を維持しながら、**配位性官能基に対する許容性**を獲得することが求められる。

　筆者は、電子求引的なケイ素化合物は系内で保護基として働くと同時にカルボン酸をケ
イ素エステルとして活性化出来ると考えた。即ち、複雑基質中のカルボン酸及び高配位性官
能基を in-situ に全てケイ素保護した後、ホウ素触媒を用いれば触媒が不活化されることな
くカルボン酸ケイ素エステル選択的にエノラート形成が可能となると考えた。その後に求
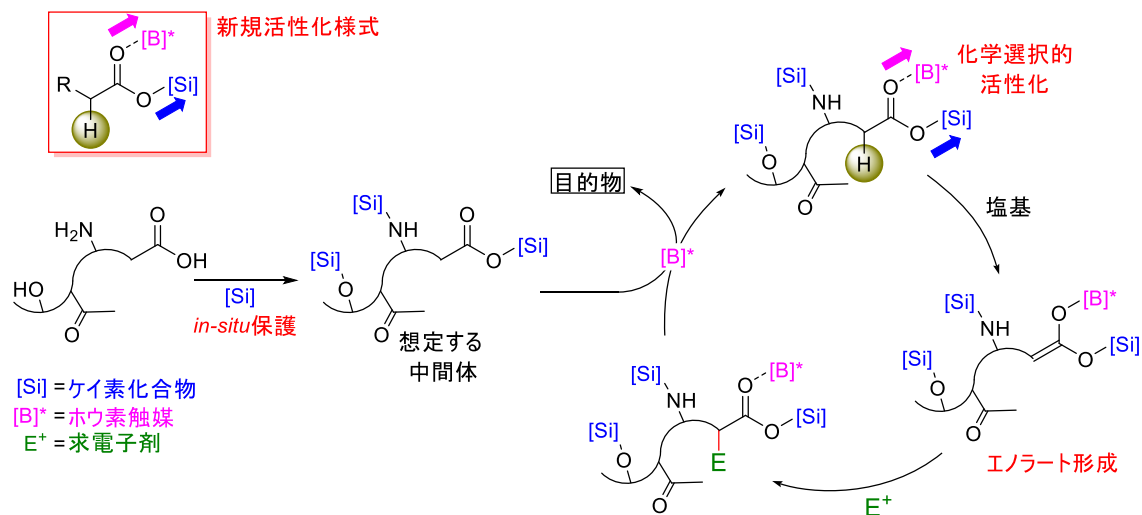電子剤と反応させることでα位求核反応が進行しうる(Figure 2-3-3)。

Figure 2-3-3　作業仮説

2-4. カルボン酸を基質とする不斉アルドール反応の現状

　不斉アルドール反応は、医薬品合成において有用な官能基密集型の骨格や、連続する不斉炭素を一度に構築可能なため重要な反応である。実際これまで数多くの不斉アルドール反応が報告[17]されておりすべてを上げるのは困難である。しかし 2-2 項で前述したとおり、カルボン酸に対するエノラート形成自体が困難なことから、カルボン酸を用いた不斉アルドール反応は当量反応、触媒反応共に報告例は殆どない[18]。

　代表的な当量反応として、Zakarian らは新規に合成したキラルなテトラミンと BuLi を用いて系内でキラルなリチウムアミド塩基を生成させることで、エノラート形成を行い不斉アルドール反応[19]を達成している(Figure 2-4-1)。本報告は、アルドール反応以外に共役付加やアルキル化にも適用可能であり汎用性が高い点で優れている。しかし、不斉源を当量用いている点やアルドール反応に適用可能なカルボン酸はα位にアリールを有する基質に限定されている点、過剰量の強い金属塩基を用いている点において改善の余地が残る。
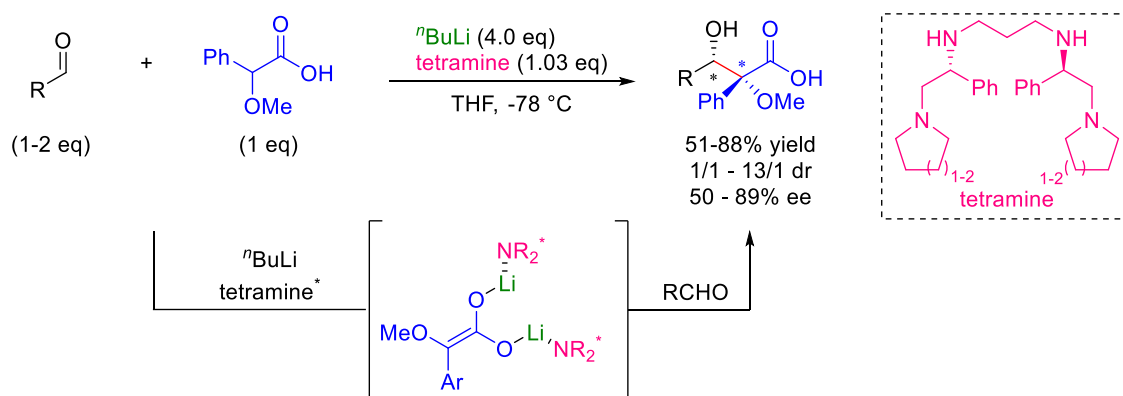

Figure 2-4-1　キラルアミンを利用したカルボン酸に対する不斉アルドール反応

　触媒的不斉反応は、中島、小谷らによって初めて報告[20]された。彼らは強力なルイス酸である $SiCl_4$ と嵩高い三級アミンである $^tBu_2NEt$ を用いることでカルボン酸のエノラート形成を行い、触媒量のルイス塩基を用いることでカルボン酸に対する初の触媒的な不斉アルドール反応を達成した。本反応はルイス塩基触媒によって活性化されたルイス酸の効果によ

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[17] Yamashita, Y.; Yasukawa, T.; Yoo, W.-J.; Kitanosono, T.; Kobayashi, S. *Chem. Soc. Rev.* **2018**, *47*, 4388.

[18] 後述する Zakarian らの報告以外に、アルデヒド、カルボン酸ともに基質は非常に限定されるが光学活性なホウ素活性化剤を当量用いる不斉アルドール反応も報告されている。
Fringuelli, F.; Piermatti, O.; Pizzo, F.; *J. Org. Chem.* **1995**, *60*, 7006.

[19] Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T. A. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian. *J. Am. Chem. Soc.* **2017**, *139*, 527.

[20] Kotani, S.; Yoshiwara, Y.; Ogasawara, M.; Sugiura, M.; Nakajima, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 15877.

り系内で cisoid 型のエノラートが生成し、環状の遷移状態を経由することで高いエナンチオ選択性を有するアルドール反応が進行する(Figure 2-4-2)。しかし本手法は強力なルイス酸を当量用いていることから、化学選択性や官能基許容性には難が残ると考えられる（2-7項で後述）。また、適用可能なアルデヒド類は芳香族アルデヒドおよびエノラート形成できない脂肪族アルデヒドに限定されている点や、ジアステレオ選択性には難が残る点で改善の余地が残る。
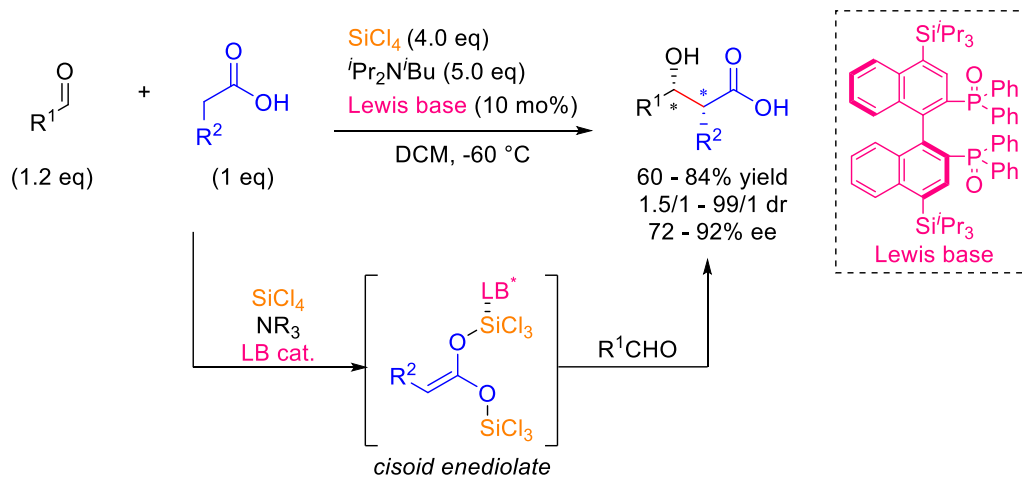

Figure 2-4-2 ケイ素試薬とルイス塩基を利用した触媒的不斉アルドール反応

　また、カルボン酸に留まらず、エステルやアミドのような酸性度の低い α プロトンを有するカルボン酸酸化度の基質であっても、複雑基質にも適用可能な化学選択的アルドール反応の報告例はない。
　そこで筆者は、官能基許容性の高いカルボン酸選択的不斉アルドール反応の開発を目標とすることにした。

2-5. ホウ素触媒及びtraceless保護法を利用した高い官能基許容性を有する化学選択的
触媒的アルドール反応の開発

アルドール反応においては、反応の進行とともにホウ素の触媒毒となるヒドロキシ基が
生成するが、この時塩基性度の高さに従いホウ素よりもハードな元素であるケイ素がカル
ボキシレートからアルコキシドへと転位することでホウ素の触媒回転が可能になると想定
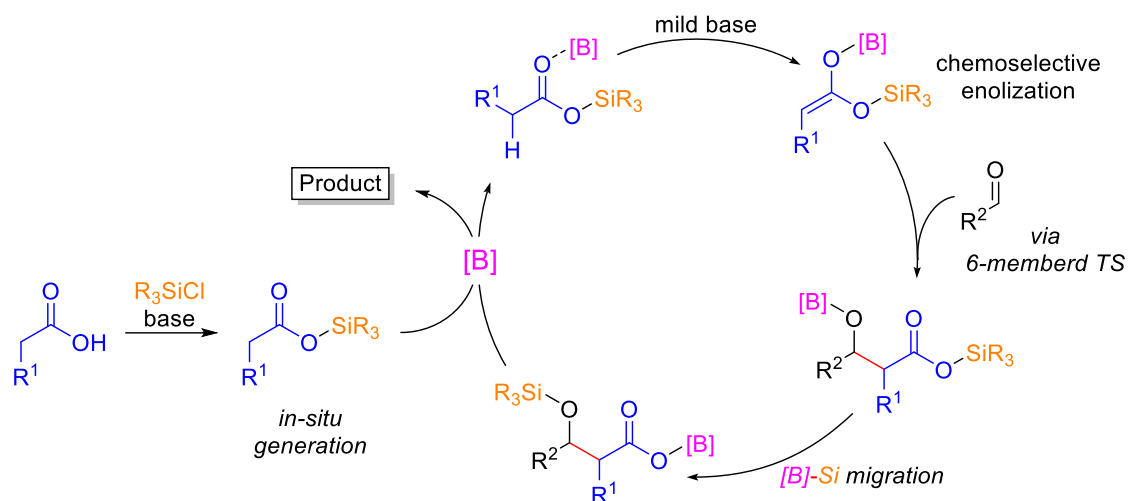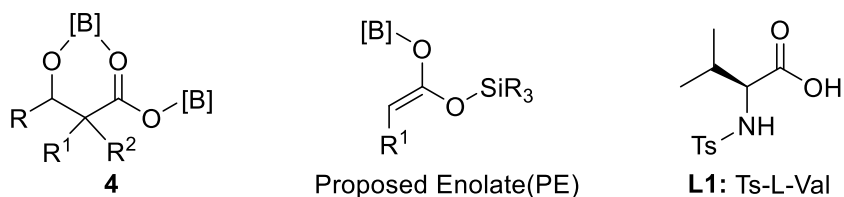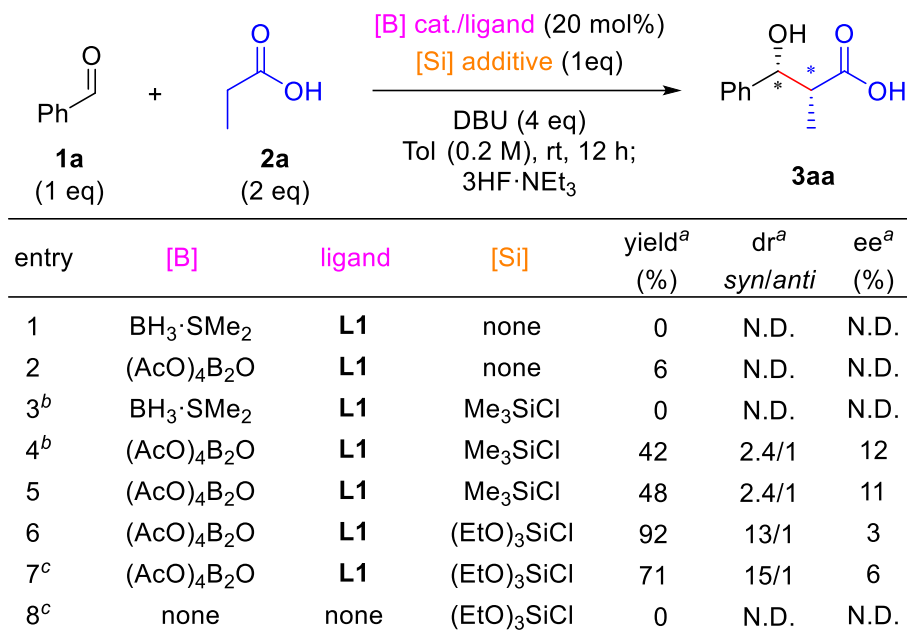した (Figure 2-5-1)。

Figure 2-5-1 想定反応機構

モデル基質としてはプロピオン酸(**2a**)とベンズアルデヒド(**1a**)、塩基としてはこれまでの
当研究室における知見から DBU を用いて検討を行った(Figure 2-5-2)。ホウ素の配位子とし
ては入手容易性を考慮して Ts-L-Val を用いている。
　検討の結果ケイ素を添加剤として用いない場合、$BH_3 \cdot SMe_2$ を用いた場合には反応は進行
せず(entry 1)、ホウ素源としてより活性の高い$(AcO)_4B_2O$ を用いた場合でも収率は 6%にと
どまり触媒回転は進行しなかった(entry 2)。これは前述のとおりアルドール付加体とホウ素
が結合したボレート **4** が安定なために、ホウ素が乖離せず触媒能を失ったものと考えてい
る。そこで、TMSCl をケイ素源として検討したところ、$BH_3 \cdot SMe_2$ を用いた場合には反応
は進行しなかったが(entry 3)、$(AcO)_4B_2O$ を用いた場合には収率 42%, dr = 2.4/1 と触媒反応
が進行するようになった(entry 4)。この時、ケイ素を最初にカルボン酸と premix すること
でジアステレオ選択性を損なうことなく収率は 48%まで上昇した(entry 5)。続いてケイ素
源を検討したところ電子求引性置換基を有する$(EtO)_3SiCl$ を用いた場合に収率 92%, dr =
13/1 まで向上した(entry 6)。これは誘起効果により α プロトンの酸性度が向上しエノラー
ト形成が容易になったことで収率が向上したものだと考えている。溶媒としてトルエンに
代えて THF を用いた場合収率は低下したものの、選択性が向上する傾向を示した(entry
7)。コントロールとしてホウ素触媒及び配位子を用いず、ケイ素のみを用いた場合には反

応は進行しなかった(entry 8)。即ち、ケイ素エステルのみからでは反応が進行せずホウ素触媒が不可欠であることを示している。

entry	[B]	ligand	[Si]	yield[a] (%)	dr[a] syn/anti	ee[a] (%)
1	$BH_3 \cdot SMe_2$	L1	none	0	N.D.	N.D.
2	$(AcO)_4B_2O$	L1	none	6	N.D.	N.D.
3[b]	$BH_3 \cdot SMe_2$	L1	Me_3SiCl	0	N.D.	N.D.
4[b]	$(AcO)_4B_2O$	L1	Me_3SiCl	42	2.4/1	12
5	$(AcO)_4B_2O$	L1	Me_3SiCl	48	2.4/1	11
6	$(AcO)_4B_2O$	L1	$(EtO)_3SiCl$	92	13/1	3
7[c]	$(AcO)_4B_2O$	L1	$(EtO)_3SiCl$	71	15/1	6
8[c]	none	none	$(EtO)_3SiCl$	0	N.D.	N.D.

4　　　Proposed Enolate(PE)　　　**L1:** Ts-L-Val

[a]Yield and diastereomeric ratio (dr) were determined by ^{1}H NMR of a crude mixture before methyl ester formation. 1,1,2,2,-Tetrachloroethane was used as an internal standard for yield determination. Enantiomeric excess (ee) was determined by HPLC analysis after methyl ester formation of 3aa. [b]The silylating reagent was added as the final component. [c]In toluene.
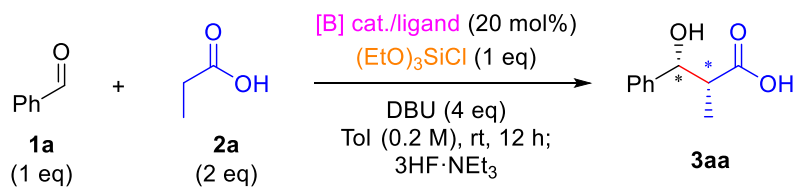
Figure 2-5-2　ケイ素添加剤の効果についての初期検討

2-6. 不斉アルドール反応の開発

　前項までの検討において、アルドール反応自体は進行するようになったものの、初期検討ではいずれのエントリーでも非常に低い不斉収率にとどまっている。そこでエナンチオ選択性の改善を目指し不斉配位子の検討をおこなった(Figure 2-6-1)。

　検討の結果、以前当研究室において報告した触媒的不斉 Mannich 型反応 [10] において有効であった BINOL 型配位子である 3,3'-diiodo-[1,1'-binaphthalene]-2,2'-diol (**L2**)を用いた場合、ジアステレオ選択性及びエナンチオ選択性が顕著に向上した(dr = >20/1, ee =99%)ものの、低収率にとどまった(entry 2)。これは、副反応として脱水反応が進行し不飽和カルボン酸が30%ほど生成したためである[21]。脱水の原因については不明であるが、生成するアルドラートのアルコキシドが触媒中心のホウ素に対し新たに配位することで、二座で配位する BINOL 型配位子の一座が解離し、塩基性の高いナフトキシドアニオンが生成し、アルドール付加体から E1cB 反応が進行しやすくなったものと考えている。3,3'位における置換基をTf 基に変更したところ収率はさらに低下し 7%であった(entry 3)。そこで BIINOL 型配位子に代えてアミノ酸誘導体を検討することにした。β 位に嵩高い三級アミノ基を有する **L4** やバリンよりも嵩高いイソロイシン **L5** を用いてもエナンチオ選択性の改善は見られなかった(entry 4 及び entry 5)。しかし、アミノ酸保護基として Ts 基から 4-OMe-C_6F_4-SO_2 に変更した場合、収率を全く損なうことなく、エナンチオ選択性は顕著に向上し 87% ee をしめした。一方で、ジアステレオ選択性は大きく低下し 2.5/1 dr であった(entry 6)。立体選択性には、アミノ酸側鎖の嵩高さよりもアミノ基の保護基の影響の方が大きいという興味深い知見が得られた。そこで、種々のアリールスルホン保護バリンを検討した。検討の結果、アリール基上にフッ素原子を導入することでエナンチオ選択性が向上し、導入するフッ素原子の数が多いほど高いエナンチオ選択性を示したが、その一方で、逆にフッ素原子の数に反比例してジアステレオ選択性は低下する傾向を示した(entry 7-9)。とくに C_6F_5-SO_2-L-Val (**L9**)では 1.6/1 dr, 85% ee であった。更なる誘導体検討を進めたところ、パラ位にフッ素原子よりも電子求引性が低い原子団[22]である H(**L10**)、 Me(**L11**) 、OMe(**L12**)、 NMe$_2$(**L13**)を導入したときに、エナンチオ選択性を損なうことなく、ジアステレオ選択性が向上する傾向を示し、とくにジメチルアミノ基(**L13**)を導入した場合に、5.5/1 dr, 86% ee とよいバランスの立体選択性を示した。更に反応濃度及び塩基当量を減じることで、更にジアステレオ選択性が向上し、69% yield, 16/1 de, 86% ee で目的とするアルドール付加体が得られた。

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[21] 塩基の当量を３当量まで減じることで脱水体は 16%まで減少したが、24% yield まで収率が低下した。

[22] OMe 基、 NMe$_2$ 基の場合、非共有電子対の効果としての電子供与効果も考えられるが、後述するＤＦＴ計算などから芳香環とパラ位の置換基の平面性は少なく、共役による電子供与効果は限定的であると考えている。

| | [B] cat./ligand (20 mol%) | | | |
| Ph-CHO + CH₃CH₂COOH | (EtO)₃SiCl (1 eq) | | | Ph-CH(OH)-CH(CH₃)-COOH |

Reaction scheme: **1a** (1 eq) + **2a** (2 eq), [B] cat./ligand (20 mol%), (EtO)$_3$SiCl (1 eq), DBU (4 eq), Tol (0.2 M), rt, 12 h; 3HF·NEt$_3$ → **3aa**

entry	ligand	yield (%)	dr syn/anti	ee (%)
1	**L1**	71	15/1	6
2	**L2**	34	>20/1	-99
3	**L3**	7	>20/1	ND
4	**L4**	43	17/1	30
5	**L5**	67	19/1	3
6	**L6**	80	2.5/1	87
7	**L7**	79	11/1	62
8	**L8**	82	4.7/1	78
9	**L9**	72	1.6/1	85
10	**L10**	69	2.3/1	85
11	**L11**	77	3.1/1	85
12	**L12**	82	1.8/1	86
13	**L13**	71	5.5/1	86
14[a]	**L13**	69	16/1	86

[a]Yield and diastereomeric ratio (dr) were determined by ^{1}H NMR of a crude mixture before methyl ester formation. 1,1,2,2,-Tetrachloroethane was used as an internal standard for yield determination. Enantiomeric excess (ee) was determined by HPLC analysis after methyl ester formation of **3aa**. [b]Concentration was 0.1 M and 3.5 eq of DBU was used.

L2 X = I
L3 X = Tf

L4 Ar = 4-Me-C$_6$H$_4$

L5 Ar = 4-Me-C$_6$H$_4$
L6 Ar = 4-MeO-C$_6$F$_4$

L1 Ar = 4-Me-C$_6$H$_4$
L7 Ar = 2,6-F$_2$-C$_6$H$_4$
L8 Ar = 2,4,6-F$_3$-C$_6$H$_4$
L9 Ar = C$_6$F$_5$
L10 Ar = 4-H-C$_6$F$_4$
L11 Ar = 4-Me-C$_6$F$_4$
L12 Ar = 4-MeO-C$_6$F$_4$
L13 Ar = 4-Me$_2$N-C$_6$F$_4$
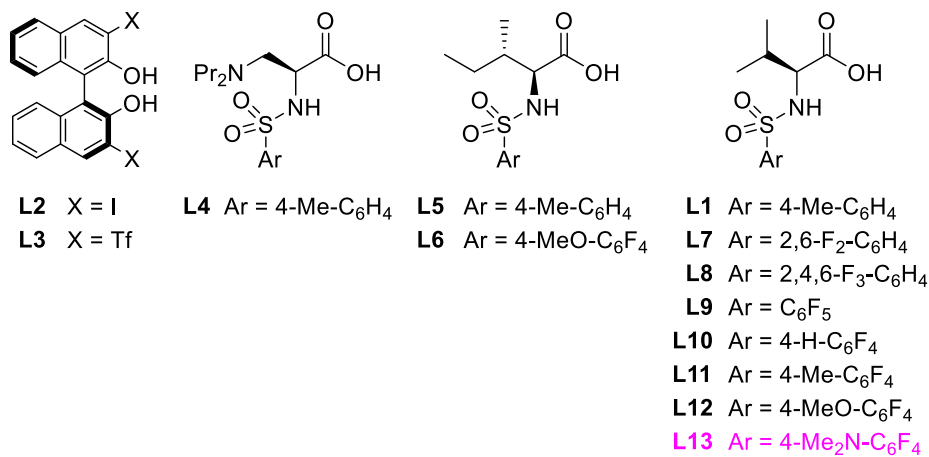
Figure 2-6-1 配位子検討

　触媒の構造と立体選択性の相関の原因に関しては明らかではないものの、2-11 項で後述する舟型六員環遷移状態を提唱した DFT 計算の結果などから次のように解釈している。まずジアステレオ選択性に関しては、アミノ酸型配位子の *N*-アリールスルホニル基の立体項よりも電子項の寄与の方が大きい(entry 1, 7-13)。更に、フッ素の置換数が多く誘起効果が大

19

きい、即ちホウ素触媒のルイス酸性が高い配位子ほどジアステレオ選択性が低下する傾向を示している(entry 1, 7, 8, 9)。これはホウ素触媒のルイス酸性が向上することで、触媒と基質の結合長が短くなり、エノラートとのアルデヒド間の立体障害が有効に作用するようになることで椅子型六員環遷移状態の寄与が無視できずジアステレオ選択性が低下したものと考えている。そのため配位子のアリール基上パラ位には適度な電子求引性を有する置換基を導入し適切な電子密度を持たせることが選択性の向上につながったと考えられる。

　一方、エナンチオ選択性の起源については明らかではないが、アリール上 2,6 位にフッ素原子を導入したときに顕著なエナンチオ選択性向上が見られたこと(entry 1, 7)やパラ位の置換基の影響をほとんど受けていない(entry 9-13)こと、また側鎖は不斉に影響しない(entry 6、12)ことなどを考慮すると、アリール上の特に 2,6 位のフッ素原子がクリティカルであると考えられる。このオルト位フッ素の効果は本アルドール反応のみならず、アリル化反応でも同様にエナンチオ選択性を向上させる傾向を示しており[23]、森田博士は触媒中心のホウ素原子と配位子のフッ素原子間に相互作用が働き配座が固定しやすくなるという仮説を示している[24]。しかし、2-11 項において後述する計算科学を用いた遷移状態の解析からは、フッ素原子とホウ素原子間の距離が遠く相互作用は考慮しにくい。ただし、フッ素原子と配位子内部の他の原子、あるいは基質との相互作用によって配座が固定されやすくなりエナンチオ選択性が向上している可能性はある。あるいは立体障害からの説明として、オルト位のフッ素とスルホニル基の立体反発によって、スルホニル-アリール間の結合の回転が阻害されることで配座が固定されやすくなっている可能性がある。

[23] Fujita, T.; Yamamoto, T.; Morita, Y.; Cheng, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2018**, *140*, 5899.

[24] 森田雄也, 東京大学大学院博士論文, 2017.

2-7. 基質一般性の検討

　得られた最適条件をもとに基質一般性の検討を行うこととし(Figure 2-7-1)、初めにカルボン酸側基質の検討を行った。検討の結果、α位にベンジルを有する基質(**4ab**)では89%, dr = >20/1, 90% ee と高収率、高立体選択的に反応が進行した。この時、4 mol% $(AcO)_4B_2O$, 8 mol% Ligand まで触媒量を減じても収率や立体選択性は大きな影響を受けず、更にグラムスケール(6 mmol)での反応にも容易に適用可能であった。ほかに、アルキン(**4ac**)やアルケン(**4ad**)、アルキルハライド類(**4ae, 4af**)を有する基質ではいずれも、高収率、高立体選択的な反応が進行した。続いて、アミド(**4ag**)、エステル(**4ah**)、ケトン(**4ai**)、ニトリル(**4aj**)などカルボン酸よりもエノラート形成しやすい基質についても検討を行ったところ、いずれもカルボン酸α位選択的に反応が進行し、副生成物は見られなかった。これは本手法がホウ素触媒のみを用いたカルボン酸活性化[25]と同等の化学選択性を有することを示している。この興味深い化学選択性については 2-8 項にて後述する。また、一級のヒドロキシ基を有する基質(**4ak**)では、ケイ素当量を増やし traceless 保護基として用いることで良好な収率、及び高い立体選択性にて目的物を与えた。その一方で、α位にアリール基を有する基質(**4al**)では、反応自体は円滑に進行するものの、低い立体選択性(3.3/1 dr, 47% ee)にとどまった。これは酸性度の高いαプロトンのためにバックグラウンドの反応が抑えられなかったためだと考えている。また、カルボン酸α位に四級炭素を構築するような 2-メチルプロピオン酸(**4am**)を用いた場合、最適条件では 91%収率ながら 42% ee にとどまった。配位子として **L13** にかえて **L2** を用いることで、立体選択性は若干向上し 66% ee であったが、収率は 36%まで低下した。

　続いてアルデヒドの基質一般性について検討を行った。求電子剤として芳香族アルデヒドを用いた場合(**4bb, 4cb, 4db, 4eb**)、芳香環上の置換基が電子供与的であっても電子求引的であっても反応は円滑に進行しいずれも高い立体選択性を示した。また複素環アルデヒド(**4fb**)でも高収率、高立体選択的に反応が進行した他、芳香環上メタ位(**4gb**)やオルト位(**4hb**)などに置換基がある場合でも反応は円滑に進行した。続いて脂肪族アルデヒドについても検討を行った。脂肪族アルデヒドは塩基性条件下、容易にエノラート形成しホモアルドールしうるため求電子剤として用いるのは非常に困難である[26]。検討の結果、芳香族アルデヒドと同一の条件では低収率にとどまったが、用いる DBU の当量(5 eq)と反応溶液の濃度(0.3 M)を上昇させることで反応が進行するようになり、ヒドロシンナムアルデヒド(**4ib**)を初めとする種々の脂肪族アルデヒド(**4jb, 4kb, 4lb, 4mb, 4nb**)に対して高収率、高立体選択的なアルドール反応が進行した。この化学選択性の起源について定かではないが、脱プロトン化時の

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[25] Nagai, H.; Morita, Y.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2016**, *18*, 2276.

[26] 酸性度の低いカルボン酸酸化度の基質を用いた脂肪族アルデヒドに対する触媒的不斉アルドール反応は金井、熊谷、柴崎らの例に留まる。(a) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (b) Iwata, M.; Yazaki, R.; Chen, I-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554.

Reaction scheme (top):

R^1–CHO (1) + carboxylic acid with R^2 (2, 2 eq)

Conditions: (AcO)$_4$B$_2$O (10 mol %), **L13** (20 mol %), (EtO)$_3$SiCl (2.0 eq), DBU (3.5 eq), THF, rt, 12 h; 3HF·NEt$_3$ → **3** (R^1–CH(OH)–CH(R^2)–COOH)

TMSCHN$_2$ → **4** (R^1–CH(OH)–CH(R^2)–COOMe)

carboxylic acids

4aa
69%, 18/1 dr, 86% ee
(**3aa**: 66%)[b]

4ab
89%, >20/1 dr, 90% ee
76%, 19/1 dr, 89% ee[c]
64%, >20/1 dr, 90% ee[d]

4ac
91%, 11/1 dr
86% ee

4ad
84%, >20/1 dr
92% ee

4ae
70%, >20/1 dr
94% ee

4af
53% (70%)[e], >20/1 dr
94% ee

4ag
82%, 16/1 dr, 94% ee
(**3ag**: 73%)[b]

4ah
72%[f,g], >20/1 dr
93% ee

4ai
57%[f,g], >20/1 dr
94% ee

4aj
81%, 7.3/1 dr
97% ee

4ak
56%[b,e,f,h,i] (88%)[e,f,h,i]
>20/1 dr, 90% ee

4al
72%, 3.3/1 dr
47% ee

4am
91%, 42% ee[j]
36%, 66% ee[j,k]

aldehydes

X	yield (%)	dr syn/anti	ee (%)
Me (**4bb**)	74[f]	16/1	87
Cl (**4cb**)	82	19/1	89
Br (**4db**)	88	18/1	85
CF$_3$ (**4eb**)	93	16/1	83

4fb
93%, >20/1 dr, 86% ee
(**3fb**: 81%)[b]

4gb
93%, 16/1 dr
90% ee

4hb
87%, >20/1 dr
90% ee

4ib
92%[j], 9.9/1 dr
92% ee

4jb
71%[j], 11/1 dr
87% ee

4kb
72%[j], >20/1 dr, 91% ee
(**5kb**: 69%)[b]

4lb
86%[j], 9.0/1 dr
90% ee

4mb
74%[j], 4.4 /1 dr
86% ee

4nb
42%[j], >20/1 dr
87% ee

Figure 2-7-1　低分子基質に対する一般性の検討

選択性ではなく炭素炭素結合形成時に選択性が生じるものと考えている。即ちアルデヒド
ホウ素エノラートがそこまで求核力が高くないためホモアルドール反応は進行しない[27]こ
とで化学選択性が生じると考えている。

　続いて多官能基を有する医薬品や天然物に対して、立体選択的な後期誘導体化の検討を行
った(Figure 2-7-2)。抗炎症薬(NSAIDs)であり、エステルのα位にアシルインドールを有する
acemetacin を用いた場合(**4an**)、カルボン酸α位選択的に反応が進行し 11/1 dr, 82% ee と高い
立体選択性にて目的物が得られた。また同じく NSAIDs であり、カルボン酸β位にオキサゾ
ールを有する oxaprozin(**4ao**)でも同様に 91%収率, 7.6/1 dr, 84% ee と反応が円滑に進行した。
また、免疫抑制剤であり、フェノール性水酸基やラクトン、オレフィンを有する mycophenolic
acid(**4ap**)に対しては、ケイ素当量を増やすことで反応が進行し、高い立体選択性(17/1 dr, 87%
ee)にて目的物が得られた。この時、中島、小谷らの手法[28]を用いた場合、用いる SiCl$_4$ の当
量を増やしても 10%収率(3.0/1 dr)にとどまる(Figure 2-7-3) 。これは、フェノール性ヒドロキ
シ基の近傍に存在するラクトンがルイス塩基として働くために反応性の高いトリクロロシ
リル基が脱保護されて traceless 保護基として機能しなかった、あるいは近傍のラクトンと
の立体障害からトリクロロシリル保護が進行しなかったと考えている。この対照実験の結
果は先行研究に比して本手法が極めて温和であることを如実に示す結果である。本手法は、
利胆剤でありトリケトンやトリオールを有するデヒドロコール酸やコール酸に対しても適
用可能であり、良好な収率と高い立体選択性にて目的物が得られた(**4aq, 4ar**)。この時用い
る配位子の立体を反転させることで逆の立体を有する isomer を容易に得ることが出来た
(*iso*-**4aq**, *iso* **4ar**)。このように本手法は、基質の立体依存ではなく触媒のエナンチオマーを使
い分けることで生成物の立体を選択的に作り分けることが可能である点において優れてい

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[27] Lin, L.; Yamamoto, K.; Mitsunuma, H.; Kanazaki, Y.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 15418

[28] Kotani, S.; Yoshiwara, Y.; Ogasawara, M.; Sugiura, M.; Nakajima, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 15877.

る。最後に、トリオールとエポキシド、共役エステルなど高反応性の官能基を複数有する、抗生物質 mupirocin について検討を行った(**3as, *iso*-3aq**)。Mupirocin は酸性、塩基性両条件において不安定であり容易にエポキシドの開環が起きることが知られている[29]が、中程度の収率ながらも高い立体選択性にて目的物が得られた。これは本手法の traceless 保護法－ホウ素触媒系の極めて温和な反応条件によるものと考えている。

multifunctional substrates

4an
from acemetacin
56%[d,e], 11/1 dr, 82% ee

4ao
from oxaprozin
91%, 7.6/1 dr, 84% ee
(**3ao**: 92%)[b]

4ap
from mycophenolic acid
69%[d,f,g], 17/1 dr, 87% ee

from dehydrocholic acid
4aq (2*R*,3*R*)
63%[d,e], >20/ 1/ <1/ <1 dr
iso-**4aq** (2*S*,3*S*)
42%[d,e,h], 39/ 4.6/ 1/ <1 dr

from cholic acid
4ar (2*R*,3*R*)
68%[d,f,g,i], >20/ 1/ <1/ <1 dr
iso-**4ar** (2*S*,3*S*)
50%[d,f,g,h,i], >20/ 1/ <1/ <1 dr

from mupirocin
3as (2*R*,3*R*)
41%[c,d,f,g,i,j], >20/ 1/ <1/ <1 dr
iso-**3as** (2*S*,3*S*)
56%[c,d,f,g,h,i,j], >20/ 1/ <1/ <1 dr

[a] General reaction conditions: **2** (0.60 mmol), **1** (0.30 mmol), (EtO)$_3$SiCl (0.60 mmol), DBU (1.05 mmol), (AcO)$_4$B$_2$O (0.03 mmol), **L13** (0.06 mmol), THF (3.0 mL), room temperature, 12 h. Isolated yield and ee were determined after conversion to the corresponding methyl esters, unless otherwise noted. Dr was determined by ^{1}H NMR of a crude mixture before methyl ester formation. [b] Isolated yield at the carboxylic acid **3** stage. [c] NMR yield. 1,1,2,2-Tetrachloroethane was used as an internal standard for yield determination. [d] Concentration was 0.2 M. [e] 4 equiv of DBU was used. [f] 4 equiv of (EtO)$_3$SiCl was used. [g] 6 equiv of DBU was used. [h] *ent*-**L13** was used. [i] 10 equiv of aldehyde **1** was used. [j] 30 mol % (AcO)$_4$B$_2$O and 60 mol % **L13** were used.

[29] Clayton, J. P.; Oliver, R. S.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans I*, **1979**, *1*, 838-846.

Figure 2-7-2　多官能基性複雑基質に対する応用例
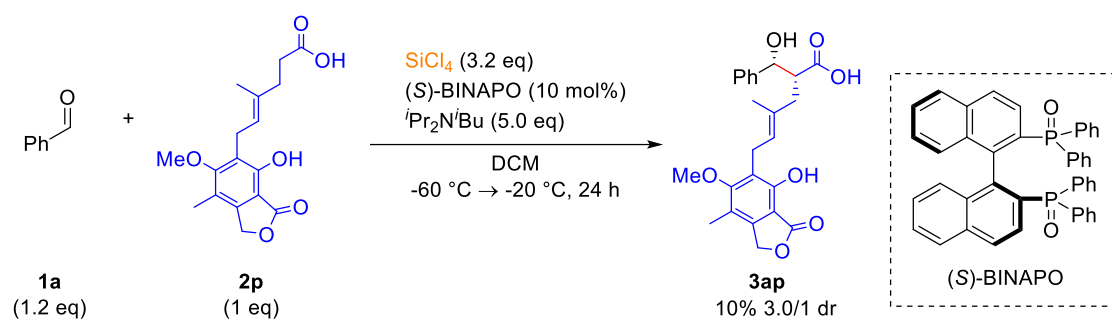
Figure 2-7-3　小谷・中島法との比較実験

2-8. 活性ケイ素エステル中間体の効用

　本反応は、ケイ素エステルを中間体として反応が進行することを想定している。実際、系内でケイ素エステルが生成していることは NMR 解析から明らかになっている[30]。また、プロピオン酸の TMS エステル(**5**)を基質とした場合、カルボン酸を基質とした場合と同等の収率、選択性にて目的物が得られる(Figure 2-8-1-(a))。更に、他のアルキルエステル類との違いを明らかにすべく *t*Bu-propionate (**6**)を基質としたコントロール実験を行ったところ(Figure 2-8-1-(b))、**6** を基質とした場合には最適条件下反応が全く進行しなかった。これは、ケイ素が単純な保護基としてだけではなく、カルボン酸の活性化にも関与しているという作業仮説を裏付ける結果である。
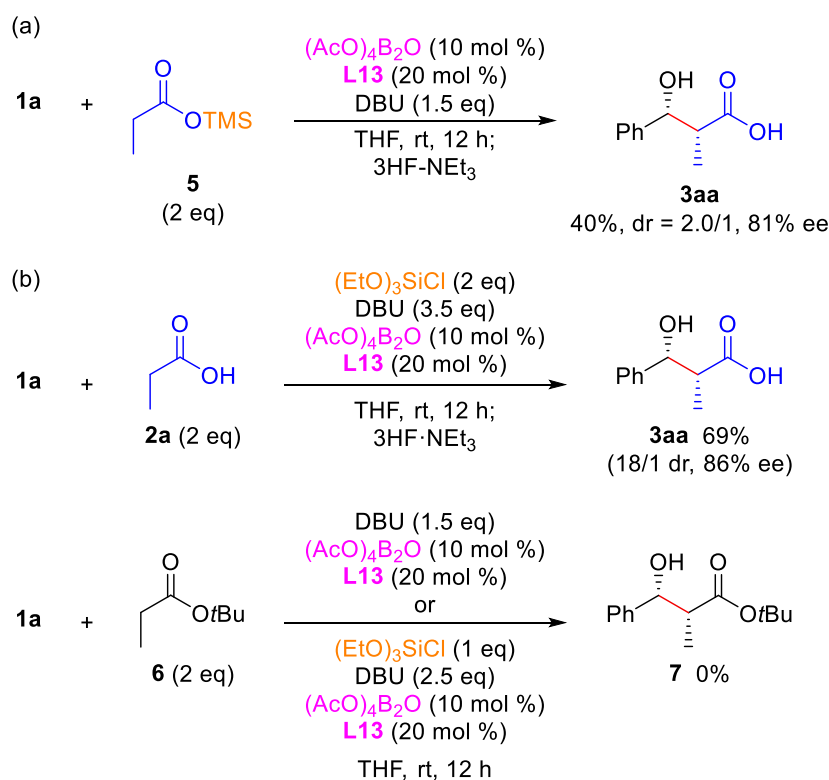
Figure 2-8-1　エステルからのアルドール反応の検討

　そこでこの活性化の起源を探るべく、種々のカルボニル α プロトンの pK_a について計算した[31](Figure 2-8-2)。計算の結果、トリエトキシシリルエステルは pK_a = 19.6 であり、これは

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[30]　See SI

[31]　According to the literature, the gas-phase $\Delta G°$ of the acid dissociation and pKa of various carbonyl groups were calculated by Gaussian 16.; Charif, I. E.; Mekelleche, S. M.; Villemin, D.; Mora-Diez, N. *THEOCHEM J. Mol. Struct.* **2007**, *818*, 1.

^{t}Bu エステル(pK_a = 26)やケトン(pK_a = 24.7)に比べて大きく活性化されていることが分かった。この pK_a 値はホウ素エステル(18.3)には劣るものの、カルボン酸が非常に活性化されているため、ケトンやエステルに対する本手法の化学選択性は脱プロトン化時に生じていると考えられる。

　ケイ素エステルの酸性度向上に関する起源は明らかになっていないが、山本らは単純な誘起効果以外に、ケイ素に対してカルボン酸が二座で配位することで高配位ケイ素が生成している可能性を指摘している[32]。あるいは、ケイ素のα効果[33]からの説明として、カルボキシ酸素原子上の非共有電子対をケイ素とエトキシ酸素のσ*軌道が安定化していることも一因として考えられる。
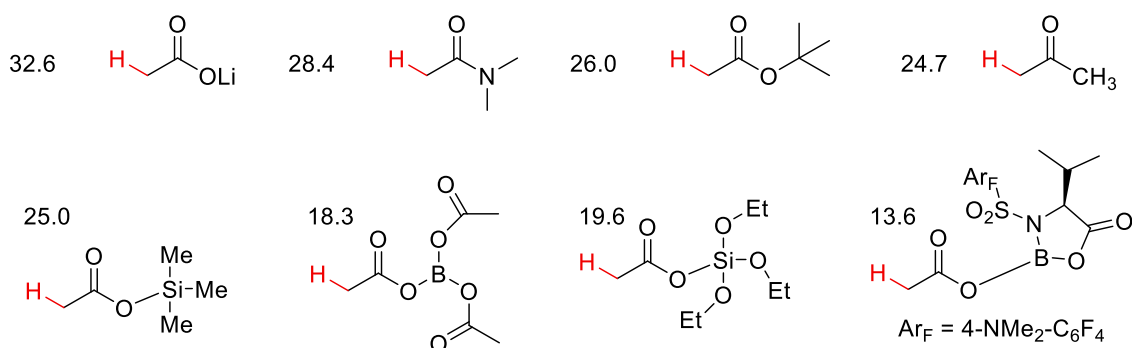
calculated by Gaussian 16 (B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p))

Figure 2-8-2 計算によるカルボニルαプロトン酸性度の見積もり

　その一方で、このケイ素エステルのカルボン酸活性化は pK_a 値の低下だけに由来するものではないこともわかっている。即ち、アルドール反応において基質由来のカルボキシレートを添加すると収率が低下する。実際、反応時間を 30 分としたとき、カルボン酸 DBU 塩を追加することで収率は 41%から 26%まで低下した(Figure 2-8-3)。これは過剰なカルボキシレートがルイス塩基としてホウ素触媒に結合し、触媒として不活性なアニオン性ボレート種が形成しやすくなるためだと考えている。

[32] Muramatsu, W.; Manthena, C.; Nakashima, E.; Yamamoto, H. *ACS Catal.* **2020**, *10*, 9594.

[33] Berkefeld, A.; Guerra, C.; Bertermann, R.; Troegel, D.; Dai, J.; Stohrer, J.; Bickelhaupt, F.; Tacke, R. *Organometallics* **2014**, *33*, 2721

Reaction scheme:

Ph–CHO (**1a**, 1 eq) + CH$_3$CH$_2$COOH (**2a**, 1 eq)

Conditions:
(EtO)$_3$SiCl (1.0 eq)
DBU (3.0 eq)
(AcO)$_4$B$_2$O (5.0 mol %)
L13 (10 mol %)
(C$_2$H$_5$COO$^-$·DBU$^+$ (1 eq))
THF, rt, **30 min**;
3HF·NEt$_3$

Product: **3aa** (Ph–CH(OH)–CH(CH$_3$)–COOH)

without C$_2$H$_5$COO$^-$·DBU$^+$: 41%
with C$_2$H$_5$COO$^-$·DBU$^+$: 26%

C$_2$H$_5$COO$^-$ + [B] ⇌ C$_2$H$_5$COO–[B]$^-$

active
boron complex

inactive anionic
borate complex
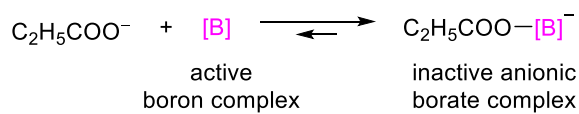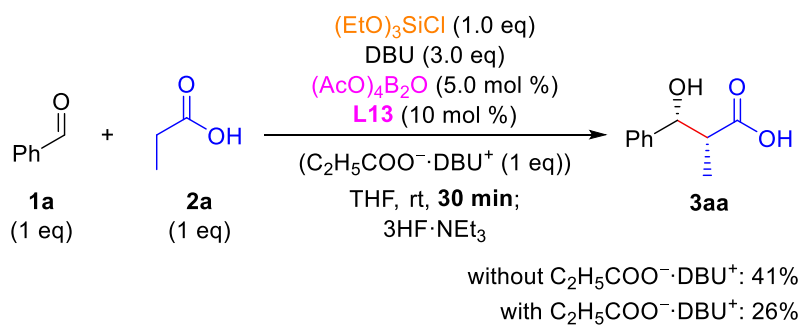
Figure 2-8-3　カルボキシレート塩添加による反応阻害の効果

2-9. 従来法との比較

　前項における、カルボキシレートをケイ素エステルに反応系中で変換することでホウ素触媒への配位による触媒不活性化を低減し反応性を高めているという作業仮説を検証するべく、ホウ素触媒のみでも進行する Mannich 型反応及びアリル化反応において対照実験を行った(Figure 2-9-(a)及び(b))。Mannich 型反応においては、ケイ素エステルを経由させることで 1-5 mol%の低触媒量下にも拘わらずプロピオン酸(**2a**)との反応では 62%収率、mycophenolic acid (**2m**)との反応では 59%と中程度の収率を示したが、その一方でケイ素を用いない場合にはそれぞれ<1%, 7%と非常に低い収率にとどまった。アリル化反応においてはこの傾向はさらに顕著で、ケイ素を用いた場合に 89%と高い収率を示したのに対し、ケイ素を用いない場合には目的物が全く得られなかった。これらの実験から、ケイ素エステルの効果として、α位求核付加反応を促進する効果があることが示唆される。

Figure 2-9 Mannich 型反応及びアリル化反応に対する応用とケイ素の反応加速効果
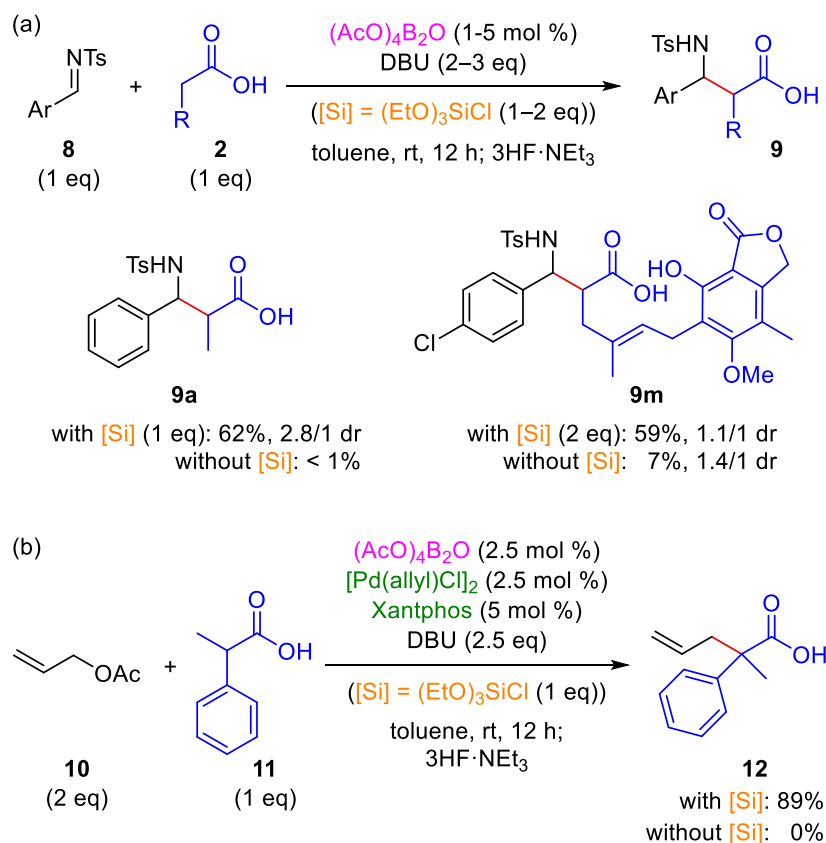
2-10. 非線形効果実験による反応機構解析

　これまでの当研究室の報告と本手法が異なる機構で進行すること、すなわちケイ素エステルからケイ素ホウ素のヘテロエノラートが生成していることを示すべく非線形効果実験[34]を行った。初めにアルドール反応について、配位子の光学過剰率と生成物の光学過剰率の関係を調査したところ(Figure2-10-1)、一次の比例関係が得られた。この事実は、ホウ素触媒が一分子のみ関与していることを支持する結果である。
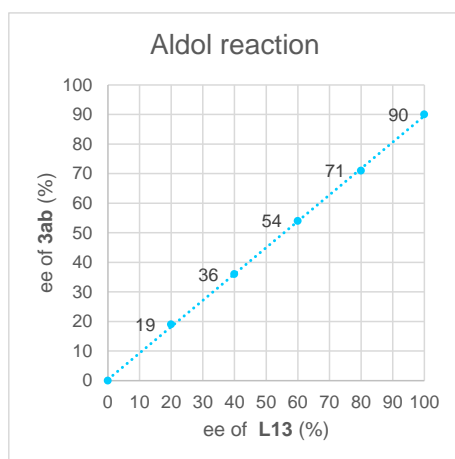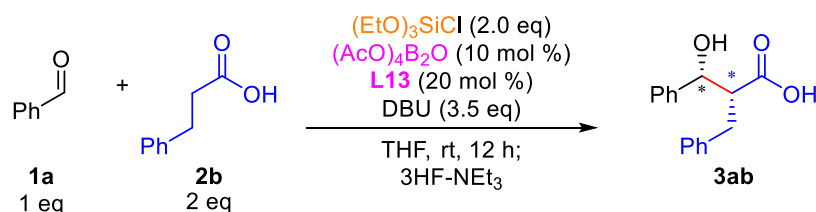
Figure 2-10-1　アルドール反応における触媒と生成物の光学純度の関係性

　前述のとおり、アルドール反応はケイ素化合物なしではホウ素が触媒回転しないため、対照実験を行うことが出来ない。そこで Mannnich 型反応を用いて対照実験を行った(Figure 2-10-2)。検討の結果、ホウ素触媒のみを用いている従来の手法(Condition A)では、非線形効果が観測され、特に配位子が 20% ee, 40% ee, 60% ee の時には不斉増幅も見られた。この結果は、ホウ素触媒のみを用いてカルボン酸を活性化する場合、ホウ素二分子によってエノラート化したジボラエンジオラート種を経由して反応が進行するという先行研究と矛盾しない[35]。その一方で、(EtO)₃SiCl をケイ素化合物として用いた場合、非線形効果は観測されず、一次の比例関係のみが得られた。この結果は、本手法が従来法とは異なる

[34] Satyanarayana, T.; Abraham, S.; Kagan, H. B. N. *Angew. Chem. Int. Ed.* **2009**, *48*, 456.

[35] 森田雄也博士論文。森田博士は速度論実験及び非線形効果の観測からホウ素二分子が関与しているジボラエンジオラート中間体を提唱した。

反応形式で反応が進行することを意味し、ホウ素ケイ素ヘテロエンジオラート種の生成を示唆するものである。
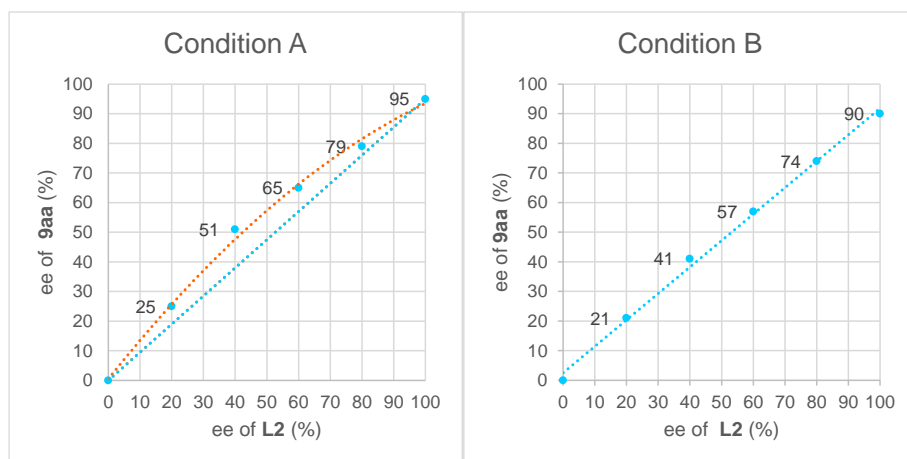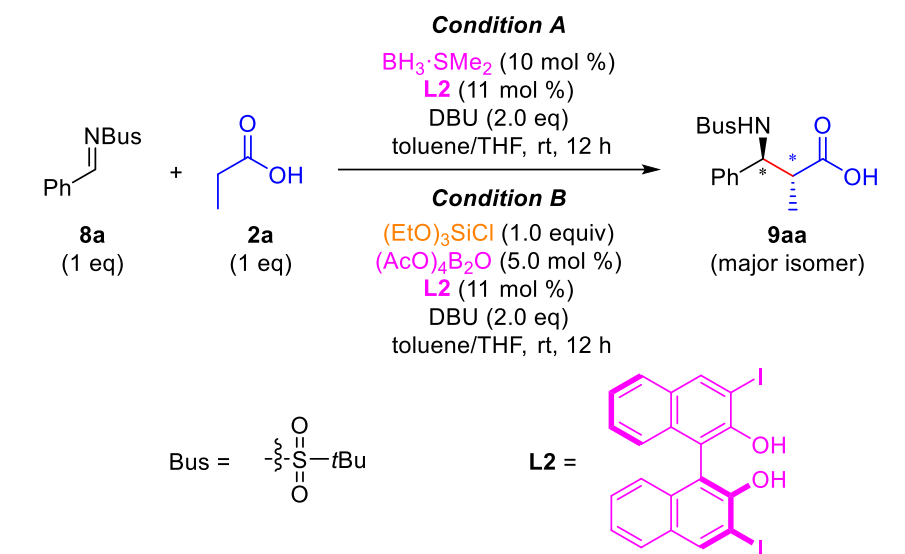
Figure 2-10-2　Mannich 型反応における触媒と生成物の光学純度の関係性

2-11. 計算科学による機構解析

　続いて、共同研究者による DFT 計算の結果を示す(Figure 2-11-1)。まず、**2a** 由来のトリエトキシシリルエステルを脱プロトン化するために考えられる中間体を探索した。その中で、ルイス酸性のキラルボロン触媒にシロキシエステルが配位する I の脱プロトン化(対応する遷移状態（TS_1）を Figure 2-11-2-A に示す)が最も低い自由エネルギー障壁（2 kcal/mol）を示す一方で、他の中間体は比較的大きな自由エネルギー障壁を示した為、I を反応経路の出発点として選択している。脱プロトン化後、I よりも 18.9 kcal/mol 安定である Z-エノラート中間体 I_2 が形成される。この時 E-エノラート形成は速度論的、熱力学的に不利であった。さらにエノラート形成後の I_2 を再構成することで、それぞれ I_2 よりも 12.3 kcal/mol または 19.0 kcal/mol 高エネルギーなエンジオラート中間体 I_3 または I_4 が生成する。I_3 からの不斉アルドール反応は、I_3 よりも 4.7 kcal/mol だけエネルギーの高い舟型六員環遷移状態 TS_2[36]（Figure 2-11-2-B）を経由してホウ素錯体内で進行する。この時、I_4 は TS_2 よりも 2.0 kcal/mol 高いため、I_4 からの経路は反応に寄与しないと考えられる。以上のことから、不斉アルドール反応は、I_3 と TS_2 を経由して進行し、(*2R,3R*)生成物に至ると結論づけられ、この点は実験結果と一致する。計算された遷移状態のうち、TS_2 は 87.7%の確率で存在したが、その他の遷移状態では、(*2S,3S*)-、(*2R,3S*)-、(*2S,3R*)-の生成物が、それぞれ 7.0%、3.5%、1.8%の確率で存在するため、理論上のジアステレオ比は 95/5 となった。この値は、**3aa** の実験結果である 18/1 dr と一致する[37]。さらに、理論上の ee 値は 85%であり、実験結果（86% ee）とよく一致している[38]。

　不斉アルドール反応の後、出発点 I より 29.1 kcal/mol エネルギー的に安定なホウ素アルドラート I_5 が生成した。この分子には酸素親和性の高いシリル基が存在するため、I_5 のホウ素原子とケイ素原子の間で配位子交換が進み、I_5 よりも 1.7 kcal/mol だけエネルギー的に高いホウ素カルボン酸塩 I_7 が生成することで触媒活性のあるホウ素分子種が再生する。この計算結果はケイ素添加剤の存在下でのみホウ素触媒のターンオーバーが可能であるという、我々の仮説・実験結果を説明するものである。

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[36] 舟型六員環遷移状態と椅子型六員環遷移状態の差異については SI 参照

[37] See SI

[38] See SI
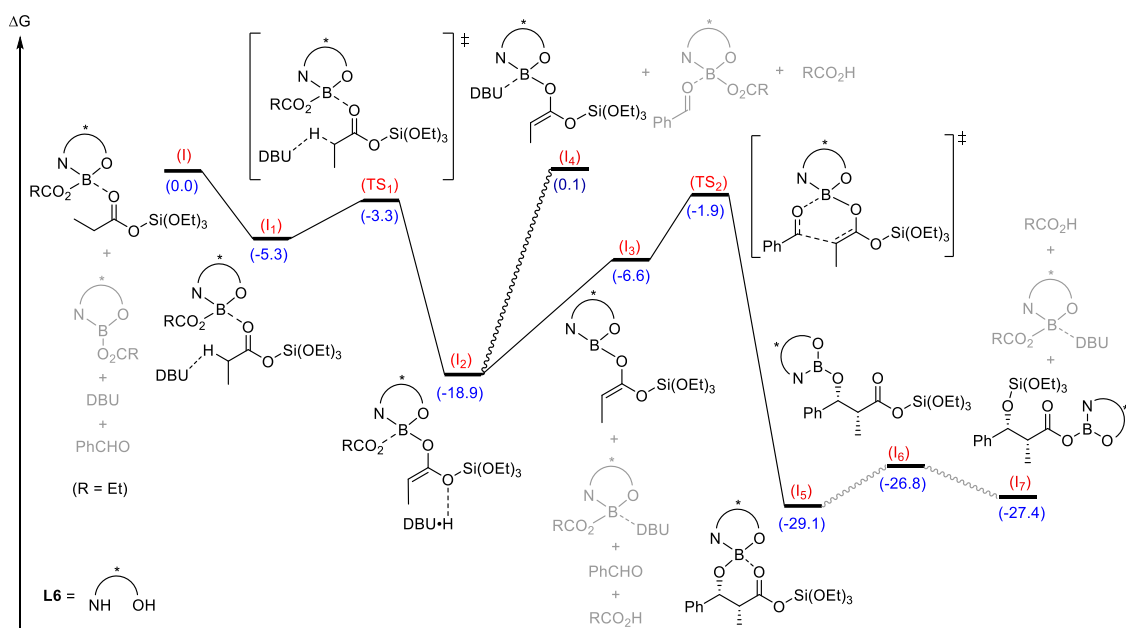
Figure 2-11-1　エネルギーダイヤグラム
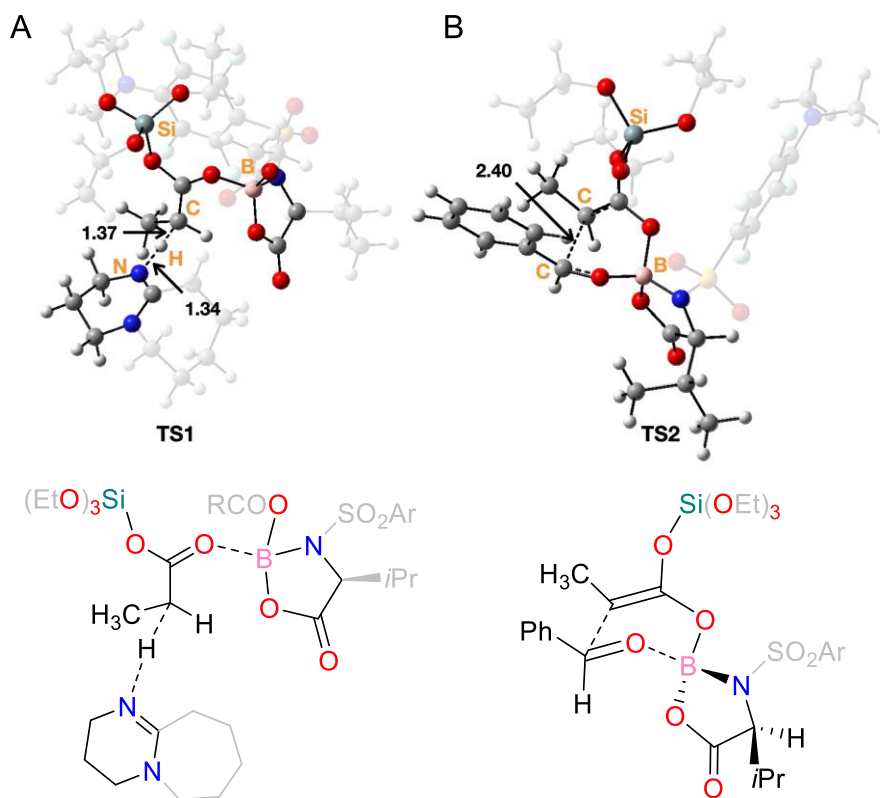
Figure 2-11-2　TS1 及び TS2 の相対配置

3. <u>総括</u>

　以上のように、筆者はケイ素を traceless 保護基として用いホウ素触媒-DBU 系と組み合わせることで温和な条件下にカルボン酸の化学選択的な活性化を実現し、高い官能基許容性を有する触媒的不斉アルドール反応の開発に成功した。実験及び計算科学による解析から、ケイ素ホウ素ヘテロエンジオラート種を中間体とする新奇な反応機構を明らかにした。
　本反応は多官能基を有する複雑な基質に対しても、立体選択的な後期誘導体化を行える強力な手法であり、医薬品類のリード化合物創生や天然物合成の新規合成経路開拓に有用であると考える。

FG = keto, ester, nitrile
amide, C=C, C≡C, halo
OH, epoxy....

up to 93% yield
up to >20 / 1 dr
up to 97% ee

Si/B hetero enediolate

✔ Chemoselective
✔ Diastereo- and enantioselective
✔ Catalyst-controlled stereodivergency
✔ DFT calculation-supported mechanism
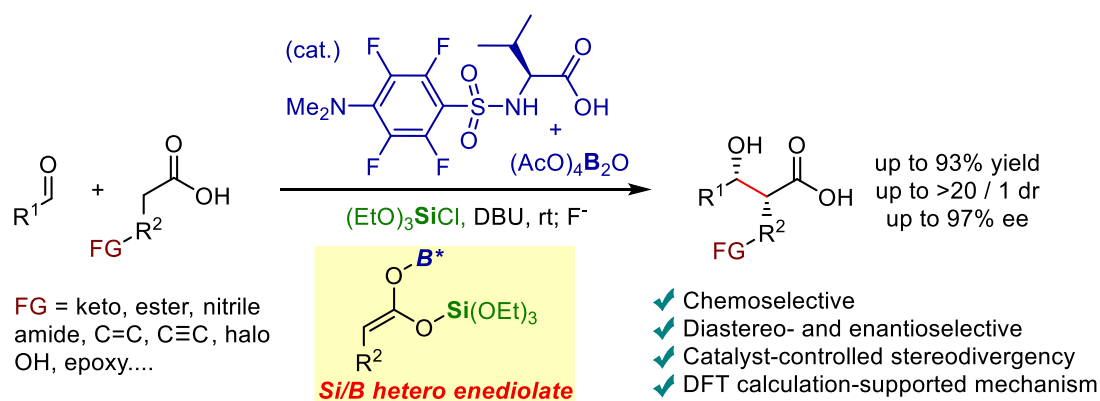
Fujita, T.; Yamane, Y.; Sameera, W. M. C.; Mitsunuma, H.; Kanai, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 24598-24604
selected as *Hot Paper*

3. 実験項

Table of Contents

1. General Method

^{1}H and ^{13}C NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), JEOL ECZ500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), and JEOL ECS400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer. Chemical shifts were reported in the scale relative to the solvent used as an internal reference for ^{1}H ($\delta = 7.26$ ppm for CDCl$_3$) and ^{13}C NMR ($\delta = 77.00$ ppm for CDCl$_3$). Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. ESI-mass spectra were measured on a Waters ZQ4000 spectrometer (for LRMS), and a JEOL JMS-T100LC AccuTOF spectrometer (for HRMS). The enantiomeric excesses (ee's) were determined by HPLC analysis conducted by JASCO HPLC systems (pump: PU-2080; detector: UV-2075, measured at 210 nm; chiral column; mobile phase: hexane/2-propanol). Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatographies were performed with silica gel 60 (KANTO CHEMICAL, spherical, 40-50 µm), Biotage Isolera One and Biotage SNAP Ultra, or Yamazen Smart Flash and Universal Column Premium. Preparative recycling gel permeation chromatography (GPC) was performed with JAI LC-9210 NEXT instrument equipped with JAIGEL-1H and JAIGEL-2H columns using CHCl$_3$ as an eluent. All non-commercially available compounds were prepared and characterized as described in Section 4 of this SI. DBU and (EtO)$_3$SiCl were purified by distillation from CaH$_2$ and used under argon atmosphere. Reagents that were not further described were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd. and used without further purification.

2. Determination of Relative and Absolute Configuration
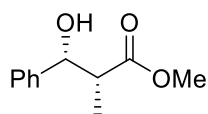
4aa: 86% ee

The spectral data of **4aa** was identical with the reported values of the *syn*-isomer[1]. HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 10.1 min (major) and 11.5 min (minor); $[\alpha]_D^{17.5}$ = 21.3 (*c* = 0.30, CHCl$_3$) for 86% ee. Based on the comparison of the reported optical rotation for the (2*R,3R*)-enantiomer ($[\alpha]_D^{20}$ = 10.7 (*c* = 1.79, CHCl$_3$) for 45% ee)[1], the absolute configuration of **4aa** was determined to be (2*R,3R*).
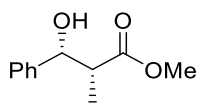
3. General procedure

Procedure A
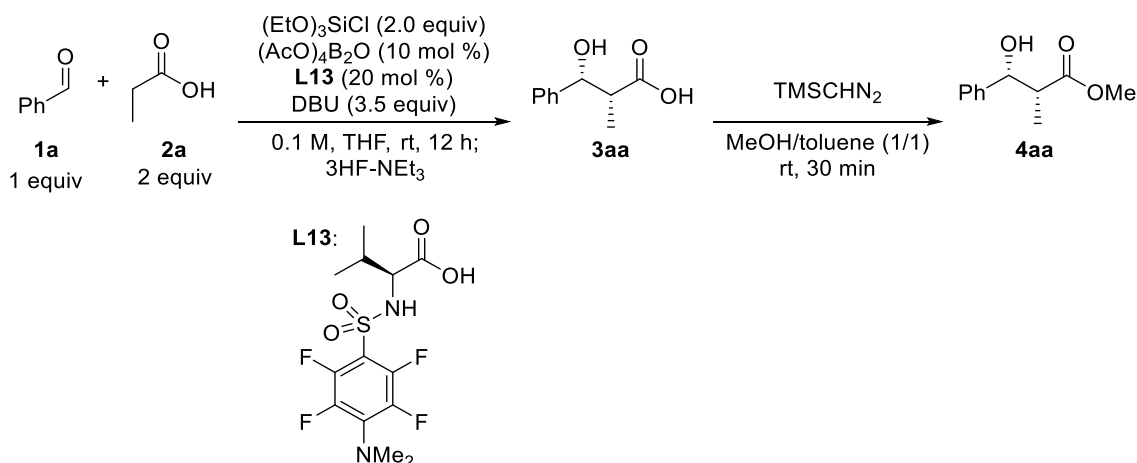
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with propionic acid (**2a**; 44.5 μL, 0.6 mmol), chlorotriethoxysilane (117.8 μL, 0.6 mmol) and DBU (156.7 μL, 1.05 mmol) in anhydrous THF (2.0 mL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (8.2 mg, 0.03 mmol), ((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl) sulfonyl)-L-valine (**L13;** 22.3 mg, 0.06 mmol) and anhydrous THF (1.0 mL). After stirring for 0.5 h, a solution of test tube B and benzaldehyde (**1a**, 30.5 μl, 0.3 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude product (**3aa**). Diastereoselectivity was determined from crude NMR at this stage. Subsequent methyl esterification was carried out without further purification. To a solution of crude

3aa in MeOH (1.0 mL) and toluene (1.0 mL) was added TMSCHN$_2$ (1.0 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure, and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra (EtOAc/hexane, gradient from 6% to 50%), affording **4aa** as a colorless oil (39.4 mg, 69% yield, *syn/anti* = 16/1).

Procedure B
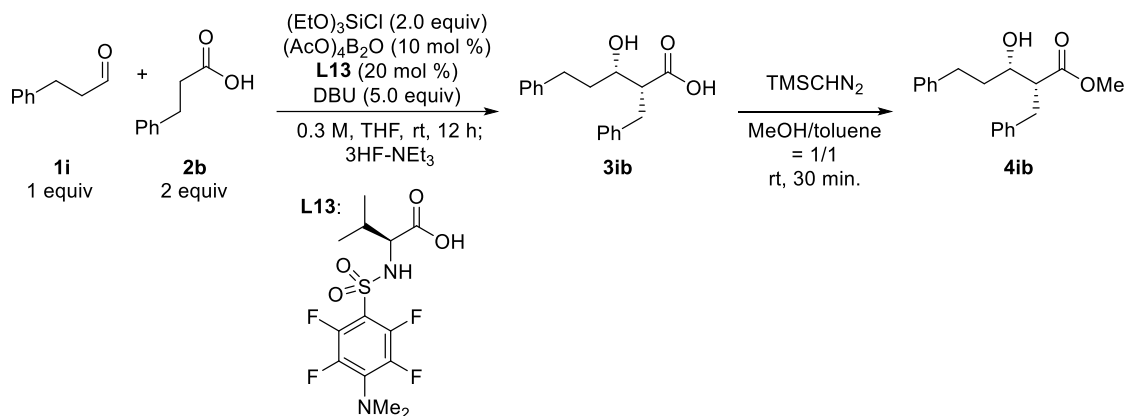
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with 3-Ph-propionic acid (**2b**, 90.1 mg, 0.6 mmol), chlorotriethoxysilane (117.8 μL, 0.6 mmol) and DBU (223.9 μL, 1.5 mmol) in anhydrous THF (0.5 mL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (8.2 mg, 0.03 mmol), ((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl) sulfonyl)-L-valine (**L13;** 22.3 mg, 0.06 mmol) and anhydrous THF (0.5 mL). After stirring for 0.5 h, a solution of test tube B and 3-phenylpropionaldehyde (**1i**, 39.9 μl, 0.3 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude product (**3ib**).

Subsequent methyl esterification was carried out without further purification. To a solution of crude **3ib** in MeOH (1.0 mL) and toluene (1.0 mL) was added TMSCHN$_2$ (1.0 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure, and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra (EtOAc/hexane, gradient from 2% to 50%), affording **4ib** as a white crystal (82.1 mg, 92% yield, *syn/anti* = 9.9/1).

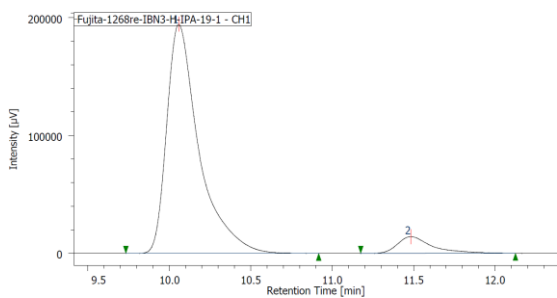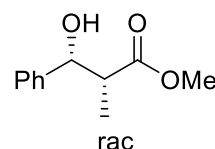**methyl (2R,3R)-3-hydroxy-2-methyl-3-phenylpropanoate (4aa)**

A colorless oil; Yield: 69% (39.4 mg); *syn/anti* = 16/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.13 (d, *J* = 7.4 Hz, 3H), 2.79 (dq, *J* = 4.0 Hz, 7.4 Hz, 1H), 2.90 (br, O*H*), 3.68 (s, 3H), 5.11 (d, *J* = 4.0 Hz, 1H), 7.27-7.34 (m, 5H)

The other spectral data of **4aa** was identical with the reported values[2]. HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 10.1 min (major) and 11.5 min (minor); $[\alpha]_D^{17.5}$ = 21.3 (*c* = 0.30, CHCl$_3$) for 86% ee.
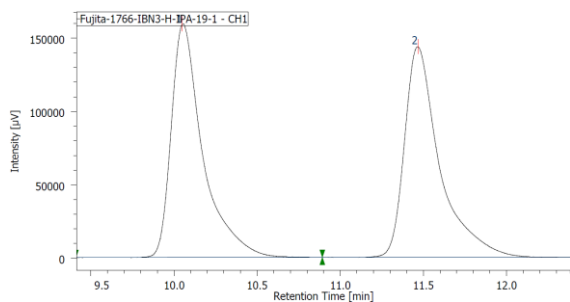
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	10.050	2099615	159350	49.865	52.584
2	Unknown	1	11.467	2111017	143691	50.135	47.416

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	10.058	2669108	194561	92.793	93.224
2	Unknown	1	11.483	207298	14142	7.207	6.776

86% ee
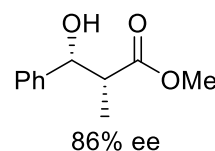
(2R,3R)-3-hydroxy-2-methyl-3-phenylpropanoic acid (3aa)
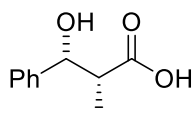
A white solid; Yield: 66% (24.0 mg, 0.2 mmol scale); *syn/anti* = 18/1 (Reverse phase HPLC, acetonitrile/water, C18 column);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.16 (d, *J* = 7.2 Hz, 3H), 2.85 (dq, *J* = 4.0 Hz, 7.2 Hz, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 7.25-7.37 (m, 5H).

Other spectral data of **3aa** were identical with the reported values[3].

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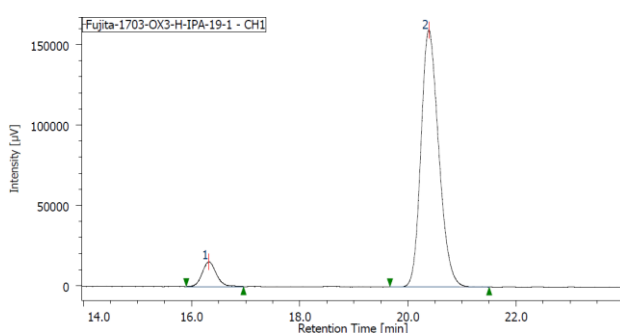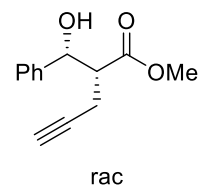**methyl (2R,3R)-2-benzyl-3-hydroxy-3-phenylpropanoate (4ab)**
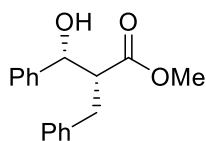
A colorless oil; Yield: 89% (70.9 mg); *syn*/*anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);
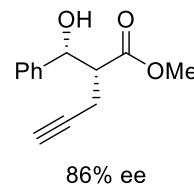
The spectral data of **4ab** was identical with the reported values[4].; HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 13.5 min (minor) and 15.6 min (major); $[\alpha]_D^{17.5}$ = 36.1 (*c* = 1.59, CHCl$_3$) for 90% ee.
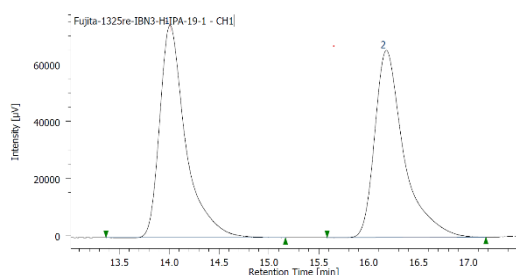
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%
1	Unknown	1	14.008	1346356	74594	50.351	53.164
2	Unknown	1	16.175	1327562	65715	49.649	46.836

rac
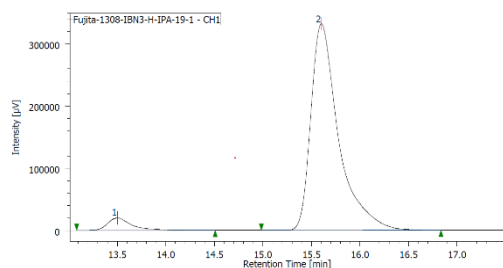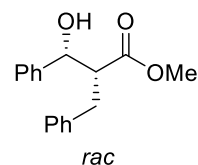
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%
1	Unknown	1	13.500	343263	20062	4.964	5.700
2	Unknown	1	15.600	6571283	331878	95.036	94.300

90% ee
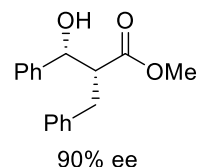
methyl (R)-2-((R)-hydroxy(phenyl)methyl)pent-4-ynoate (4ac)
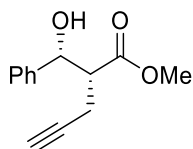
A colorless oil; Yield: 91% (59.3 mg); *syn*/*anti* = 11/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

The spectral data of **4ac** was identical with the reported values[2].; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 16.3 min (minor) and 20.4 min (major); $[\alpha]_D^{17.5}$ = 6.15 (*c* = 1.03, CHCl$_3$) for 86% ee.
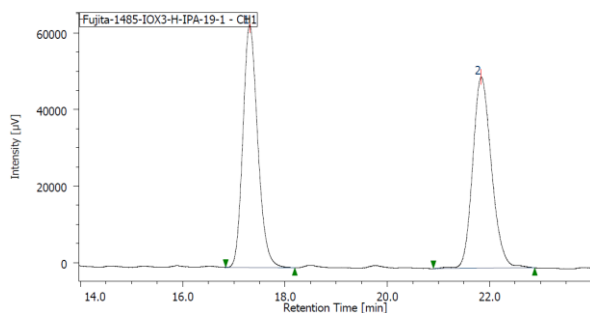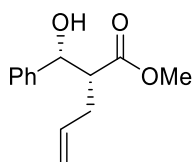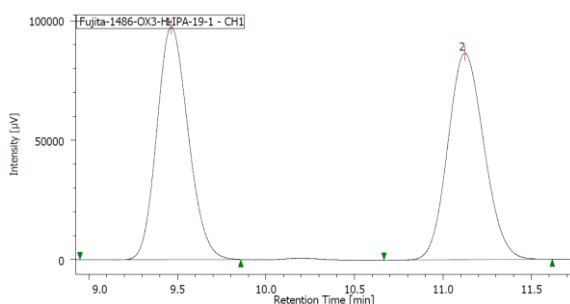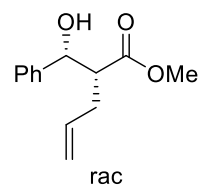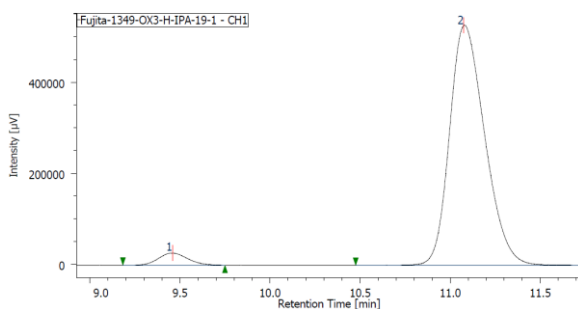
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	17.308	1275861	63416	49.946	55.955
2	Unknown	1	21.833	1278600	49919	50.054	44.045

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	16.317	278128	15366	7.104	8.782
2	Unknown	1	20.383	3637204	159599	92.896	91.218

86% ee

methyl (*R*)-2-((*R*)-hydroxy(phenyl)methyl)pent-4-enoate (4ad)

A colorless oil; Yield: 84% (55.3 mg); *syn*/*anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

The spectral data of **4ad** was identical with the reported values[2].; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 9.5 min (minor) and 11.1 min (major); for 92% ee. $[\alpha]_D^{17.5}$ = 13.5 (*c* = 1.04, CHCl$_3$).
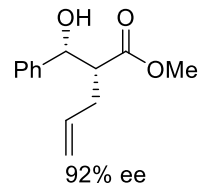

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	9.467	1202196	97798	49.341	53.009
2	Unknown	1	11.125	1234325	86694	50.659	46.991

rac

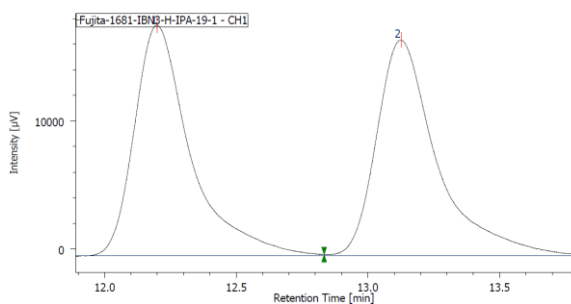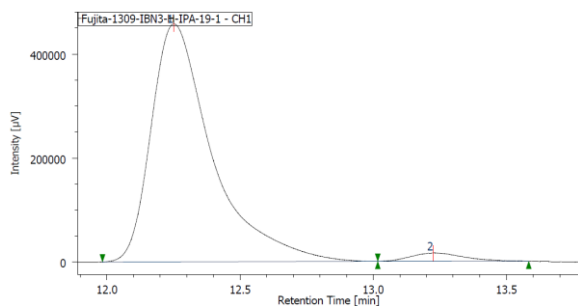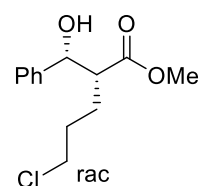| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	9.458	301280	26818	4.037	4.839
2	Unknown	1	11.075	7160854	527419	95.963	95.161

92% ee

methyl (*R*)-5-chloro-2-((*R*)-hydroxy(phenyl)methyl)pentanoate (4ae)
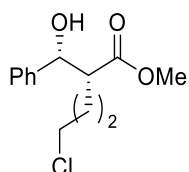
A colorless oil; Yield: 70% (52.9 mg); *syn/anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

The spectral data of **4ae** was identical with the reported values[2].; HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 12.3 min (major) and 13.2 min (minor); $[\alpha]_D^{17.5}$ = 28.1 (c = 0.79, CHCl$_3$) for 94% ee.
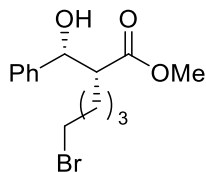

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	12.200	267971	18022	49.775	51.653
2	Unknown	1	13.125	270390	16868	50.225	48.347

rac

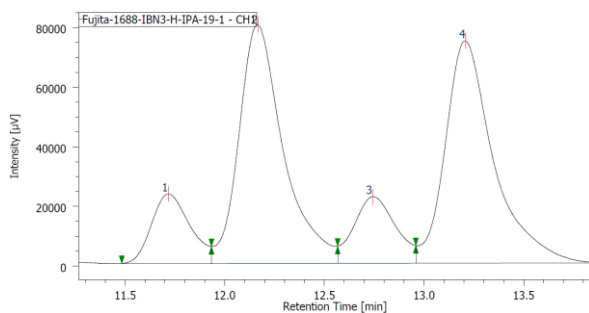| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	12.250	7272779	457727	97.072	96.640
2	Unknown	1	13.225	219348	15914	2.928	3.360

94% ee
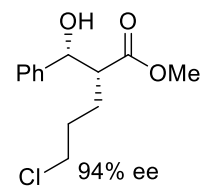
**methyl (*R*)-6-bromo-2-((*R*)-hydroxy(phenyl)methyl)hexanoate (4af)**

A colorless oil; Yield: 53% (47.7 mg); *syn*/*anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%); 70% NMR yield

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.30-1.48 (m, 2H), 1.61-1.65 (m, 1H), 1.75-1.80 (m, 3H), 2.70-2.74 (m, 1H), 2.77 (br, O*H*), 3.30-3.37 (m, 2H), 3.61 (s, 3H), 4.96 (d, *J* = 5.2 Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 26.0, 26.1, 32.5, 33.3, 51.7, 52.7, 74.0, 126.0, 127.8, 128.4, 141.4, 175.2; IR (KBr): 3334, 2921, 1726, 1160, 748, 699 cm^{-1}; LRMS (ESI): m/z 337 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{14}$H$_{19}$BrO$_3$ [M+Na]$^+$ 337.0410 Found 337.0413; HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 12.1 min (major) and 13.1 min (minor); [α]$_D^{17.5}$ = 25.6 (*c* = 0.63, CHCl$_3$) for 94% ee.


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	11.717	311879	23360	9.949	11.658
2	Unknown	1	12.167	1238876	80105	39.519	39.975
3	Unknown	1	12.742	323788	22345	10.329	11.151
4	Unknown	1	13.208	1260316	74577	40.203	37.216

rac (syn & anti)
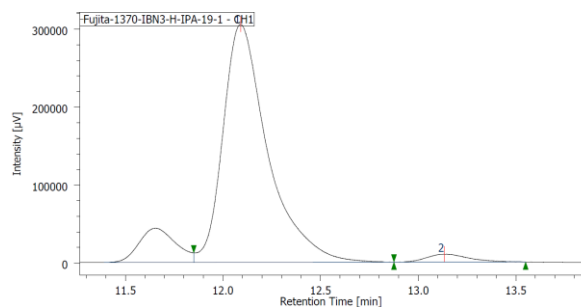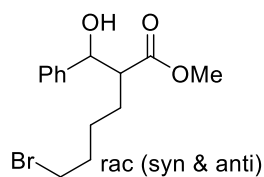
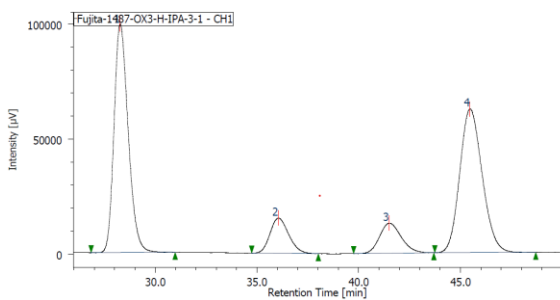| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	12.092	4857690	305173	96.980	96.788
2	Unknown	1	13.133	151259	10126	3.020	3.212

94% ee
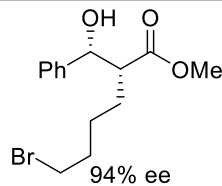
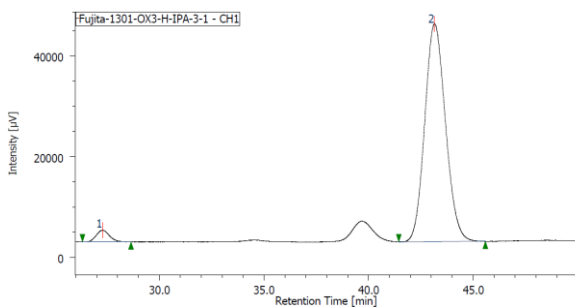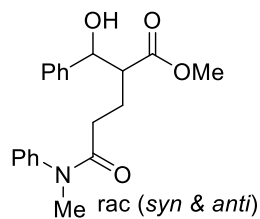**methyl (*R*)-2-((*R*)-hydroxy(phenyl)methyl)-5-(methyl(phenyl)amino)-5-oxopentanoate (4ag)**
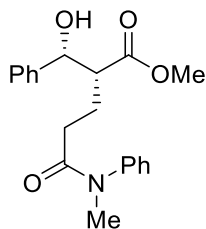
A colorless oil; Yield: 82% (84.3 mg); *syn*/*anti* = 12/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 12% to 100%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.97-2.06 (m, 3H), 2.14-2.17 (m, 1H), 2.72 (m, 1H), 3.21 (*minor,* s, 3H), 3.23 (s, 3H), 3.46 (s, 3H), 3.57 (*minor*, s, 3H), 4.73 (*minor*, d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 5.7 Hz, 1H), 7.10-7.40 (m, 10H). Other spectral data of **7ag** were identical with the reported values[2].; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 3/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 27.3 min (minor) and 43.1 min (major); [α]$_D^{17.5}$ = 19.5 (*c* = 0.87, CHCl$_3$) for 94% ee.


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	28.275	4807237	99450	41.620	52.256
2	Unknown	1	36.050	978239	15333	8.469	8.057
3	Unknown	1	41.492	970501	13097	8.402	6.882
4	Unknown	1	45.467	4794417	62435	41.509	32.806

rac (*syn & anti*)

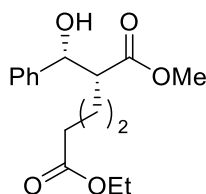| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	27.283	100530	2307	3.274	5.074
2	Unknown	1	43.142	2970146	43155	96.726	94.926

94% ee
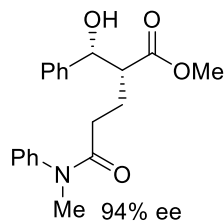
(*R*)-2-((*R*)-hydroxy(phenyl)methyl)-5-(methyl(phenyl)amino)-5-oxopentanoic acid (3ag)
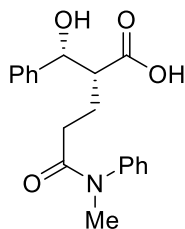
A white solid; Yield: 73% (48.0 mg, 0.2 mmol scale); *syn*/*anti* = 16/1 (Reverse phase HPLC, acetonitrile/water gradient, C18 column then GPC);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.74 (m, 1H), 1.82-1.94 (m, 2H), 2.03 (m, 1H), 3.19 (s, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 6.87 (m, 1H), 7.25-7.32 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.1, 32.2, 37.6, 51.0, 72.2, 125.8, 126.8, 127.3, 128.2, 128.3, 129.9, 141.0, 142.7, 174.3, 177.3; IR (KBr): 3465, 2952, 1719, 1325, 1164, 1125, 1068, 843, 703 cm^{-1}; LRMS (ESI): m/z 326 [M-H]$^-$; HRMS (ESI): m/z calcd for C$_{19}$H$_{21}$NO$_4$ [M-H]$^-$ 326.1397 Found 326.1405; [α]$_D$$^{17.5}$ = 9.9 (*c* = 1.01, MeOH) for 94% ee.

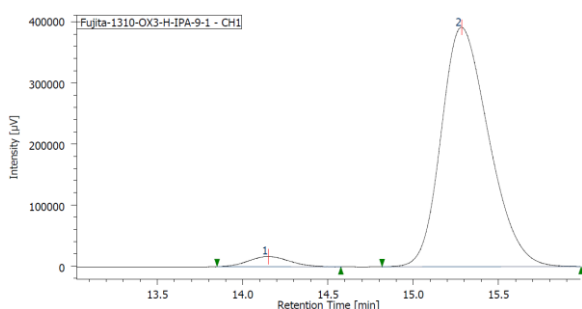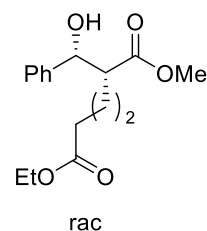**6-ethyl 1-methyl (*R*)-2-((*R*)-hydroxy(phenyl)methyl)hexanedioate (4ah)**

A colorless oil; Yield: 72% (63.2 mg); *syn*/*anti* = >20/1 (concentration was 0.2 M, 4 eq of DBU, General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 1.48-1.55 (m, 1H), 1.60-1.68 (m, 2H), 1.74-1.81 (dt, *J* = 8.6, 10.9 Hz, 1H), 2.22-2.26 (m, 2H), 2.71-2.75 (m, 1H), 2.80 (br, O*H*), 3.61 (s, 3H), 4.08 (q, *J* = 7.1 Hz 2H), 4.97 (d, *J* = 5.7 Hz, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.2, 22.9, 26.4, 34.0, 51.7, 52.6, 60.3, 74.0, 126.0, 127.8, 128.3, 141.4, 173.2, 175.1; IR (KBr): 3334, 2921, 1726, 1160, 748, 699 cm^{-1}; IR (KBr): 3451, 2912, 1730, 1252, 1173, 1017, 700 cm^{-1}; LRMS (ESI): m/z 317 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{16}$H$_{22}$O$_5$ [M+Na]$^+$ 317.1359 Found 317.1351; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 9/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 14.2 min (minor) and 15.3 min (major); [α]$_D$$^{17.5}$ = 21.7 (*c* = 0.43, CHCl$_3$) for 93% ee.
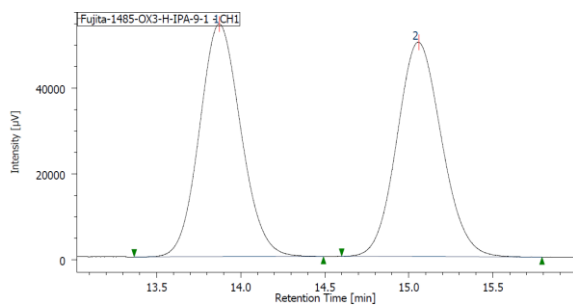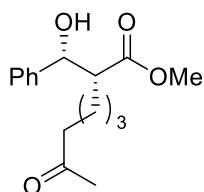
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	13.875	929138	54270	50.047	52.041
2	Unknown	1	15.058	927389	50013	49.953	47.959

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	14.150	281039	16732	3.559	4.092
2	Unknown	1	15.283	7616629	392124	96.441	95.908

93% ee
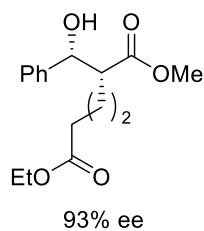
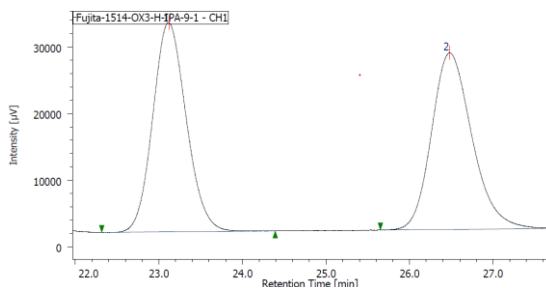**methyl (R)-2-((R)-hydroxy(phenyl)methyl)-7-oxooctanoate (4ai)**
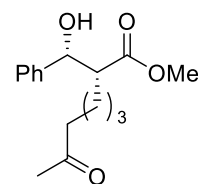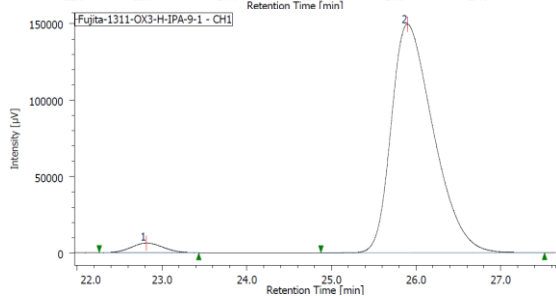

A colorless oil; Yield: 57% (47.6 mg); *syn*/*anti* = >20/1 (concentration was 0.2 M, 4 eq of DBU General procedure A, SiO$_2$: grad. EtOAc/hexane = 8% to 66%);
^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.16-1.25 (m, 2H), 1.45-1.64 (m, 3H), 1.70-1.76 (m, 1H), 2.09 (s, 3H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.69 (m, 1H), 2.71 (br, O*H*), 3.60 (s, 3H), 4.96 (d, *J* = 5.2 Hz, 1H), 7.25-7.36 (m, 5H). Other spectral data of **7ai** were identical with the reported values[2].; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 9/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 22.8 min (minor) and 25.9 min (major); [α]$_D^{17.5}$ = 25.3 (*c* = 0.86, CHCl$_3$) for 94% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	23.117	874270	31444	49.456	54.236
2	Unknown	1	26.475	893516	26532	50.544	45.764
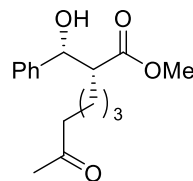
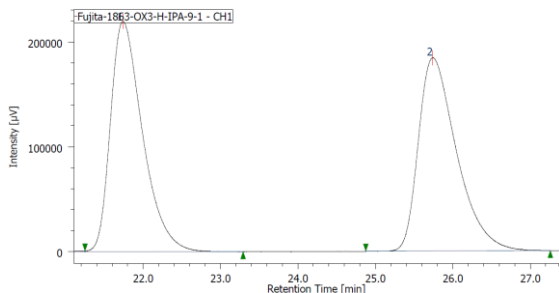| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	22.817	169099	6339	3.176	4.072
2	Unknown	1	25.900	5155786	149336	96.824	95.928

rac

94% ee

methyl (*R*)-4-cyano-2-((*R*)-hydroxy(phenyl)methyl)butanoate (4aj)
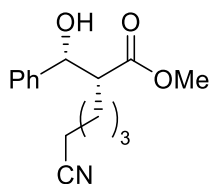
A colorless oil; Yield: 81% (37.7 mg); *syn/anti* = 7.3/1 (0.2 mmol scale, General procedure A, SiO₂: grad. EtOAc/hexane = 8% to 66%);

^{1}H NMR (500 MHz, CDCl₃): δ = 1.98 (m, 1H), 2.07 (m, 1H), 2.29-2.42 (m, 2H) 2.61 (d, *J* = 5.2 Hz, *OH*), 2.84 (m, 1H), 2.92 (*minor*, m, 1H), 3.68 (s, 3H), 3.75 (*minor*, s, 3H), 4.84 (*minor*, d, *J* = 8.0 Hz, 1H), 5.12 (dd, *J* = 2.9, 5.2 Hz, 1H), 7.30-7.38 (m, 5H); ^{13}C NMR (125 MHz, CDCl₃): δ = 15.6, 22.5, 51.3, 52.2, 73.6, 119.0, 125.8, 128.1, 128.6, 140.7, 171.1; IR (KBr): 3471, 2952, 2248, 1732, 1448, 1213, 1167, 1024, 769, 703 cm^{-1}; LRMS (ESI): m/z 256 [M+Na]$^+$; HRMS (ESI): m/z calcd for C₁₃H₁₅NO₃ [M+Na]$^+$ 256.0945 Found 256.0947; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 9/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 21.7 min (major) and 25.7 min (minor); [α]$_D^{17.5}$ = 32.5 (*c* = 0.85, CHCl₃) for 97% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	21.742	6317990	219733	50.055
2	Unknown	1	25.742	6303980	184342	49.945

rac
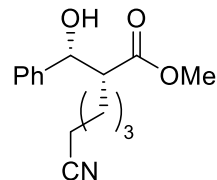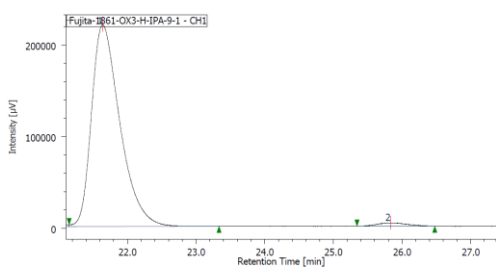
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	21.642	6304236	219650	98.294
2	Unknown	1	25.833	109426	3619	1.706

97% ee

(*R*)-9-hydroxy-2-((*R*)-hydroxy(phenyl)methyl)nonanoic acid (4ak)

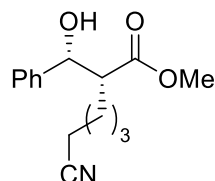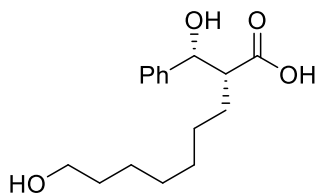A white solid; Yield: 56% (31.4 mg); *syn*/*anti* = >20/1 (General procedure A, SiO$_2$: grad. MeOH/DCM = 2% to 20%);

^{1}H NMR (500 MHz, CD$_3$OD): δ = 1.24-1.40 (m, 8H), 1.48-1.53 (m, 2H), 1.68-1.85 (m, 2H), 2.64 (m, 1H), 3.53 (t, *J* = 6.9 Hz, 2H), 4.73 (d, *J* = 8.0 Hz, 1H), 7.24-7.36 (m, 5H); ^{13}C NMR (125 MHz, CD$_3$OD): δ = 26.8, 28.6, 29.7, 30.4, 30.6, 33.6, 55.6, 63.0, 76.1, 127.8, 128.5, 129.1, 144.4, 177.9; IR (KBr): 3365, 2928, 2852, 1704, 1457, 1273, 1200, 1048, 695 cm^{-1}; LRMS (ESI): m/z 279 [M-H]$^-$; HRMS (ESI): m/z calcd for C$_{16}$H$_{24}$O$_4$ [M-H]$^-$ 279.1601 Found 279.1606; HPLC (chiral column: CHIRALPAK AZ3; solvent: hexane/2-propanol = 9/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 14.9 min (major) and 17.5 min (minor); [α]$_D$$^{17.5}$ = 18.9 (*c* = 1.0, MeOH) for 90% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	14.942	2170307	59986	50.140
2	Unknown	1	17.533	2158147	48455	49.860

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	15.042	2813122	75573	95.018
2	Unknown	1	18.208	147484	1676	4.982

rac

90% ee

methyl (2R,3R)-2-(4-chlorophenyl)-3-hydroxy-3-phenylpropanoate (4al)

A colorless oil; Yield: 72% (41.2 mg, 0.2 mmol scale); *syn/anti* = 3.3/1 (SiO$_2$, grad. Hex/EtOAc 4% to 34%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.55 (s, 3H), 3.83 (d, *J* = 6.3 Hz, 1H), 5.28 (d, *J* = 6.3 Hz, 1H), 7.19-7.29 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 52.2, 58.6, 74.7, 126.4, 128.0, 128.3, 128.6, 130.1, 133.0, 133.8, 140.5, 172.7; IR (KBr): 3448, 3060, 3034, 2921, 2360, 2339, 1715, 1448, 1209, 1051, 765, 694 cm^{-1}; LRS (ESI): m/z 313 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{16}$H$_{15}$ClO$_3$ [M+Na]$^+$ 313.0602 Found 313.0608; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 11.3 min (minor) and 14.2 min (major); [α]$_D^{17.5}$ = 24 (*c* =0.55, MeOH) for 47% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	11.308	2484649	158549	50.356
2	Unknown	1	14.167	2449503	126180	49.644

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	11.417	343941	22365	26.669
2	Unknown	1	14.308	945703	49279	73.331

47% ee

methyl (*S*)-3-hydroxy-2,2-dimethyl-3-phenylpropanoate (4am)

A colorless oil; Yield: 33% (15.0 mg, 0.2 mmol scale with **L7**); SiO$_2$, grad. Hex/EtOAc: 4% to 34%; The spectral data of **7am** was identical with the reported values[5]. HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 11.0 min (major) and 11.5 min (minor); $[\alpha]_D^{17.5}$ = -3.2 (*c* =0.87, MeOH) for 66% ee.
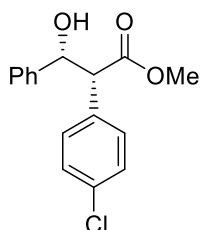

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	11.025	923681	74211	49.822
2	Unknown	1	11.508	930281	71283	50.178

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	10.975	2462912	192724	82.749
2	Unknown	1	11.450	513437	42931	17.251

66% ee

methyl (2R,3R)-2-benzyl-3-hydroxy-3-(p-tolyl)propanoate (4bb)

A colorless oil; Yield: 41% (35.1 mg); *syn/anti* = >20/1 (General procedure A, SiO_2: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.34 (s, 3H), 2.96-3.03 (m, 3H), 3.43 (s, 3H), 4.99 (d, *J* = 5.2 Hz, 1H), 7.08-7.26 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.1, 33.3, 51.5, 55.2, 74.0, 126.0, 126.3, 128.3, 128.8, 129.1, 137.5, 138.3, 139.2, 174.6; IR (KBr): 3456, 2921, 1730, 1439, 1164, 1022, 703 cm^{-1}; LRMS (ESI): m/z 307 [M+Na]$^+$; HRMS (ESI): m/z calcd for $C_{18}H_{20}O_3$ [M+Na]$^+$ 307.1305 Found 307.1303; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 14.2 min (minor) and 16.3 min (major); [α]$_D^{17.5}$ = 27.8 (*c* = 0.59, CHCl$_3$) for 87% ee.
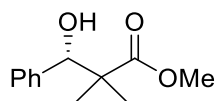

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	14.242	2297388	137982	49.892	53.186
2	Unknown	1	16.325	2307352	121453	50.108	46.814

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	14.217	256868	15199	6.518	7.320
2	Unknown	1	16.292	3684031	192437	93.482	92.680

87% ee

methyl (*2R,3R*)-2-benzyl-3-(4-chlorophenyl)-3-hydroxypropanoate (4cb)

A colorless oil; Yield: 82% (75.2 mg); *syn/anti* = 19/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 2% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.89-3.02 (m, 3H and O*H*), 3.44 (s, 3H), 5.03 (d, *J* = 4.6 Hz, 1H), 7.05-7.34 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 33.1, 51.6, 55.0, 73.3, 126.4, 127.5, 128.4, 128.6, 128.7, 133.6, 138.8, 139.7, 174.5; IR (KBr): 3456, 2947, 1727, 1491, 1164, 1013, 826, 703 cm^{-1}; LRMS (ESI): m/z 327 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{17}$ClO$_3$ [M+Na]$^+$ 327.0758 Found 327.0751; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 10.2 min (minor) and 12.5 min (major); [α]$_D^{17.5}$ = 17.2 (*c* = 2.14, CHCl$_3$) for 89% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	10.033	4798179	385406	49.970	54.603
2	Unknown	1	12.358	4803924	320430	50.030	45.397

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	10.167	349787	28404	5.450	6.627
2	Unknown	1	12.500	6067752	400194	94.550	93.373

89% ee

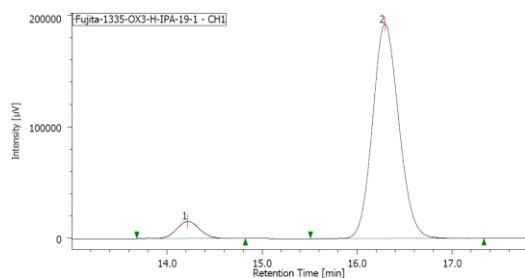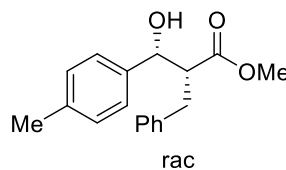**methyl (*2R,3R*)-2-benzyl-3-(4-bromophenyl)-3-hydroxypropanoate (4db)**

A colorless oil; Yield: 88% (92.2 mg); *syn/anti* = 18/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 2% to 50%);
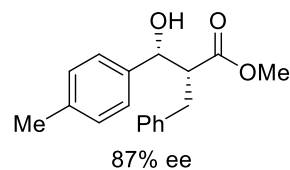
52

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.88-3.00 (m, 4H), 3.45 (s, 3H), 5.00 (d, J = 4.0 Hz, 1H), 7.04-7.50 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 33.0 , 51.6, 54.9, 73.3, 121.7, 126.4, 127.9, 128.4, 128.7, 131.5, 138.7, 140.2, 174.5; IR (KBr): 3467, 3030, 2949, 1729, 1487, 1435, 1165, 1071, 1011, 826, 700 cm^{-1}; LRMS (ESI): m/z 371 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{17}$BrO$_3$ [M+Na]$^+$ 371.0253, 373.0233 Found 371.0265, 373.0225; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 11.0 min (minor) and 13.8 min (major); [α]$_D$$^{17.5}$ = 8.8 (c = 1.93, CHCl$_3$) for 85% ee.
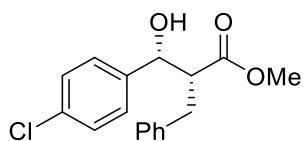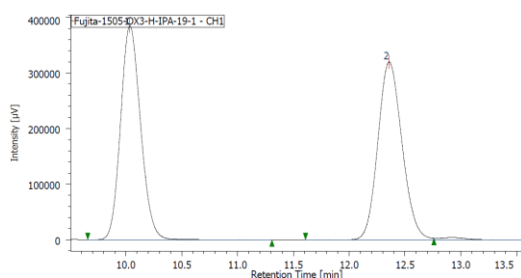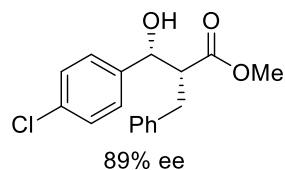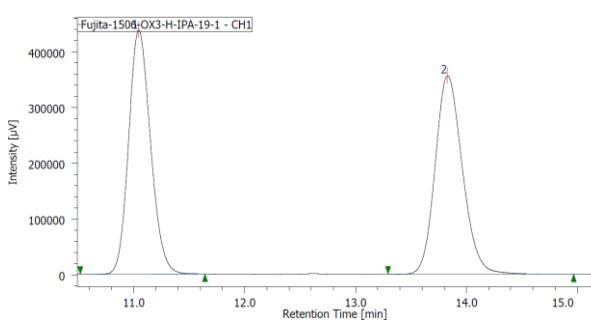

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	11.042	6007293	438554	49.769
2	Unknown	1	13.825	6063017	355994	50.231

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	11.033	152835	10588	7.539	8.887
2	Unknown	1	13.817	1874318	108559	92.461	91.113
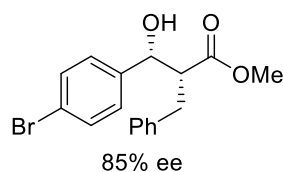
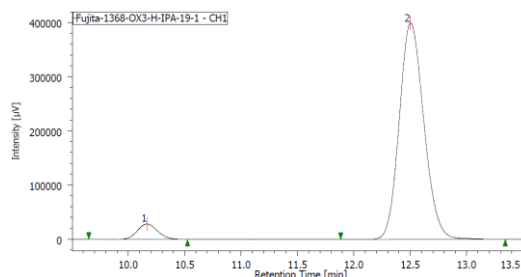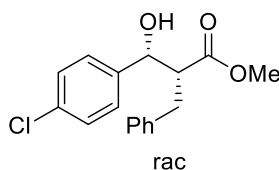**methyl (2*R*,3*R*)-2-benzyl-3-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate (4eb)**
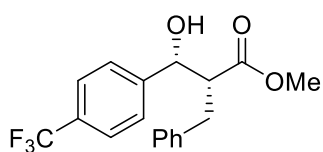
A white soid; Yield: 93% (94.2 mg); *syn/anti* = 16/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.85 (dt, *J* = 9.2, 10.3 Hz, 1H), 2.99-3.03 (m, 2H), 3.09 (br, OH), 3.47 (s, 3H), 5.13 (br, 1H), 7.03-7.25 (m, 5H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 32.5, 51.5, 54.4, 72.9, 122.7, 125.1(q, $^3J_{F-C}$ = 3.6 Hz), 127.2(q, $^1J_{F-C}$ = 245.1 Hz), 128.4, 129.6(q, $^2J_{F-C}$ = 32.6 Hz), 138.3, 144.9, 174.4; ^{19}F NMR (368 MHz, CDCl3): δ = 70.4(s, 3F); IR (KBr): 3465, 2952, 1719, 1325, 1164, 1125, 1068, 843, 703 cm^{-1}; LRMS (ESI): m/z 361 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{18}$H$_{17}$F$_3$O$_3$ [M+Na]$^+$ 361.1022 Found 361.1035; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 7.0 min (minor) and 8.1 min (major); [α]$_D^{17.5}$ = 22.9 (*c* = 1.11, CHCl$_3$) for 83% ee.
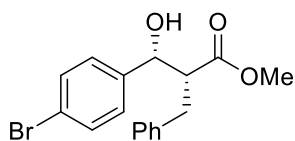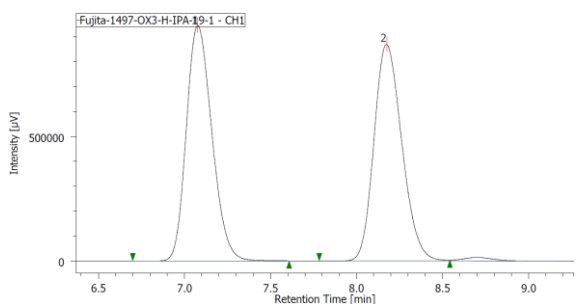

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	7.075	9771665	947665	49.925	52.101
2	Unknown	1	8.175	9801055	871242	50.075	47.899

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	7.025	233576	9864	8.616	6.439
2	Unknown	1	8.108	2477531	143325	91.384	93.561

83% ee
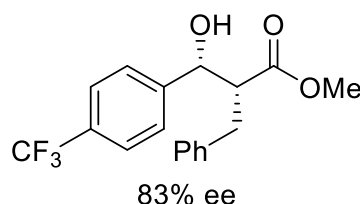
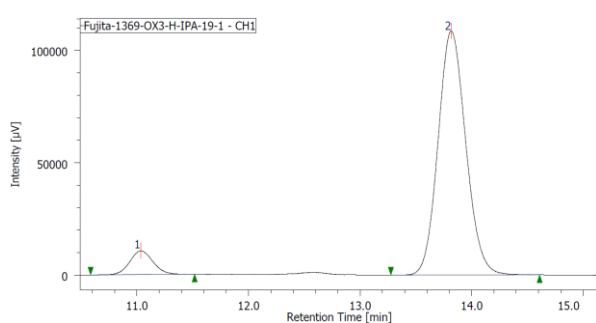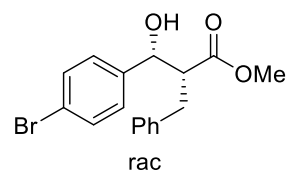**methyl (*2R,3R*)-2-benzyl-3-hydroxy-3-(naphthalen-2-yl)propanoate (4fb)**
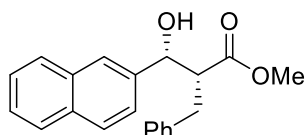
White solid; Yield: 93% (89.6 mg); *syn/anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.97 (dd, *J* = 4.6, 13.7 Hz, 1H), 3.06 (dt, *J* = 10.9, 13.7 Hz, 1H), 3.13-3.18 (m, 1H), 3.43 (s, 3H), 5.23 (d, *J* = 4.6 Hz, 1H), 7.06-7.07 (m, 2H), 7.15-7.21 (m, 3H), 7.48-7.50 (m, 3H), 7.83-7.90 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 33.0, 51.6, 55.0, 74.1, 123.9, 125.2, 126.0, 126.2, 126.3, 127.7, 128.1, 128.2, 128.3, 128.8, 133.0, 133.2, 138.6, 139.0, 174.7; IR (KBr):

3451, 3030, 2952, 1718, 1160, 1022, 748, 700 cm^{-1} LRMS (ESI): m/z 343 [M+Na]$^+$; HRMS (ESI): m/z calcd for $C_{21}H_{20}O_3$ [M+Na]$^+$ 343.1305 Found 343.1301; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 19.3 min (minor) and 22.9 min (major); $[\alpha]_D^{17.5}$ = 3.2 (c = 1.06, CHCl$_3$) for 86% ee.
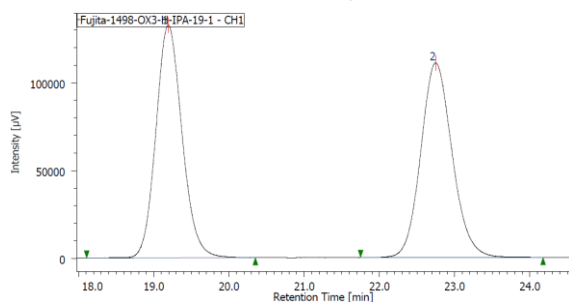
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	19.192	3200472	132514	49.899	54.468
2	Unknown	1	22.750	3213457	110776	50.101	45.532
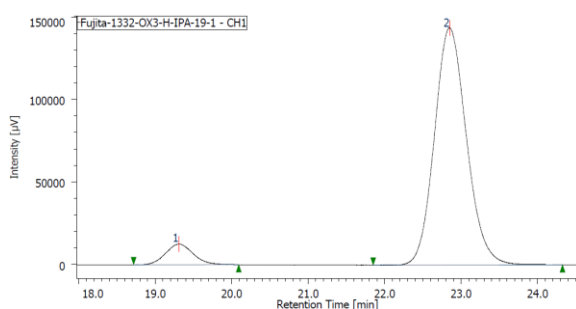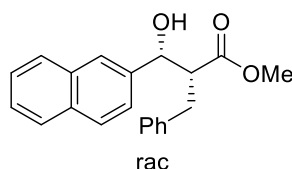
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	19.308	312411	12424	6.948	7.959
2	Unknown	1	22.850	4183942	143677	93.052	92.041
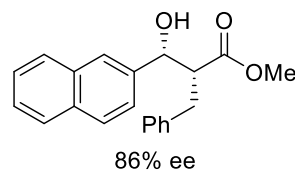
(2R,3R)-2-benzyl-3-hydroxy-3-(naphthalen-2-yl)propanoic acid (3fb)
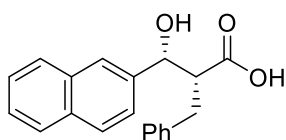
A white solid; Yield: 81% (49.6 mg, 0.2 mmol scale); *syn*/*anti* = >20/1 (Reverse phase HPLC, acetonitrile/water gradient, C18 column then GPC);

^{1}H NMR (500 MHz, CD$_3$OD): δ = 2.97-3.25 (m, 3H), 4.99 (d, *J* = 7.6 Hz, 1H), 7.11-7.22 (m, 5H), 7.42-7.46 (m, 2H), 7.54-7.57 (m, 1H), 7.80-7.84 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ =35.6, 58.1, 76.2, 125.7, 126.7, 126.9, 127.1, 127.2, 128.6, 129.0, 129.3, 129.9, 134.57, 134.62, 141.1, 141.5, 176.7; IR (KBr): 3261, 3030, 2927, 1697, 1486, 1209, 1169, 977, 742 cm^{-1}; LRMS (ESI): m/z 305 [M-H]$^-$; HRMS (ESI): m/z calcd for $C_{20}H_{18}O_3$ [M-H]$^-$ 305.1183 Found 305.1187; $[\alpha]_D^{17.5}$ = 39.0 (c = 1.6, MeOH) for 86% ee.

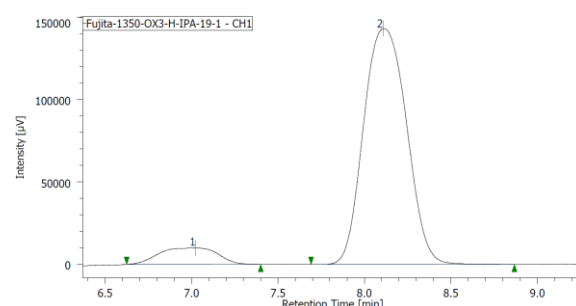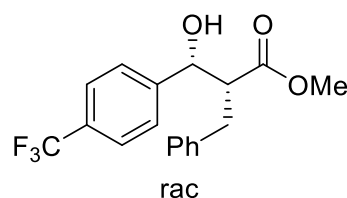**methyl (*2R,3R*)-2-benzyl-3-(3-chlorophenyl)-3-hydroxypropanoate (4gb)**
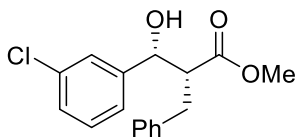
White solid; Yield: 93% (85.3 mg); *syn*/*anti* = 16/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 4% to 34%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.97 (dt, *J* = 9.2, 9.7 Hz, 1H), 2.98-3.02 (m, 3H), 3.46 (s, 3H), 5.03 (d, *J* = 4.0 Hz, 1H), 7.05-7.42 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 32.9, 51.7, 54.8, 73.2, 124.2, 126.3, 126.4, 128.0, 128.4, 128.7, 130.0, 134.4, 168.7, 164.3, 174.5; IR (KBr): 3460, 2952, 1728, 1435, 1164, 1022, 699 cm^{-1}; LRMS (ESI): m/z 327 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{27}$ClO$_3$ [M+Na]$^+$ 327.0758 Found 327.0757; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 9.7 min (minor) and 13.1 min (major); [α]$_D$$^{17.5}$ = 22.3 (*c* = 2.19, CHCl$_3$) for 90% ee.


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	9.633	3468288	319967	49.826	59.826
2	Unknown	1	13.083	3492454	214861	50.174	40.174

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.683	601251	55376	5.063
2	Unknown	1	13.125	11274195	652896	94.937

90% ee

methyl (*2R,3R*)-2-benzyl-3-(2-chlorophenyl)-3-hydroxypropanoate (4hb)


White solid; Yield: 87% (79.5 mg); *syn*/*anti* = >20/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 4% to 34%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.74 (dd, *J* = 3.4, 13.7 Hz, 1H), 3.04 (dd, *J* = 10.9, 13.7 Hz, 1H), 3.27 (dt, *J* = 3.4, 10.9 Hz, 1H), 3.37 (br, O*H*), 3.53 (s, 3H), 5.47 (br, 1H), 6.99-7.70 (m, 9H); ^{13}C NMR

56

(125 MHz, CDCl$_3$): δ = 31.7, 50.9, 51.8, 70.5, 126.4, 126.9, 128.3, 239.6, 228.7, 128.9, 129.6, 131.5, 137.9, 139.0, 175.6; IR (KBr): 3477, 2943, 1734, 1438, 1204, 1160, 1034, 752, 700 cm^{-1}; LRMS (ESI): m/z 327 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{27}$ClO$_3$ [M+Na]$^+$ 327.0758 Found 327.0752; HPLC (chiral column: CHIRALPAK IBN5; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 11.1 min (minor) and 16.4 min (major); [α]$_D^{17.5}$ = 74.3 (c = 1.59, CHCl$_3$) for 87% ee.


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	10.975	3662493	260209	49.716	60.128
2	Unknown	1	16.150	3704332	172548	50.284	39.872

rac

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	11.108	233338	16880	6.653	9.857
2	Unknown	1	16.358	3274090	154357	93.347	90.143

87% ee

methyl (2R,3S)-2-benzyl-3-hydroxy-5-phenylpentanoate (4ib)

White solid; Yield: 92% (82.1 mg); *syn/anti* = 9.9/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 2% to 50% and GPC);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.78-1.87 (m, 2H), 2.50 (br, O*H*), 2.64-2.70 (m, 1H), 2.79-2.82 (m, 1H), 2.85-3.02 (m, 3H), 3.55 (s, 3H), 3.63 (*mino*r, s, 3H), 3.87 (dt, *J* = 4.6, 9.2 Hz, 1H), 4.01 (*minor*, ddd, *J* =4.6, 9.7, 9.7 Hz), 7.11-7.30 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 32.1, 33.3, 35.9, 51.6, 53.2, 71.1, 126.0, 126.4, 128.44, 128.46, 128.47, 128.7, 139.1, 141.6, 175.0; IR (KBr): 3334, 2921, 1726, 1160, 748, 699 cm^{-1}; LRMS (ESI): m/z 321 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{19}$H$_{22}$O$_3$ [M+Na]$^+$ 321.1461 Found 321.1465; HPLC (chiral column: CHIRALPAK AZ3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 13.1 min (major) and 16.4 min (minor); [α]$_D^{17.5}$ = 6.1 (c = 0.49, CHCl$_3$) for 92% ee.

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	13.050	1806201	103224	39.169	44.770
2	Unknown	1	15.275	489953	24182	10.625	10.488
3	Unknown	1	16.175	1809518	81769	39.241	35.465
4	Unknown	1	17.408	505587	21388	10.964	9.276

rac (*syn & anti*)

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	13.117	3436276	189689	95.720	96.345
2	Unknown	1	16.408	153658	7196	4.280	3.655

92% ee

(4*S*,5*R*)-5-benzyl-4-hydroxy-6-methoxy-6-oxohexyl benzoate (4jb)

A colorless oil; Yield: 71% (75.8 mg); *syn*/*anti* = 11/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 8% to 66%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.63-1.69 (m, 2H), 1.82-1.88 (m, 1H), 2.00-2.06 (m, 1H), 2.75 (*minor*, m, 1H), 2.80-2.84 (m, 1H) 2.98-3.03 (m, 2H), 3.56 (s, 3H), 3.62 (*minor*, s, 3H), 3.69 (*minor*, m, 1H), 3.92 (dt, *J* = 5.2, 7.4 Hz, 1H), 4.36 (t, *J* = 6.3 Hz, 2H), 7.15-7.21 (m, 4H), 7.24-7.28 (m, 1H), 7.42-7.45 (m, 2H), 7.54-7.58 (m, 1H), 8.02-8.05 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 25.3, 30.7, 33.4, 51.6, 53.2, 64.6, 71.4, 126.4, 128.3, 128.4, 128.7, 129.5, 130.2, 132.9, 139.0, 166.6, 174.9; IR (KBr): 3491, 2952, 1718, 1452, 1275, 1164, 1115, 1025, 712 cm^{-1} LRMS (ESI): m/z 379 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{21}$H$_{24}$O$_5$ [M+Na]$^+$ 379.1516 Found 379.1519; HPLC (chiral column: CHIRALPAK IC3; solvent: hexane/2-propanol = 9/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 17.2 min (major) and 20.7 min (minor); [α]$_D$$^{17.5}$ = 6.3 (*c* = 2.12, CHCl$_3$) for 87% ee.
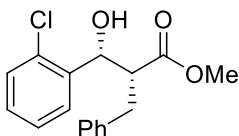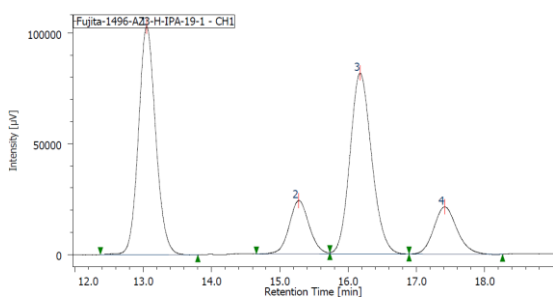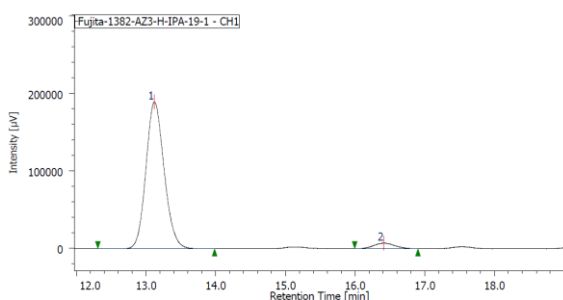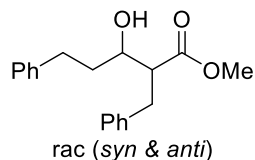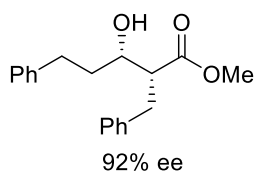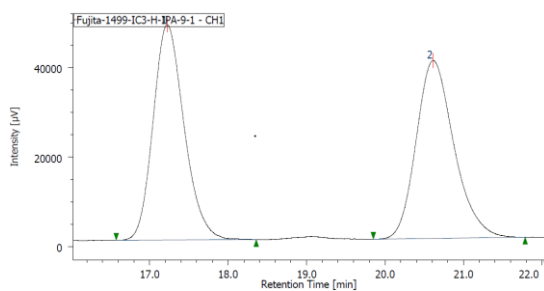
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	17.225	1322101	48126	49.846	54.753
2	Unknown	1	20.608	1330259	39771	50.154	45.247

rac
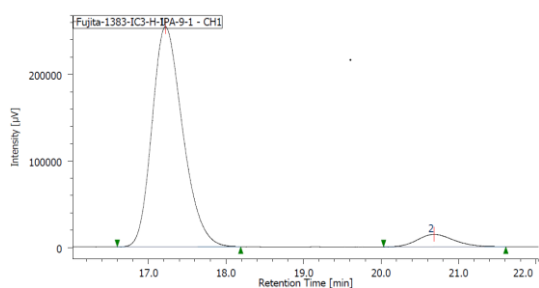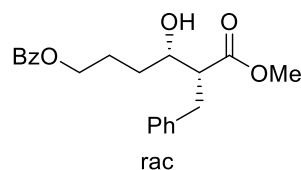
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	17.217	6998624	254621	93.627	94.654
2	Unknown	1	20.683	476367	14380	6.373	5.346

87% ee
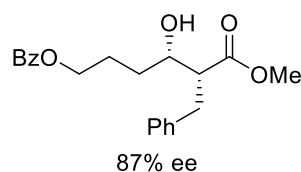
methyl (*2R,3S*)-2-benzyl-3-hydroxy-5-methylhexanoate (4kb)
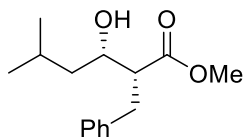
A colorless oil; Yield: 72% (54.1 mg); *syn*/*anti* = >20/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 4% to 34%);

The spectral data of **7kb** was identical with the reported values[6].; HPLC (chiral column: CHIRALPAK IC3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 7.2 min (major) and 8.2 min (minor); $[\alpha]_D^{17.5}$ = 25.3 (*c* =0.57, CHCl$_3$) for 91% ee.
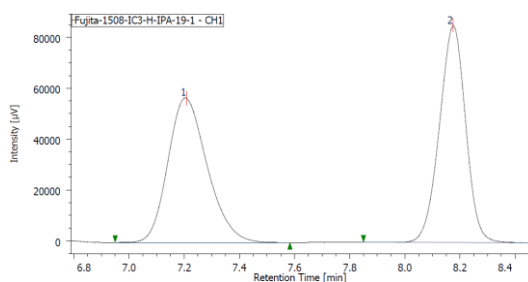
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	7.208	561190	56667	49.859	39.860
2	Unknown	1	8.175	564364	85500	50.141	60.140

rac
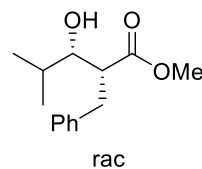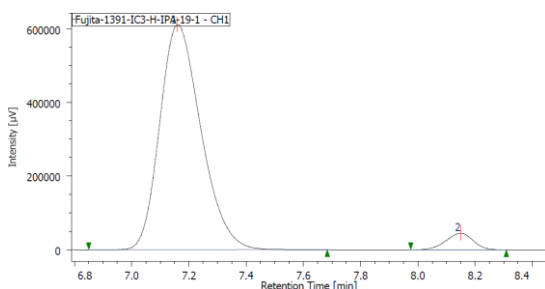
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	7.158	6107730	611772	95.361	93.135
2	Unknown	1	8.150	297136	45094	4.639	6.865

91% ee
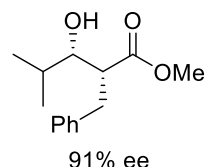
(2R,3S)-2-benzyl-3-hydroxy-5-methylhexanoic acid (3kb)
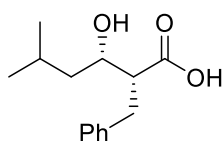
A white solid; Yield: 69% (32.4 mg, 0.2 mmol scale); *syn/anti* = >20/1 (Reverse phase HPLC, acetonitrile/water gradient, C18 column);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.90 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H), 1.33 (m, 1H), 1.52 (m, 1H), 1.81 (m, 1H), 2.81-2.90 (m, 2H), 3.04 (m, 1H), 3.96 (m, 1H). 7.19-7.30 (m, 5H). Other spectral data of **5kb** were identical with the reported values[6].

methyl (2R,3S)-2-benzyl-3-hydroxy-5,5-dimethylhexanoate (4lb)
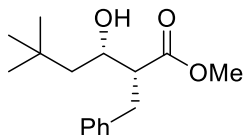
A colorless oil; Yield: 86% (68.6 mg); *syn/anti* = 9.0/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 4% to 34%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.97 (s, 9H), 1.36 (dd, *J* = 2.0, 14.3 Hz, 1H), 1.44 (dd, *J* = 8.6, 14.3 Hz, 1H), 2.00-2.06 (m, 1H), 2.65 (*minor*, m, 1H), 2.72-2.76 (m, 1H), 2.90 (dd, *J* = 4.9, 14.1 Hz, 1H), 3.00 (dd, *J* = 10.6, 14.1 Hz, 1H), 3.57 (s, 3H), 3.62 (*minor*, s, 3H), 3.80 (*minor*, m, 1H), 4.00 (ddd, *J* = 2.0, 4.9, 10.6 Hz, 1H), 7.15-7.28 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 30.0, 30.3, 33.3, 48.1, 51.6, 54.7, 69.5, 126.3, 128.4, 128.8, 139.3, 175.1; IR (KBr): 3334, 2921, 1726, 1160, 748, 699 cm^{-1}; IR (KBr): 3491, 2952, 1717, 1439, 1360, 1204, 1152, 1060 cm^{-1} LRMS (ESI): m/z 287 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{16}$H$_{24}$O$_3$ [M+Na]$^+$ 287.1618 Found 287.1617; HPLC (chiral column: CHIRALPAK IBN3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 6.1 min (minor) and 6.6 min (major); [α]$_D^{17.5}$ = 16.7 (*c* = 1.74, CHCl$_3$) for 90% ee.
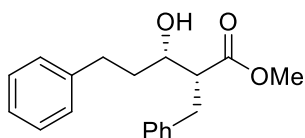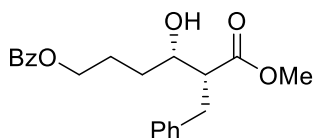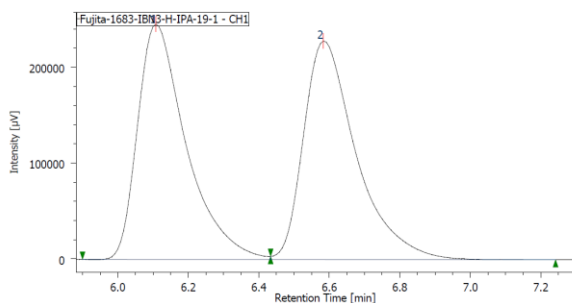
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	6.108	2344899	245427	49.829	51.841
2	Unknown	1	6.583	2361018	227993	50.171	48.159

rac
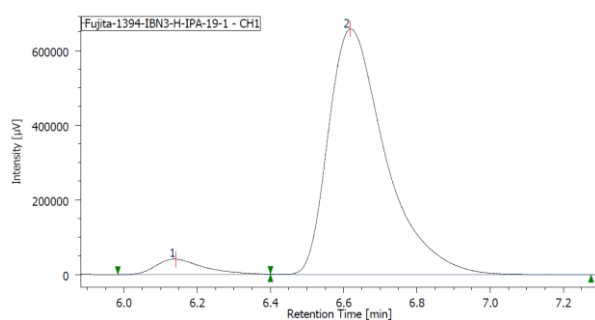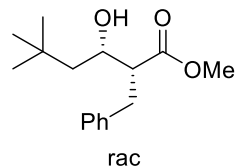
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	6.142	373999	41194	4.994	5.886
2	Unknown	1	6.617	7114554	658696	95.006	94.114

90% ee
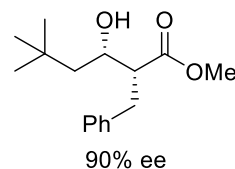
**methyl (2R,3S)-2-benzyl-3-cyclopropyl-3-hydroxypropanoate (4mb)**
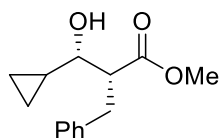
A colorless oil; Yield: 74% (52.0 mg); *syn*/*anti* = 4.4/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.25-0.29 (m, 1H), 0.34-0.37 (m, 1H), 0.54-0.58 (m, 2H), 0.92 (*minor*, m, 1H), 1.01-1.08 (m, 1H), 2.94 (ddd, *J* = 4.6, 5.7, 14.9 Hz, 1H), 3.02 (m, 1H), 3.10-3.14 (m, 2H), 3.56 (s, 3H), 3.61 (*minor*, s, 3H), 7.18-7.28 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 2.7, 3.1, 15.6, 34.1, 51.5, 54.1, 126.3, 128.4, 128.8, 139.4, 174.4; IR (KBr): 3460, 3017, 2943, 1732, 1434, 1164, 1034, 700 cm^{-1} LRMS (ESI): m/z 257 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{14}$H$_{18}$O$_3$ [M+Na]$^+$ 257.1148 Found 257.1148; HPLC (chiral column: CHIRALPAK OJ3-IC3 connected in series; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 28.6 min (major) and 37.4 min (mimor); [α]$_D^{17.5}$ = 44.4 (*c* = 0.65, CHCl$_3$) for 86% ee.
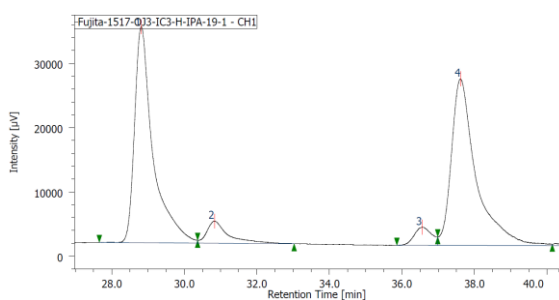
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	28.808	1189738	33609	44.857	51.113
2	Unknown	1	30.833	142824	3432	5.385	5.219
3	Unknown	1	36.558	95690	2820	3.608	4.289
4	Unknown	1	37.617	1224037	25894	46.150	39.379

rac
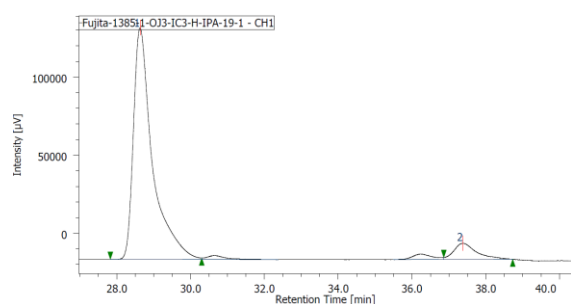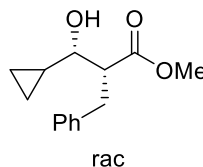
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	28.633	5294726	148331	92.304	93.475
2	Unknown	1	37.383	441471	10353	7.696	6.525

86% ee
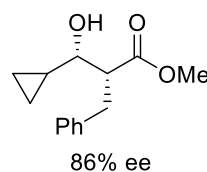
methyl (*2R,3S*)-2-benzyl-3-cyclohexyl-3-hydroxypropanoate (4nb)
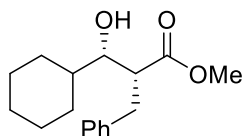
A colorless oil; Yield: 42% (34.2 mg); *syn*/*anti* = >20/1 (General procedure B, SiO$_2$: grad. EtOAc/hexane = 4% to 34%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.00-1.28 (m, 5H), 1.42-1.48 (m, 1H), 1.61-1.68 (m, 2H), 1.76-1.80 (m, 2H), 2.02 (m, 1H), 2.90-3.00 (m, 3H), 3.52 (s, 3H), 3.62 (dd, *J* = 4.6, 9.2 Hz, 1H), 7.16-7.28 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 25.9, 26.3, 28.2, 29.4, 32.7, 40.5, 50.1, 51.6, 126.3, 128.4, 128.7, 139.5, 175.7; IR (KBr): 3443, 2926, 2843, 1717, 1426, 1160, 1043 cm^{-1} LRMS (ESI): m/z 299 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{24}$O$_3$ [M+Na]$^+$ 299.1618 Found 299.1621; HPLC (chiral column: CHIRALPAK OJ3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 8.2 min (major) and 8.9 min (mimor); [α]$_D^{17.5}$ = 18.6 (*c* = 0.56, CHCl$_3$) for 87% ee.
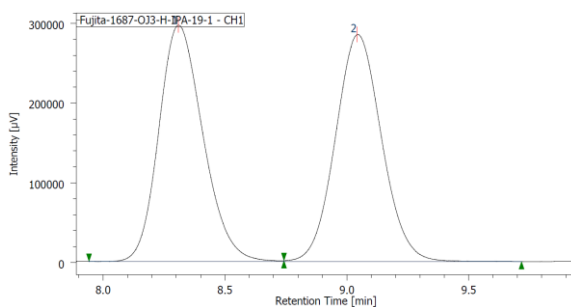

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	8.308	3729391	296403	49.875	51.036
2	Unknown	1	9.042	3748035	284364	50.125	48.964

rac
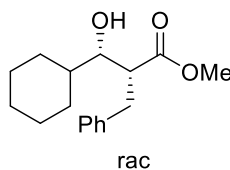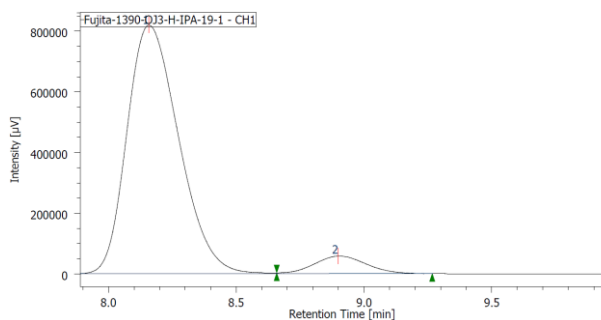
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	8.158	11519528	819189	93.427	93.418
2	Unknown	1	8.900	810515	57720	6.573	6.582

87% ee
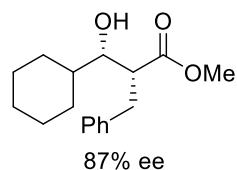
methyl (2R,3S)-2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)-3-hydroxy-3-phenylpropanoate (4an)
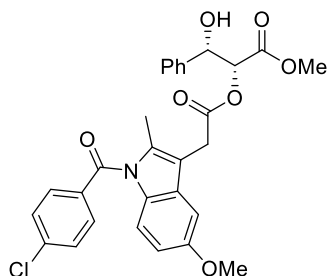
A clear yellow oil; Yield: 56% (59.5 mg); *syn*/*anti* = 11/1 (concentration 0.2 M, 4 eq of DBU, General procedure A, SiO$_2$: grad. EtOAc/hexane = 8% to 66% then GPC);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.25 (s, 3H),), 3.70 (d, *J* = 20.0 Hz, 1H), 3.70 (d, *J* = 20.0 Hz, 1H) , 3.74 (s, 3H), 3.82 (s, 3H), 5.21 (d, *J* = 3.4 Hz, 1H), 5.29 (d, *J* = 3.4 Hz, 1H), 6.69 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.88-6.93 (m, 2H), 7.15-7.23 (m, 5H), 7.45-7.48 (m, 2H), 7.61-7.64 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 13.3, 29.7, 52.6, 55.7, 73.2, 76.0, 101.0, 111.8, 112.0, 115.0, 125.9, 126.6, 128.2, 128.4, 129.1, 130.5, 130.7, 131.2, 133.8, 135.9, 138.5, 139.3, 156.2, 168.2, 169.7; IR (KBr): 3474, 2926, 1742, 1678, 1595, 1478, 1360, 1321, 1221, 1147, 1086, 838, 752 cm^{-1}; LRMS (ESI): m/z 558 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{29}$H$_{26}$ClNO$_7$ [M+Na]$^+$ 558.1290 Found 558.1271 HPLC (chiral column: CHIRALPAK IBN5-IBN3 connected in series; solvent: hexane/2-propanol = 6/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 55.9 min (major) and 61.1 min (mimor); [α]$_D^{17.5}$ = 15.3 (*c* = 0.81, CHCl$_3$) for 82% ee.
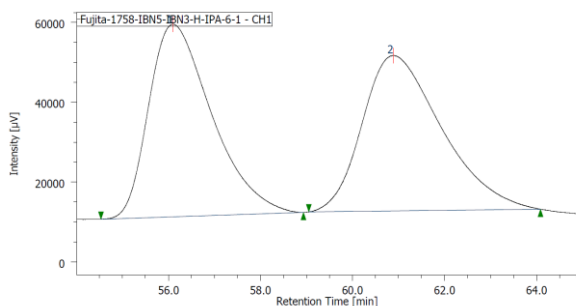
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	56.100	4578635	48120	49.604	55.333
2	Unknown	1	60.892	4651726	38844	50.396	44.667

rac
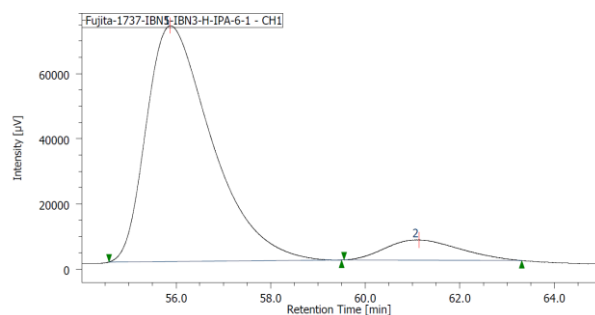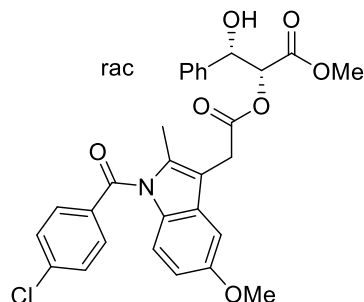
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	55.875	6953136	72415	91.098	92.074
2	Unknown	1	61.133	679476	6234	8.902	7.926

82% ee
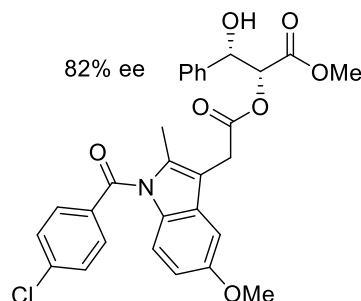
**methyl (2*R*,3*R*)-2-((4,5-diphenyloxazol-2-yl)methyl)-3-hydroxy-3-phenylpropanoate (4ao)**
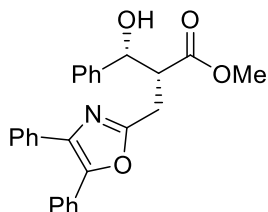
A colorless oil; Yield: 91% (75.0 mg); *syn/anti* = 7.6/1 (General procedure A, SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.15 (dd, *J* = 5.2, 16.0 Hz, 1H), 3.24 (dd, *J* = 8.0, 16.0 Hz, 1H), 3.42 (m, 1H), 3.67 (s, 3H), 3.72 (*minor*, s, 3H), 5.09 (*minor*, d, *J* = 6.9 Hz, 1H), 5.30 (m, 1H), 7.33-7.60 (m, 15H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 25.3, 50.3, 52.2, 125.4, 125.9, 126.5, 127.7, 127.8, 128.1, 128.4, 128.5, 128.6, 128.7, 132.0, 134.6, 141.1, 145.4, 161.5, 173.4; IR (KBr): 3396, 3034, 2917, 1734, 1573, 1443, 1209, 1169, 1051, 765, 695 cm^{-1} LRMS (ESI): m/z 436 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{26}$H$_{23}$NO$_4$ [M+Na]$^+$ 436.1519 Found 436.1523; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 49.1 min (minor) and 55.6 min (major); [α]$_D^{17.5}$ = 26.3 (*c* = 0.63, CHCl$_3$) for 84% ee.
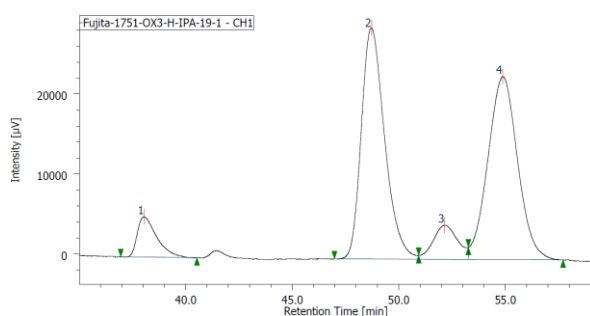
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	38.050	319310	5049	6.295	8.269
2	Unknown	1	48.717	2196997	28884	43.315	47.299
3	Unknown	1	52.142	341036	4268	6.724	6.989
4	Unknown	1	54.867	2214781	22866	43.666	37.443

rac (syn and anti)
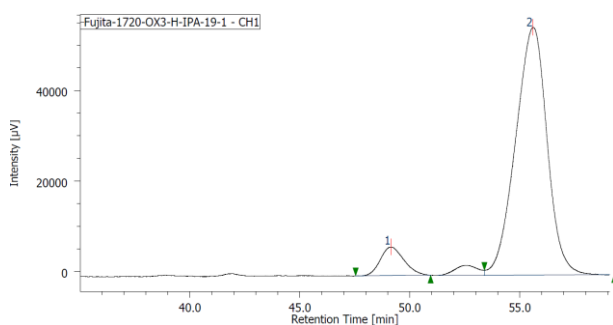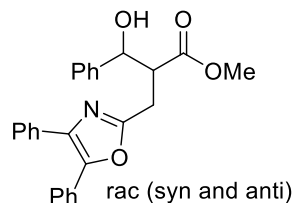
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	49.142	467659	6294	7.886	10.317
2	Unknown	1	55.600	5462659	54708	92.114	89.683

84% ee
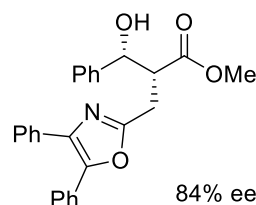
(2R,3R)-2-((4,5-diphenyloxazol-2-yl)methyl)-3-hydroxy-3-phenylpropanoic acid (4ao)
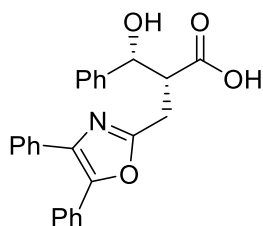
A white solid; Yield: 92% (73.7 mg, 0.2 mmol sacale); *syn*/*anti* = 7.1/1 (Reverse phase HPLC, acetonitrile/water gradient, C18 column then GPC);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.07 (dd, *J* = 17.2, 4.0 Hz, 1H), 3.26 (dd, *J* = 17.2, 9.7 Hz, 1H), 3.38 (m, 1H), 4.99 (d, *J* = 2.9 Hz, 1H), 7.27-7.52 (m, 15H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 23.7, 49.2, 125.8, 126.49, 126.53, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.6, 128.7, 128.9, 131.0, 133.8, 140.3, 145.9, 162.7, 175.3; IR (KBr): 3448, 3060, 3034, 2921, 2360,2339, 1715, 1448, 1209, 1051, 765, 694 cm^{-1}; LRMS (ESI): m/z 398 [M-H]$^-$; HRMS (ESI): m/z calcd for C$_{25}$H$_{21}$NO$_4$ [M-H]$^-$ 398.1397 Found 398.1406; [α]$_D^{17.5}$ = -6.1 (*c* = 0.69, MeOH) for 84% ee.

methyl (*R,E*)-2-((*R*)-hydroxy(phenyl)methyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (4ap)
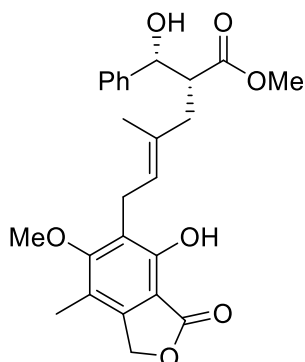
A colorless oil; Yield: 69% (39.8 mg (TM)+23.0 mg (over reaction TMSCHN$_2$ with ArOH to give *ArOMe*)); *syn/anti* = 17/1 (concentration was 0.2 M, 4 eq of (EtO)$_3$SiCl, 6 eq of DBU, General procedure A General procedure A, SiO$_2$: grad. EtOAc/hexane = 8% to 66% then GPC);

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.72 (s, 3H), 2.13 (s, 3H), 2.30 (dd, *J* = 4.0 Hz, 13.7 Hz, 1H), 2.41 (dd, *J* = 10.9, 13.7 Hz, 1H), 2.90-2.94 (m, 2H), 3.33 (d, *J* = 6.9 Hz, 2H), 3.43 (s, 3H), 3.73 (s, 3H), 4.92 (d, *J* = 5.2 Hz, 1H), 5.19 (s, 2H), 5.22 (t, *J* = 6.9 Hz, 1H), 7.24-7.32 (m, 5H), 9.63(br, ArOH); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 11.5, 15.9, 22.6, 37.5, 51.3, 51.6, 61.0, 70.0, 74.1, 106.3, 116.7, 122.0, 124.4, 126.1, 127.7, 128.3, 133.0, 141.3, 143.9, 153.6, 163.6, 172.9, 174.9; IR (KBr): 3439, 2943, 1733, 1625, 1456, 1365, 1164, 1134, 1074, 1025, 970, 700 cm^{-1}, LRMS (ESI): m/z 463 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{25}$H$_{28}$O$_7$ [M+Na]$^+$ 463.1727 Found 463.1743; HPLC (chiral column: CHIRALPAK OX3; solvent: hexane/2-propanol = 1/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 18.0 min (major) and 22.3 min (mimor); [α]$_D$$^{17.5}$ = 3.6 (*c* = 0.55, CHCl$_3$) for 87% ee.


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%
1	Unknown	1	18.483	12831912	231256	50.527	54.558
2	Unknown	1	22.750	12564234	192612	49.473	45.442

87% ee

methyl (2R,4R)-4-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((R)-hydroxy(phenyl)methyl)pentanoate (4aq)

A white solid; Yield: 63% (99.2 mg); *dr* = >20/1/<1/<1 (concentration 0.2 M, DBU 4 eq, General procedure A, short pad column by DCM/ MeOH = 10/1 before Methylation), SiO$_2$: grad. EtOAc/hexane = 6% to 50%);

^{1}H NMR (400 MHz, CDCl$_3$): δ =0.75 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H), 1.22-1.35 (m. 4H), 1.39 (s, 3H), 1.60 (dt, *J* = 14.3 Hz, 4.6 Hz, 1H), 1.79-2.14 (m, 8H), 2.19-2.14 (m, 6H), 2.61 (d, *J* = 2.9 Hz, 1H), 2.79-2.92 (m, 4H), 3.59 (s, 3H), 4.94 (dd, *J* = 5.7 Hz, 2.9 Hz, 1H), 7.28-7.34 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 11.7, 18.5, 21.8, 25.0, 27.5, 32.7, 34.3, 35.2, 35.9, 36.4, 38.5, 42.7, 44.9, 45.4, 46.0, 46.8, 48.9, 50.8, 51.56, 51.63, 56.8, 74.6, 125.9, 127.7, 128.3, 141.5, 175.2, 208.8, 209.1, 212.0; IR (KBr): 3460, 2957, 2874, 1709, 1452, 1382, 1269, 1195, 1022, 913, 734, 700 cm^{-1}; LRMS (ESI): m/z 545 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{32}$H$_{42}$O$_6$ [M+Na]$^+$ 545.2874 Found 545.2888; [α]$_D^{17.5}$ = 27.5 (*c* = 1.2, CHCl$_3$).

methyl (2S,4R)-4-((8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((S)-hydroxy(phenyl)methyl)pentanoate (*iso*-4aq)

A white solid; Yield: 42% (64.5 mg); *dr* = 39/4.6/1/ND (concentration 0.2 M, DBU 4 eq, *ent*-**L13**, General procedure with *ent*-**L6** (short pad column by DCM/ MeOH = 10/1 before Methylation), SiO$_2$: Toluene/EtOAc = 2/1);

^{1}H NMR (400 MHz, CDCl$_3$): δ =0.72 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 3H), 1.00-1.25 (m, 3H), 1.37 (s, 3H), 1.45-1.61 (m, 2H), 1.90 -2.12 (m, 9H), 2.19-2.35 (m, 6H), 2.75-2.92 (m, 4H), 3.61 (s, 3H), 4.96 (d, *J* = 4.9 Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 11.6, 19.1, 21.8, 25.1, 27.4, 32.6, 35.2, 35.5, 36.0, 36.5, 38.5, 42.7, 44.9, 45.5, 46.2, 46.8, 48.9, 50.8, 51.6, 51.9, 56.9, 76.7, 126.0, 127.5, 128.2, 141.4, 176.3, 208.7, 209.0, 211.9; IR (KBr): 3439, 2952, 2878, 1709, 1434, 1386, 1360, 1273, 1164, 1022, 774, 703 cm^{-1}; LRMS (ESI): m/z 545 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{32}$H$_{42}$O$_6$ [M+Na]$^+$ 545.2874 Found 545.2847; [α]$_D^{17.5}$ = -8.6 (*c* = 0.88, CHCl$_3$).

methyl (4*R*)-2-(hydroxy(phenyl)methyl)-4-((3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*,17*R*)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (4ar)

A colorless oil; Yield: 68% (56.8 mg (TM)+23.0 mg (over reaction with TMSCHN$_2$)); *dr* = >20/1/<1/<1 (4 eq of (EtO)$_3$SiCl, 6 eq of DBU, 10 eq of PhCHO, General procedure A, SiO$_2$: grad. DCM/MeOH = 2% to 20%);

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.58 (s, 3H), 082 (s, 3H), 0.84 (d, *J* = 6.3 Hz, 3H), 1.03 (m, 1H), 1.14-1.20 (m, 3H), 1.35 (m, 3H), 1.46 (m, 4H), 1.59-1.70 (m, 5H), 1.79-1.87 (m, 4H) 2.07-2.19 (m, 2H), 2.80 (ddd, *J* = 2.7 Hz, 4.9 Hz, 11.2 Hz, 1H), 3.13 (br, 4H, O*H*), 3.38 (m, 1H), 3.47 (s, 3H), 3.77 (s, 1H), 3.87 (s, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 7.20-7.27 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 12.4, 17.2, 22.4, 23.2, 26.3, 27.6, 28.0, 29.2, 30.3, 34.0, 34.3, 34.5, 34.7, 35.2, 39.4, 41.4, 41.7, 46.4, 47.5, 51.2, 51.5, 68.4, 71.9, 73.1, 74.9, 126.1, 127.7, 128.2, 141.8, 175.3; IR (KBr): 3397, 1934, 2860, 1719, 1434, 1365, 1190, 1078, 1043, 908, 734, 700 cm^{-1}; LRMS (ESI): m/z 551 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{32}$H$_{48}$O$_6$ [M+Na]$^+$ 551.3343 Found 551.3341; [α]$_D^{17.5}$ = 36.1 (*c* = 0.62, CHCl$_3$).

methyl (2*S*,4*R*)-2-((*S*)-hydroxy(phenyl)methyl)-4-((3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*,17*R*)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (*iso*-4ar)

A colorless oil; Yield: 50% (53.0 mg); *dr* = >20/1/<1/<1 (4 eq of (EtO)$_3$SiCl, 6 eq of DBU, 10 eq of PhCHO, General procedure A, SiO$_2$: grad. DCM/MeOH = 2% to 20%);

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.51 (s, 3H), 084 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.93-1.11 (m, 4H), 1.35-1.75 (m, 14H), 1.90 (m, 2H), 2.11-2.20 (m, 2H), 2.52 (br, 4H, O*H*), 2.75 (dt, *J* = 5.2 Hz, 7.2 Hz, 1H), 3.43 (m, 1H), 3.57 (s, 3H), 3.80 (s 1H), 3.88 (s 1H), 4.91 (d, *J* = 5.2 Hz, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 12.4, 17.9, 22.4, 23.1, 26.5, 27.3, 28.1, 30.2, 33.3, 34.4, 34.6, 35.2, 35.3, 39.3, 39.4, 41.4, 41.7, 46.5, 47.7, 51.0, 51.8, 68.5, 72.2, 73.0, 74.1, 126.1, 127.6, 128.2, 141.5, 176.4; IR (KBr): 3393, 2937, 2869, 2243, 1720, 1436, 1376, 1195, 1166, 1078, 1043, 912, 732, 701 cm^{-1}; LRMS (ESI): m/z 551 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{32}$H$_{48}$O$_6$ [M+Na]$^+$ 551.3343 Found 551.3347; [α]$_D^{17.5}$ = -2.43 (*c* = 0.82, CHCl$_3$).

(*R*)-9-4-((2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-(((2*S*,3*S*)-3-((2*S*,3*S*)-3-hydroxybutan-2-yl)oxiran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)-3-methylbut-2-enoyl)oxy)-2-((*R*)-hydroxy(phenyl)methyl)nonanoic acid (3as)

A colorless oil; NMR Yield: 41%; *dr* = >20/1/<1/<1 (concentration was 0.2 M, 4 eq of (EtO)$_3$SiCl, 6 eq of DBU, 2 eq of PhCHO, 30 mol% of (AcO)$_4$B$_2$O and 60 mol% of **L13**). The reaction was carried out according to General procedure A, and was subjected to the following modified work-up/purification procedures at neutral pH: To the reaction mixture (stirred for 12 h at room temperature under an argon atmosphere) was added 4.2 eq of tetrabutylammonium difluorotriphenylsilicate, and the mixture was stirred for 5 minutes before it was quenched with H$_2$O (1.5 mL). Products were extracted with CH$_2$Cl$_2$/MeOH = 10:1, and filtered through celite covered with a thin layer of SiO$_2$ to remove excess tetrabutylammonium salts. The solvent was removed under reduced pressure and the NMR yield was determined by ^{1}H NMR in the presence of mesitylene as an internal standard. After yield calculation, the crude mixture was purified by SiO$_2$ column chromatography (MeOH/CH$_2$Cl$_2$ =

5% to 8%) to give **3as**.

^{1}H NMR (500 MHz, CD$_3$OD) : δ = 0.94 (d, *J* = 7.4 Hz, 3H), 1.19 (d, *J* = 6.3 Hz, 3H),1.28-1.35 (m, 9H), 1.59-1.68 (m, 6H), 1.92 (m, 1H), 2.15-2.17 (m, 5H), 2.63 (d, *J* = 13.7 Hz, 1H), 2.70 (dd, *J* = 7.4, 2.3 Hz, 1H), 2.80 (td, *J* = 5.9, 2.1 Hz, 1H), 3.36 (m, 1H, overlapped on reference peak), 3.55 (d, *J* = 10.3 Hz, 1H), 3.72-3.87 (m, 4H), 4.04 (t, *J* = 6.3 Hz, 2H), 4.78 (d, *J* = 6.9 Hz, 1H), 5.73 (br, 1H), 7.18-7.36 (m, 5H); ^{13}C NMR (125 MHz, CD$_3$OD): δ = 12.3, 19.2, 20.3, 26.2, 27.0, 28.6, 29.5, 29.8, 30.2, 30.3, 30.5, 33.0, 35.4, 41.7, 43.8, 43.9, 55.7, 56.9, 61.3, 64.8, 66.4, 70.0, 70.3, 70.7, 71.6, 76.2, 76.1, 118.3, 127.7, 128.4, 129.1, 144.4, 159.0, 168.4, 178.7; IR (KBr): 3421, 2928, 2856, 1710, 1643, 1461, 1400, 1227, 1151, 1055 cm^{-1}; LRMS (ESI): m/z 605.3 [M-H]$^-$; HRMS (ESI): m/z calcd for C$_{34}$H$_{52}$O$_{10}$ [M-H]$^-$ 605.3331, Found 605.3332; [α]$_D^{17.5}$ = -9.4 (*c* = 0.50, MeOH).

(*S*)-9-4-((2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-(((2*S*,3*S*)-3-((2*S*,3*S*)-3-hydroxybutan-2-yl)oxiran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)-3-methylbut-2-enoyl)oxy)-2-((*S*)-hydroxy(phenyl)methyl)nonanoic acid (*iso*-3as)

A colorless oil; NMR Yield: 56%; *dr* = >20/1/<1/<1 (concentration was 0.2 M, 4 eq of (EtO)$_3$SiCl, 6 eq of DBU, 2 eq of PhCHO, 30 mol% of (AcO)$_4$B$_2$O and 60 mol% of ***ent*-L13**). The reaction was carried out according to General procedure A, and was subjected to the modified work-up/purification procedures at neutral pH explained above for **3as**.

^{1}H NMR (500 MHz, CD$_3$OD) : δ = 0.94 (d, *J* = 7.4 Hz, 3H), 1.19 (d, *J* = 6.3 Hz, 3H),1.28-1.34 (m, 9H), 1.60-1.68 (m, 6H), 1.95 (m, 1H), 2.15-2.24 (m, 5H), 2.63 (dd, *J* = 15.5, 1.7 Hz, 1H), 2.70 (dd, *J* = 8.0, 2.3 Hz, 1H), 2.80 (td, *J* = 5.7, 2.3 Hz, 1H), 3.36 (m, 1H, overlapped on reference peak), 3.55 (d, *J* = 12.0 Hz, 1H), 3.74-3.78 (m, 4H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.75 (d, *J* = 7.4 Hz, 1H), 5.73 (br, 1H), 7.23-7.36 (m, 5H); ^{13}C NMR (125 MHz, CD$_3$OD): δ = 12.3, 19.2, 20.3, 27.0, 28.6, 29.6, 29.8, 29.8 30.1, 30.5, 30.9, 33.0, 34.3, 41.7, 43.8, 44.0, 55.6, 56.9, 61.3, 64.8, 66.4, 70.0, 70.3, 70.7, 71.6, 76.0, 76.2, 118.3, 127.8, 128.5, 129.1, 144.4, 159.0, 168.4, 178.1; IR (KBr): 3433, 2925, 2852, 1712, 1644, 1455, 1378, 1227, 1152, 1098 cm^{-1}; LRMS (ESI): m/z 605.3 [M-H]$^{+-}$; HRMS (ESI): m/z calcd for C$_{34}$H$_{52}$O$_{10}$ [M-H]$^-$ 605.3331, Found 605.3331; [α]$_D^{17.5}$ = -17.8 (*c* = 1.00, MeOH).

Determination of diastereo ratio of 5as and *iso*-3as

70

To a solution of **3as** or ***iso*-3as** (1.8 mg) in THF/MeOH = 2/1 (90 µL), 2 N NaOH aq. (15 µL) was added. The mixture was stirred at room temperature. After 3 h, the reaction mixture was acidified with 3 M HCl aq., and products were extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified by Pasteur column chromatography to give **3ak** as white solids.

The spectral data of the hydrolyzed product was identical to **3ak** prepared from **1a** and **2k**, while the diastereomer of **3ak** (*anti*-aldol product) was not detected by ^{1}H NMR analysis. Enantiopurity was determined by HPLC using the same conditions as **3ak.**

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%
1	Unknown	1	14.975	3731777	101838	96.011
2	Unknown	1	17.775	155063	3106	3.989

92% ee

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%
1	Unknown	1	15.092	157534	5263	2.776	3.610
2	Unknown	1	17.408	5517382	140542	97.224	96.390

94% ee

71

4. Synthesis and Characterization of Known/New Compounds

((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl)sulfonyl)-L-valine (L13)

To a solution of L-valine *tert*-butyl ester hydrochloride (5.0 g, 23.8 mmol) in DCM (100 mL), ^{i}PrNEt$_2$ (9.44 mL, 49.9 mmol) was added, and the mixture was stirred for 10 min. The solution was cooled to 0 °C, and then pentafluorobenzenesulfonyl chloride (3.19 mL, 21.67 mmol) was added dropwise at 0 °C. The solution was warmed to rt and stirred overnight. The reaction was quenched with sat. NaHCO$_3$ aq. The product was extracted with DCM. The combined organic layer was washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and purified by silica gel column chromatography to give the title product as a white powder (5.47 g, 63% yield).

To a solution of *tert*-butyl ((perfluorophenyl)sulfonyl)-L-valinate (2.42 g, 6 mmol) in toluene (30 mL), dimethylamine solution, 2 M dimethylamine in THF (15 mL, 30 mmol) was added, and the mixture was stirred overnight. H$_2$O was added to the reaction mixture and the product was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the crude mixture was roughly purified by short pad silica gel column chromatography to give the colorless oil, which was used in next reaction without further purification. To a solution of the ester in DCM (5 mL), TFA (5 mL) was added and stirred overnight. The mixture was concentrated under reduced pressure. The title compound was purified by recrystallization from EtOAc/Hex (2.05 g, 55%, 2 steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.91 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 2.25 (m, 1H), 3.07 (t, J = 2.7 Hz, 6H), 4.08 (dd, J = 4.5 Hz, 9.9 Hz, 1H), 5.58 (d, J = 9.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 16.9, 19.0, 31.3, 42.9, 60.9, 108.4 (t, $^2J_{F-C}$ = 14.4 Hz), 135.4 (t, $^2J_{F-C}$ = 14.4 Hz), 140.0 (dtt, $^1J_{F-C}$ = 248.3 Hz, $^2J_{F-C}$ = 16.8 Hz, $^3J_{F-C}$ = 4.8 Hz), 145.0 (dtt, $^1J_{F-C}$ = 254.3 Hz, $^2J_{F-C}$ = 12.0 Hz, $^3J_{F-C}$ = 6.0 Hz), 176.1; ^{19}F NMR (368 MHz, CDCl3): δ = -151.7 (d, J = 22.8 Hz, 2F), -139.5 (d, J = 22.8 Hz, 2F); IR (KBr): 3273, 2969, 1720, 1628, 1530, 1485, 1439, 1356, 1246, 1168, 1082, 977 cm^{-1}; LRMS (ESI): m/z 371 [M-H]$^-$; HRMS (ESI): m/z calcd for C$_{13}$H$_{16}$F$_4$N$_2$O$_4$S [M-H]$^-$ 371.0694 Found 371.0707; [α]$_D$$^{17.5}$ = 38.8 (c = 1.86, CHCl$_3$).

tert-butyl ((2,4,6-trifluorophenyl)sulfonyl)-L-valinate
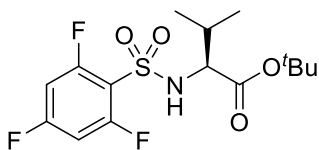
86% yield, ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.85 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.27 (s, 9H), 2.11 (m, 1H), 3.84 (dd, J = 10.3, 4.6 Hz, 1H), 5.60 (d, J = 10.3 Hz, NH), 6.74 (t, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 16.9, 18.9, 27.6, 31.4, 61.5, 82.5, 101.7 (ddd, $^2J_{\text{F-C}}$ = 27.4 Hz, $^2J_{\text{F-C}}$ = 29.8 Hz, $^4J_{\text{F-C}}$ = 4.8 Hz), 114.9 (dt, $^2J_{\text{F-C}}$ = 16.7 Hz, $^4J_{\text{F-C}}$ = 4.8 Hz), 160.5 (ddd, $^1J_{\text{F-C}}$ = 258.7 Hz, $^3J_{\text{F-C}}$ = 7.2 Hz, $^3J_{\text{F-C}}$ = 15.5 Hz), 164.9 (dt, $^1J_{\text{F-C}}$ = 256.3 Hz, $^3J_{\text{F-C}}$ = 15.5 Hz), 169.8; ^{19}F NMR (368 MHz, CDCl$_3$): δ = -103.1 (t, J = 11.2 Hz, 2F), -99.7 (t, J = 11.2 Hz, 1F); IR (KBr): 3333, 3091, 2968, 1612, 1360, 1158, 1041, 869 cm^{-1}; LRMS (ESI): m/z 390 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{15}$H$_{20}$F$_3$NO$_4$S [M+Na]$^+$ 390.0963 Found 390.0958. [α]$_\text{D}^{28.3}$ = +35.7 (c = 0.23, CHCl$_3$).

((2,4,6-trifluorophenyl)sulfonyl)-L-valine (L8)
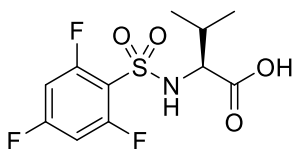
100% yield, ^{1}H NMR (500 MHz, CDCl$_3$): δ 0.91 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 2.18-2.27 (m, 1H), 4.07 (dd, J = 9.7, 4.6 Hz, 1H), 5.74-5.77 (m, 1H), 6.76 (t, J = 8.6 Hz, 2H), 10.24 (s, COOH); ^{13}C NMR (125 MHz, CDCl$_3$): δ 16.9, 18.9, 31.2, 61.0, 101.9 (ddd, $^2J_{\text{F-C}}$ = 25.0 Hz, $^2J_{\text{F-C}}$ = 28.6 Hz, $^4J_{\text{F-C}}$ = 3.6 Hz), 114.9 (dt, $^2J_{\text{F-C}}$ = 16.7 Hz, $^4J_{\text{F-C}}$ = 6.0 Hz), 160.5 (ddd, $^1J_{\text{F-C}}$ = 258.7 Hz, $^3J_{\text{F-C}}$ = 6.0 Hz, $^3J_{\text{F-C}}$ = 15.5 Hz), 165.1 (dt, $^1J_{\text{F-C}}$ = 257.5 Hz, $^3J_{\text{F-C}}$ = 15.5 Hz), 176.2; ^{19}F NMR (368 MHz, CDCl3): δ = -102.6 (s, 2F), -98.1 (s, 1F); IR (KBr): 3855, 2978, 1741, 1609, 1449, 1185, 854 cm^{-1}; LRMS (ESI): m/z 334 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{11}$H$_{12}$F$_3$NO$_4$S [M+Na]$^+$ 334.0337 Found 334.0348; [α]$_\text{D}^{28.0}$ = +42.6 (c = 0.30, CH$_3$Cl).

((perfluorophenyl)sulfonyl)-L-valine (L9)
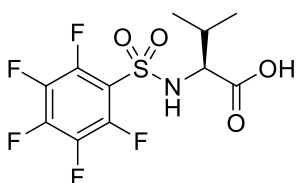
73% (after recrystallization) ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.92 (d, J = 7.2 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 2.30 (m, 1H), 4.17 (dd, J = 4.0 Hz, 9.7 Hz, 1H), 5.64 (d, J = 9.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): ^{13}C NMR (125 MHz, CDCl$_3$): δ = 16.8, 18.9, 31.2, 61.3, 116.2 (tt, $^2J_{\text{F-C}}$ = 16.9 Hz, $^3J_{\text{F-}}$

$_C$ = 4.7 Hz), 137.7 (dddd, $^1J_{F-C}$ = 256.5 Hz, $^2J_{F-C}$ = 16.0 Hz, $^2J_{F-C}$ = 13.2, Hz, $^3J_{F-C}$ = 12.2 Hz), 144.1 (dddd, $^1J_{F-C}$ = 263.1 Hz, $^2J_{F-C}$ = 17.9 Hz, $^3J_{F-C}$ = 4.7 Hz), 144.5 (dtt, $^1J_{F-C}$ = 254.6 Hz, $^2J_{F-C}$ = 14.1 Hz, $^3J_{F-C}$ = 4.7, Hz), 175.7; ^{19}F NMR (368 MHz, CDCl3): δ = -158.6 (d, J = 22.8 Hz, 2F), -145.1 (t, J = 22.8 Hz, 1F), -136.0 (d, J = 22.8 Hz, 2F); IR (KBr): 3343, 3217, 2965, 1734, 1502, 1400, 1295, 1180, 1134, 1101, 993 cm^{-1}; LRMS (ESI): m/z 346 [M-H]$^-$; HRMS (ESI): m/z calcd for $C_{11}H_{10}F_5NO_4S$ [M-H]$^-$ 346.0178 Found 346.0191 [α]$_D^{17.5}$ = 31.0 (c = 2.34, CHCl$_3$).

5. Mechanistic Studies

Acceleration by Silyl ester Formation in Mannich and Allylation Reactions

Mannich-Type Reaction
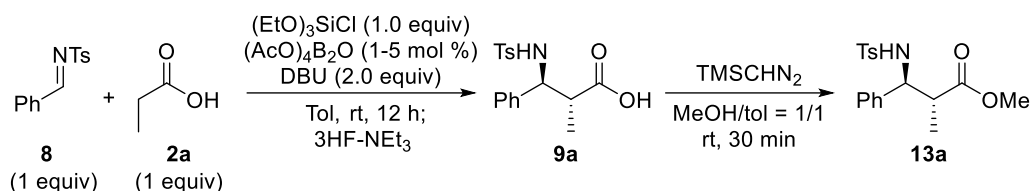
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with propionic acid (**2a**; 22.2 µL, 0.3 mmol), chlorotriethoxysilane (58.9 µL, 0.3 mmol) and DBU (89.6 µL, 0.6 mmol) in anhydrous toluene (500 µL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (0.8 mg, 0.003 mmol) in anhydrous toluene (500 µL). After stirring for 0.5 h, a solution of test tube B and *N*-benzylidene-2-methylpropane-2-sulfonamide (**8**; Ts-Imine, 77.8 mg, 0.3 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude product.

Subsequent methyl esterification was carried out without further purification. To a solution of crude **9a** in MeOH (1.0 mL) and toluene (1.0 mL) was added TMSCHN$_2$ (1.0 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra grad; EtOAc/Hex; 6% to 50%, affording to **13a** as 63.3 mg, (62% yield, 2.8/1 dr).

The spectral data of **13a** was identical with the reported values[7].

methyl (*E*)-2-((4-chlorophenyl)((4-methylphenyl)sulfonamido)methyl)-6-(4,6-dimethoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (13m)
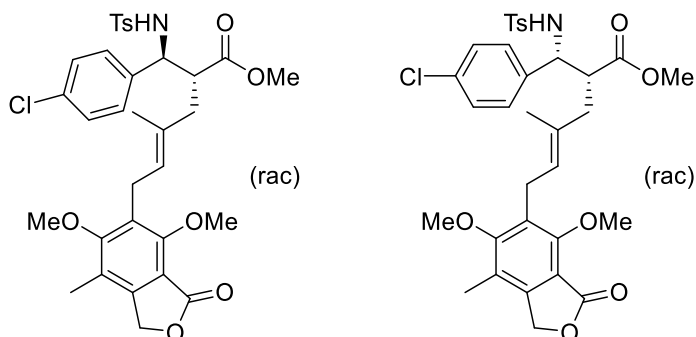
A colorless oil; Yield: 59% (125.1 mg); *dr* = 1.1/1 (2 eq of $(EtO)_3SiCl$, 5 mol% of $(AcO)_4B_2O$ and 3 eq of DBU, SiO_2: grad. EtOAc/hexane = 8% to 66%);

(diastereomer-1, stereochemistry not determined)

^{1}H NMR (500 MHz, CDCl$_3$) : δ = 1.77 (s, 3H), 2.17 (s, 3H), 2.21 (dd, *J* = 6.3 Hz, 14.3 Hz, 1H), 2.31 (s, 3H), 2.35 (m, 1H), 2.78 (m, 1H), 3.39 (d, *J* = 6.9 Hz, 2H), 3.42 (s, 3H), 3.79 (s, 3H), 4.05 (s, 3H), 4.52 (dd, *J* = 4.6 Hz, 9.2 Hz, 1H), 5.13 (s, 2H), 5.25 (t, *J* = 6.9 Hz, 1H), 6.09 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.00-7.04 (m, 4H), 7.35 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 11.5, 16.0, 21.3, 23.5, 40.3, 50.1, 51.7, 57.6, 61.1, 62.6, 68.3, 112.4, 120.0, 126.6, 126.7, 127.7, 128.4, 128.5, 129.1, 130.9, 133.2, 137.6, 137.8, 143.0, 146.7, 156.7, 162.8, 168.9, 174.2; IR (KBr): 3508, 3273, 2991, 2948, 2869, 1757, 1739, 1722, 1598, 1448, 1359, 1334, 1317, 1195, 1161, 1126, 1091, 1039, 970, 913, 812, 667 cm^{-1}; LRMS (ESI): m/z 664 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{33}$H$_{36}$ClNO$_8$S [M+Na]$^+$ 664.1742 Found 664.1775.

(diastereomer-2, stereochemistry not determined)

^{1}H NMR (500 MHz, CDCl$_3$) : δ = 1.71 (s, 3H), 2.14 (s, 3H), 2.30 (dd, *J* = 7.4 Hz, 8.3 Hz, 1H), 2.35 (s, 3H), 2.89 (dd, *J* = 7.4 Hz, 7.7 Hz, 1H), 3.32 (s, 1H), 3.36 (d, *J* = 6.9 Hz, 2H), 3.75 (s, 3H), 4.03 (s, 3H), 4.40 (dd, *J* = 7.7 Hz, 8.3 Hz, 1H), 5.13 (m, 3H), 5.57 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.00-7.09 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 11.5, 15.9, 21.4, 23.4, 38.6, 50.3, 51.6, 58.2, 61.0, 62.6, 68.3, 120.0, 126.1, 127.0, 128.3, 128.4, 128.5, 129.1, 129.3, 131.6, 133.6, 136.5, 137.1, 143.4, 146.8, 156.7, 162.7, 168.9, 172.6; IR (KBr): 3264, 2987, 2948, 2864, 1757, 1743, 1713, 1598, 1434, 1360, 1321, 1160, 1129, 1090, 1036, 913, 814, 662 cm^{-1}; LRMS (ESI): m/z 664 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{33}$H$_{36}$ClNO$_8$S [M+Na]$^+$ 664.1742 Found 664.1778.

Allylation

(e)
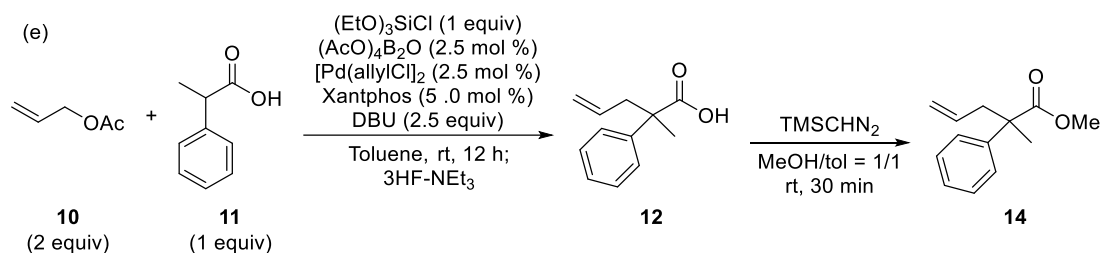
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with 2-ph propionic acid (**11**; 41.0 µL, 0.3 mmol), chlorotriethoxysilane (58.9 µL, 0.3 mmol) and DBU (111.9 µL, 0.75 mmol) in anhydrous toluene (500 µL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (2.1 mg, 0.0075 mmol), [Pd(allyl)Cl]$_2$ (2.7 mg, 0.0075 mmol) and Xantphos (8.7 mg, 0.015 mmol) in anhydrous toluene (500 µL). After stirring for 0.5 h, a yellow suspension of test tube B and allyl acetate (**10**, 64.6 µL, 0.6 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude product.

Subsequent methyl esterification was carried out without further purification. To a solution of crude **12** in MeOH (1.0 mL) and toluene (1.0 mL) was added TMSCHN$_2$ (1.0 M in hexane) until generation of H$_2$ stopped. After stirring for 30 min at room temperature, a few drops of acetic acid were added. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra grad; EtOAc/Hex; 2% to 20%, affording to **14** as 55.3 mg, (89% yield). The spectral data of **14** was identical with the reported values[8].

Inhibitory Effects of Carboxylate
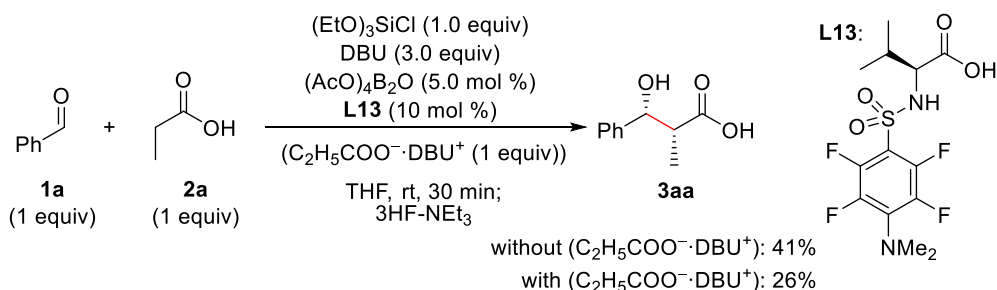
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with propionic acid (**2a**; 0.2 or 0.4 mmol), chlorotriethoxysilane (39.3 µL, 0.2 mmol) and DBU (0.6 or 0.8 mmol) in

anhydrous THF (0.5 mL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (2.7 mg, 0.01 mmol), ((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl) sulfonyl)-$_L$-valine (**L13**; 7.4 mg, 0.02 mmol) and anhydrous THF (0.5 mL). After stirring for 0.5 h, a solution of test tube B and benzaldehyde (**1a**, 20.3 µL, 0.2 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 30 min at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (3**aa**).

Non-linear Effects experiments

(a) aldol reaction
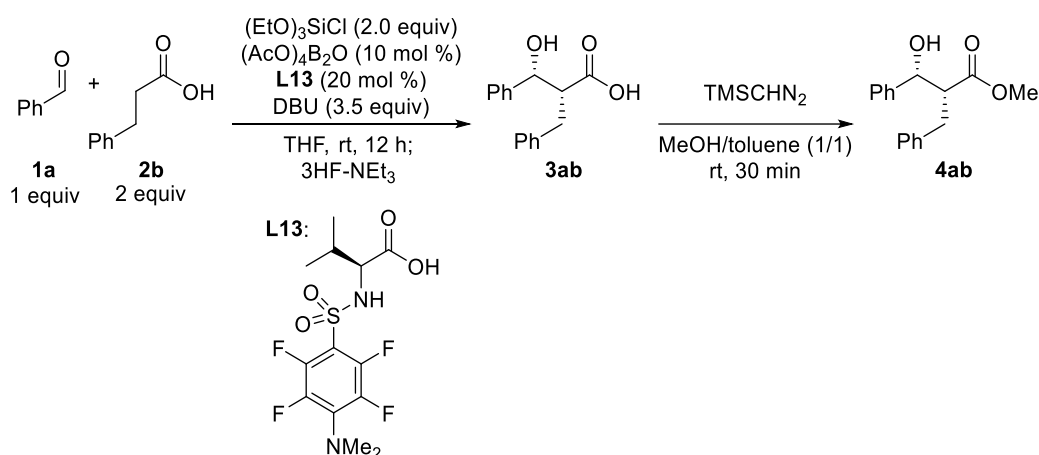
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with 3-phenylpropionic acid (**2b**; 60.1 mg, 0.4 mmol), chlorotriethoxysilane (78.5 µL, 0.4 mmol) and DBU (104.5 µL, 0.7 mmol) in anhydrous THF (0.5 mL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (5.5 mg, 0.02 mmol), ((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl) sulfonyl)-L-valine (**L13**; 14.9 mg, 0.04 mmol) and anhydrous THF (0.5 mL). After stirring for 0.5 h, a solution of test tube B and benzaldehyde (**1a**, 20.3 µL, 0.2 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (3**ab**).

Subsequent methyl esterification was carried out without further purification. To a solution of crude **4ab** in MeOH (1.0 mL) and toluene (1.0 mL) was added TMSCHN$_2$ (1.0 M in hexane) until the color

of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra. Determined ees were shown in the table.

y = 0.8914x + 0.4286
R² = 0.9997

ee of L13	ee of 4ab
0%	0%
20%	19%
40%	36%
60%	54%
80%	71%
100%	90%
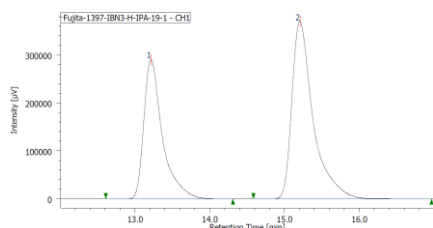
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%
1	Unknown	1	13.217	5007559	290891	40.666
2	Unknown	1	15.208	7306337	370336	59.334

with 20% ee of L13

78
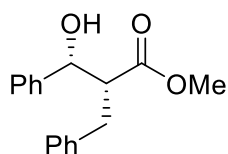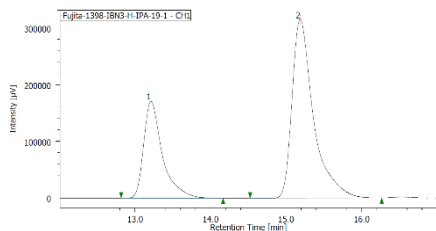
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	13.208	2925217	170644	32.046
2	Unknown	1	15.192	6202855	315692	67.954

with 40% ee of **L13**
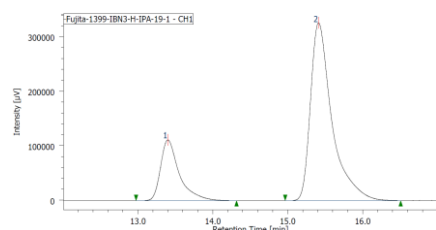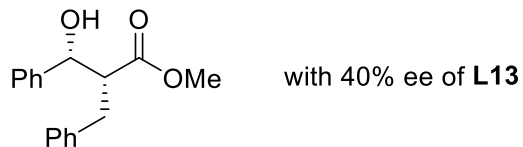
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	13.400	1922521	111501	22.864
2	Unknown	1	15.408	6485815	326578	77.136

with 60% ee of **L13**
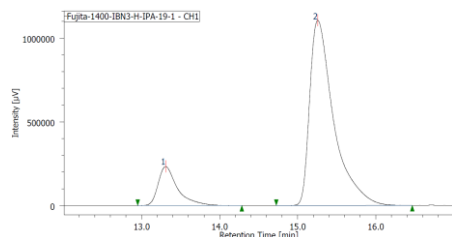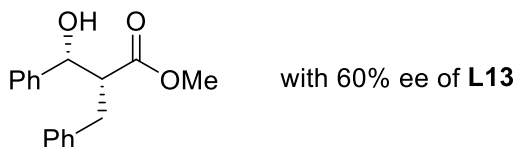
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	13.308	3987259	233039	14.485
2	Unknown	1	15.258	23539762	1106500	85.515

with 80% ee of **L13**
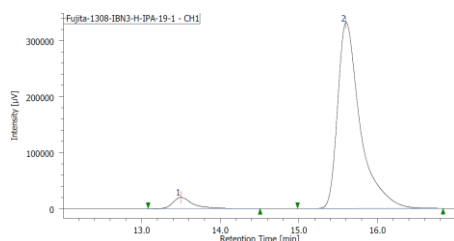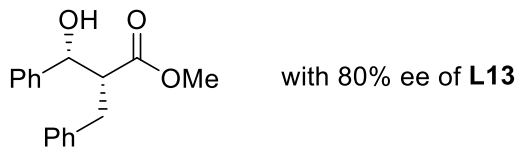
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	13.500	343263	20062	4.964
2	Unknown	1	15.600	6571283	331878	95.036

with 100% ee of **L13**
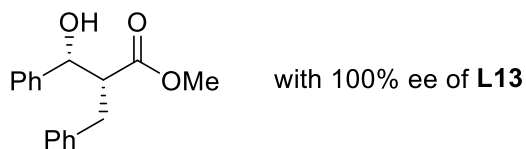
(b) Mannich reaction

Condition A
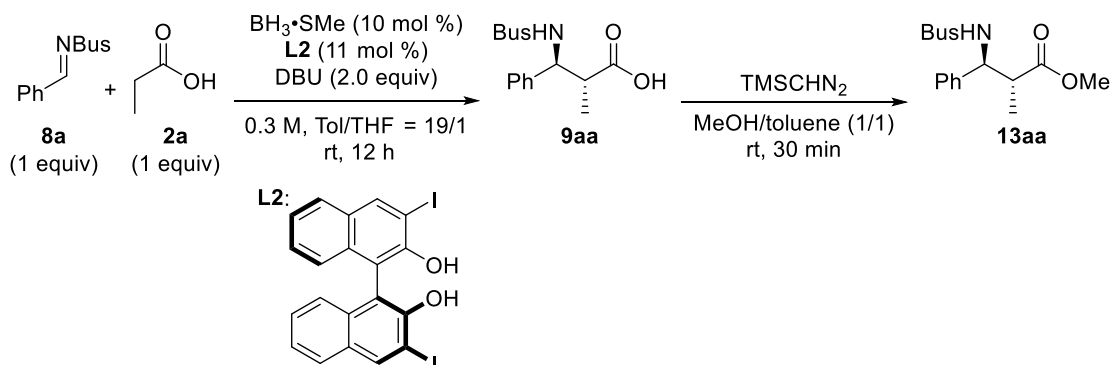
A flame-dried 10 mL test tube, equipped with a magnetic stirring bar, was charged with (*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-diol (**L2**; (*S*)-I_2-BINOL, 17.8 mg, 0.033 mmol) in anhydrous toluene (950 µL) and THF (50 µL). To the solution, borane–dimethyl sulfide complex [1 M in 2-Me THF (30 µL, 0.03 mmol)] was added slowly. After stirring for 1 h, propionic acid (**2a**; 22.2 µL, 0.3 mmol) was added to the solution. After stirring for 0.5 h, *N*-benzylidene-2-methylpropane-2-sulfonamide (**8a**; Bus-Imine, 67.6 mg, 0.3 mmol) was added to a reaction mixture. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product.

Subsequent methyl esterification was carried out without further purification. To a solution of crude **9aa** in MeOH (1.0 mL) and toluene (1.0 mL) was added $TMSCHN_2$ (1 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra. Determined ee was shown in the table.

HPLC (chiral column: CHIRALPAK IBN5; solvent: hexane/2-propanol = 19/1; flow rate: 1.0 mL/min; detection: at 210 nm; rt): t_R = 9.8 min (major) and 12.3 min (mimor).

ee of **L2** (%)	ee of **13aa** (%)
0	0
20	25
40	51
60	65
80	79
100	95
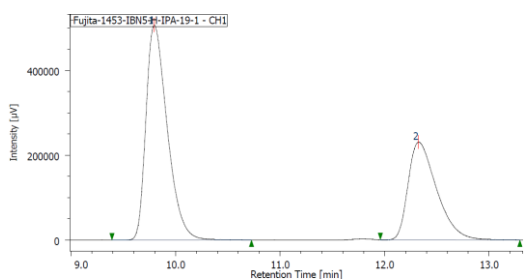
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.792	7171778	507471	62.191
2	Unknown	1	12.325	4360014	230629	37.809

with 20% ee of **L2**
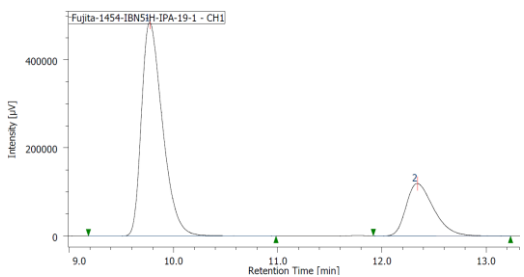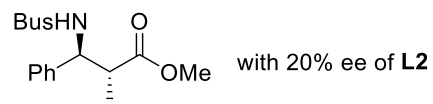
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.775	6812969	485715	75.678
2	Unknown	1	12.342	2189642	119351	24.322

with 40% ee of **L2**
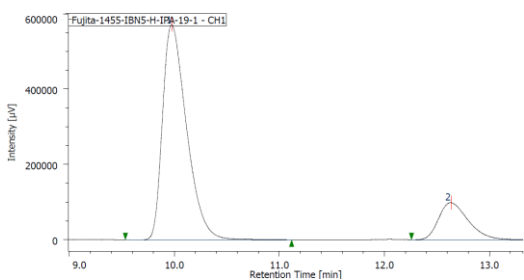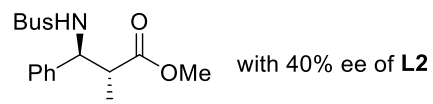
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.975	9075381	571807	82.429
2	Unknown	1	12.633	1934507	98408	17.571

with 60% ee of **L2**
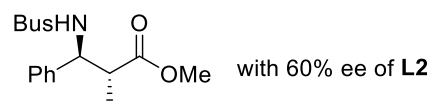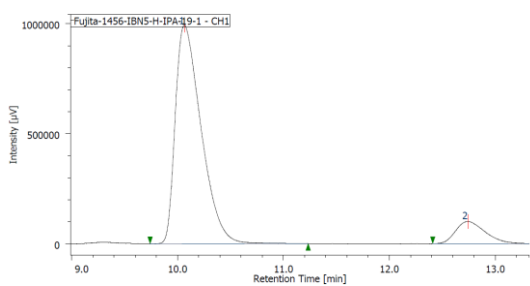
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	10.067	16785722	991926	89.457
2	Unknown	1	12.742	1978345	100754	10.543

with 80% ee of **L2**
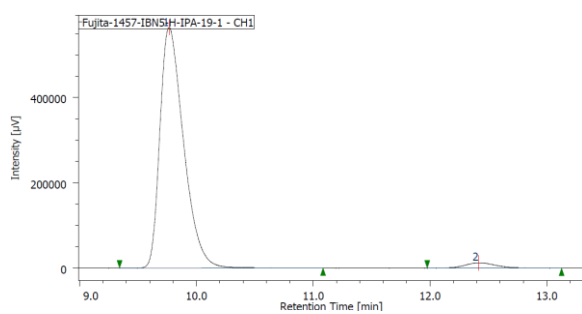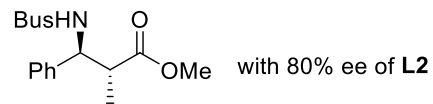
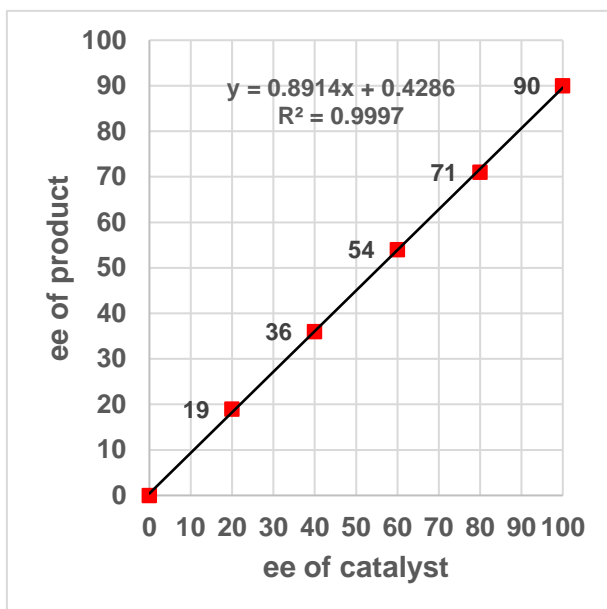| #	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.767	7927737	564884	97.257
2	Unknown	1	12.417	223562	12268	2.743
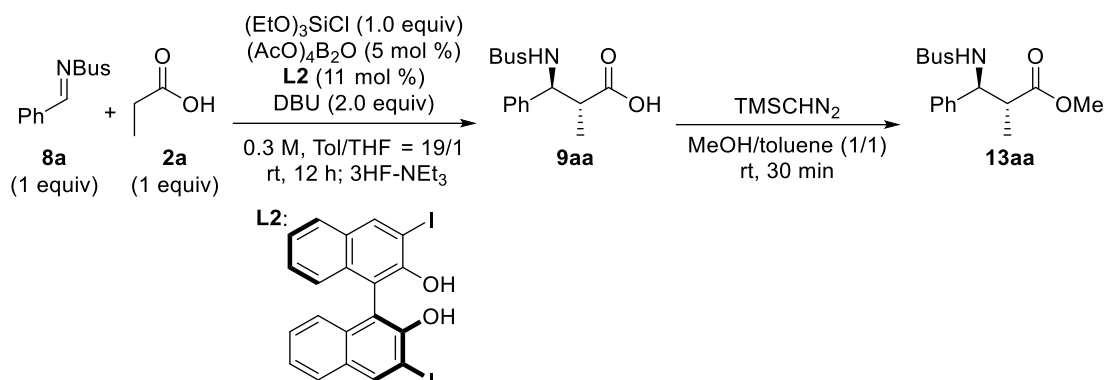
with 100% ee of **L2**

Condition B


A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with propionic acid (**2a**; 22.2 µL, 0.3 mmol), chlorotriethoxysilane (58.9 µL, 0.3 mmol) and DBU (89.6 µL, 0.6 mmol) in anhydrous toluene (475 µL) and THF (25 µL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (4.1 mg, 0.015 mmol) and (*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-diol (**L2**; (*S*)-I_2-BINOL, 17.8 mg, 0.033 mmol) in anhydrous toluene (475 µL) and THF (25 µL). After stirring for 0.5 h, a solution of test tube B and *N*-benzylidene-2-methylpropane-2-sulfonamide (**8a**; Bus-Imine, 67.6 mg, 0.3 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product.

Subsequent methyl esterification was carried out without further purification. To a solution of crude **9aa** in MeOH (1.0 mL) and toluene (1.0 mL) was added $TMSCHN_2$ (1.0 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra. Determined ee was shown in the table.

ee of **L2**(%)	ee of **13aa**(%)
0	0
20	21
40	41
60	57
80	74
100	90
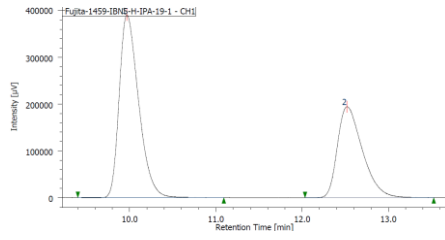
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.967	6097348	390832	60.955
2	Unknown	1	12.517	3905672	194515	39.045

BusHN / Ph / O / OMe — with 20% ee of **L2**
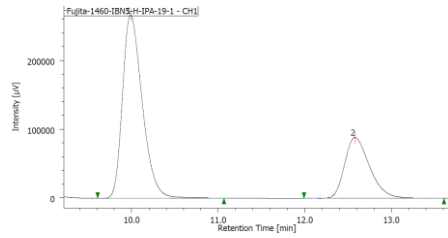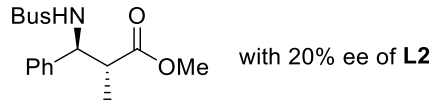
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.992	4217607	267022	70.468
2	Unknown	1	12.583	1767537	88544	29.532

BusHN / Ph / O / OMe — with 40% ee of **L2**
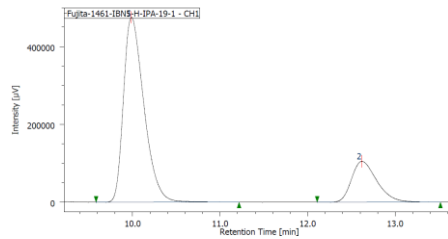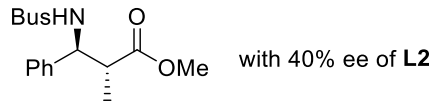
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.983	7701058	475308	78.478
2	Unknown	1	12.617	2111905	104959	21.522

BusHN / Ph / O / OMe — with 60% ee of **L2**
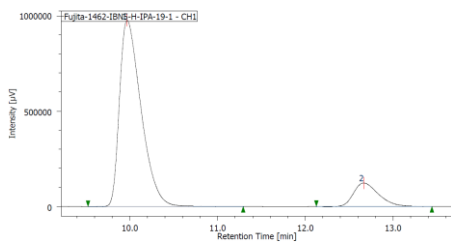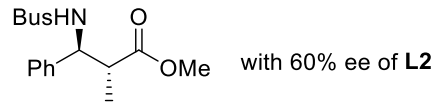
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	9.967	16602622	976028	87.180
2	Unknown	1	12.667	2441429	123168	12.820

BusHN / Ph / O / OMe — with 80% ee of **L2**
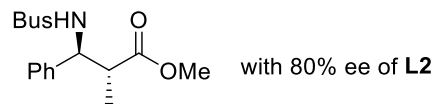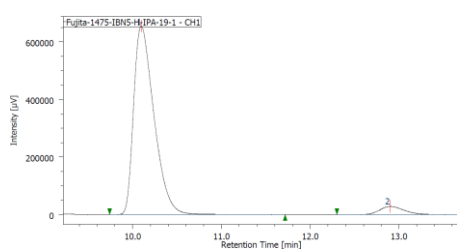
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	10.100	10429326	654723	95.014
2	Unknown	1	12.900	547324	28344	4.986

with 100% ee of **L2**
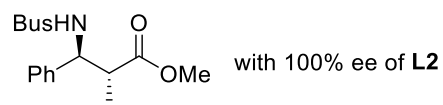
6. Screening of Silyl Source

Si source (1 equiv)
DBU (3 equiv)
$BH_3 \cdot SMe_2$ (10 mol %)
L13 (20 mol %)
0.2 M, Tol, rt, 12 h;
$3HF\text{-}NEt_3$

1a (2 equiv) + **2a** (1 equiv) → **3aa**

L13:

entry	Silyl source	yield	dr
1	-	21%	1.6/1
2	TMSCl	35%	1.1/1
3	TESCl	8%	1/1.5
4	TIPSCl	4%	1/1.3
5	TBDPSCl	3%	1.3/1
6	$(EtO)_3SiCl$	46%	1.5/1
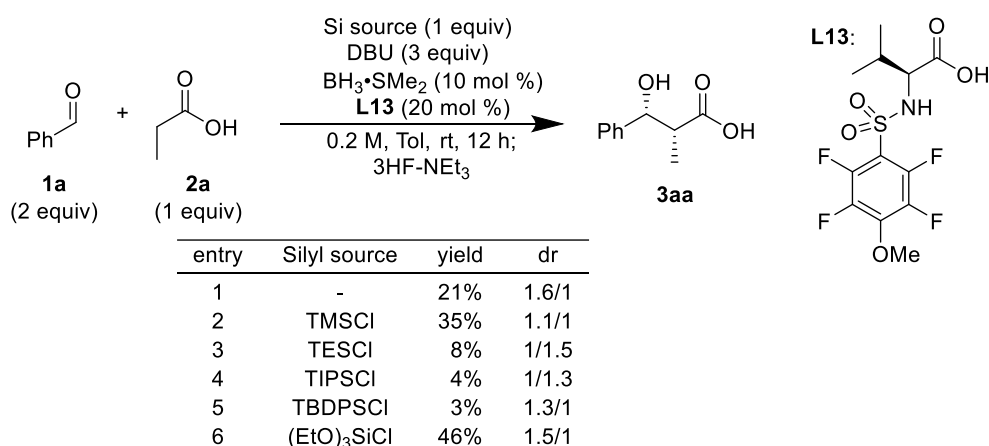
A frame-dried 10 mL test tube, equipped with a magnetic stirring bar, was charged with BH_3–SMe_2 (20 μL of 2 M DCM solution, 0.04 mmol), ((4-(methoxy)-2,3,5,6-tetrafluorophenyl) sulfonyl)-L-valine (**L13**; 14.4 mg, 0.04 mmol) in anhydrous toluene (1.0 mL). After stirring for 0.5 h, propionic acid (**2a**; 14.8 μL, 0.2 mmol) was added to a reaction mixture. After stirring for 0.5 h, chlorosilane (0.2 mmol), DBU (90 μL, 0.6 mmol) and benzaldehyde (**1a**, 20.3 μL, 0.2 mmol) were added sequentially. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (**3aa**).

7. Reaction with Silyl Esters

a) NMR analysis for siloxy ester formation
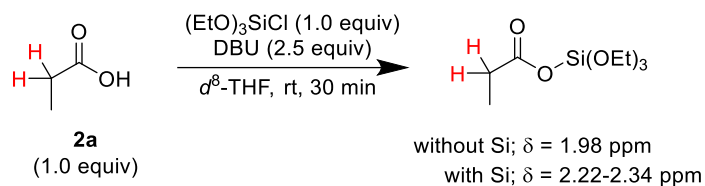
2a
(1.0 equiv)

without Si; δ = 1.98 ppm
with Si; δ = 2.22-2.34 ppm

A flame-dried 10 mL test tube, equipped with a magnetic stirring bar, was charged with propionic acid (**4a**; 14.8 µL, 0.2 mmol), chlorotriethoxysilane (39.3 µL, 0.2 mmol) and DBU (74.6 µL, 0.5 mmol) in d_8-THF (0.5 mL). After stirring for 0.5 h, crude reaction mixture was analyzed by NMR. ^{1}H NMR showed full conversion of **4a** to the corresponding siloxy ester.

b) Reaction using silyl ester

1a
(1 equiv)

5
(2 equiv)

3aa
40%, dr = 2.0/1, 81% ee
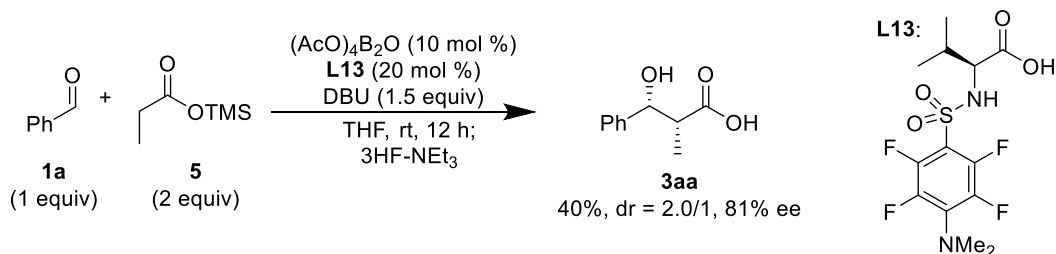
A flame-dried 10 mL test tube A, equipped with a magnetic stirring bar, was charged with TMS propionate **5** (105 µL, 0.6 mmol) and DBU (67.2 µl, 0.45 mmol) in anhydrous THF (2.0 mL). Another frame-dried 10 mL test tube B, equipped with a magnetic stirring bar, was charged with tetraacetoxy diboroxane (8.2 mg, 0.03 mmol), ((4-(methoxy)-2,3,5,6-tetrafluorophwnyl) sulfonyl)-L-valine (**L13**; 22.3 mg, 0.06 mmol) and anhydrous THF (1.0 mL). After stirring for 0.5 h, a solution of test tube B and benzaldehyde **1a** (30.5 µL, 0.3 mmol) were added sequentially to a test tube A. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere. Subsequently, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were washed with aqueous HCl (1 M), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (**3aa**).

Subsequent methyl esterification was carried out without further purification. To a solution of crude **3aa** in MeOH (0.5 mL) and toluene (0.5 mL) was added TMSCHN$_2$ (1.0 M in hexane) until the color of the solution became yellow. After stirring for 30 min at room temperature, a few drops of acetic acid were added until the yellow color of the solution disappeared. The solvent was evaporated under reduced pressure and the remaining residue was purified by Biotage Isolera One and Biotage SNAP Ultra. This result supports our working hypothesis that the reaction proceeds from silyl ester.

8. Computed pK_a Values

32.6 H—CH$_2$—C(=O)—OLi   28.4 H—CH$_2$—C(=O)—N(Me)$_2$ 26.0 H—CH$_2$—C(=O)—O—tBu   24.7 H—CH$_2$—C(=O)—CH$_3$

25.0   H—CH$_2$—C(=O)—O—Si(Me)$_2$Me

18.3   H—CH$_2$—C(=O)—O—B(O—C(=O)CH$_3$)$_2$

19.6   H—CH$_2$—C(=O)—O—Si(OEt)$_3$

13.6   Ar$_F$ = 4-NMe$_2$-C$_6$F$_4$
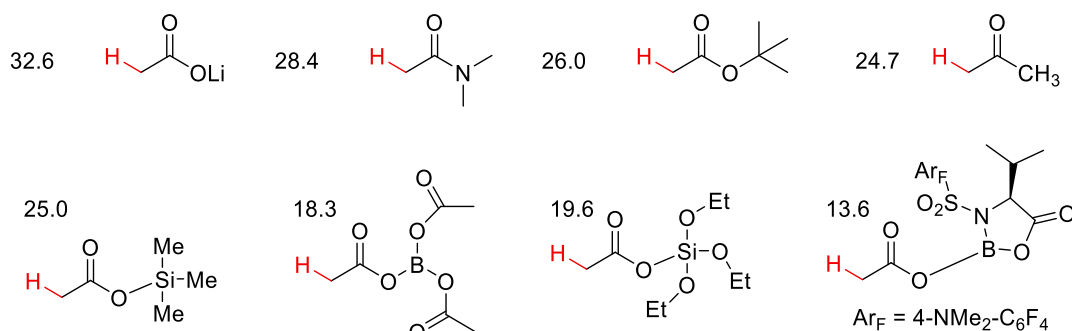
According to the literature[9], the gas-phase ΔG° of the acid dissociation and pK_a of various carbonyl groups were calculated by Gaussian 16[10] (B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)).

9. NMR Analysis of Enediolate Structure

2b (Ph-CH$_2$-CH$_2$-COOH), 1 equiv

1) (EtO)$_3$SiCl (1.0 equiv)
NEt$_3$ (4 equiv)
2) Cy$_2$BOTf (1.1 equiv)

d_8-toluene, rt, 30 min

→ E (determined by NOE) + Z

E/Z = 1.7 / 1
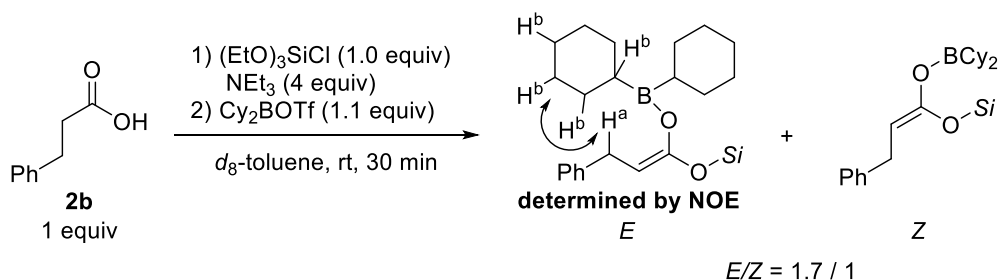
A flame-dried 4 mL test tube, equipped with a magnetic stirring bar, was charged with propionic acid (2b; 15.0 mg, 0.1 mmol), (EtO)$_3$SiCl (0.1 mmol) and NEt$_3$ (55.8 µL, 0.5 mmol) in anhydrous d_8-toluene (250 µL). After stirring for 0.5 h, Cy$_2$BOTf (35.9 mg, 0.11 mmol) was added to the solution. The reaction mixture was stirred for 30 min at room temperature under an argon atmosphere. Subsequently, the reaction mixture was analyzed by ^{1}H NMR in d_8-toluene.

For the (EtO)$_3$Si ester, a mixture of E/Z enediolates were produced in a 1.7/1 ratio (Chart A). Stereochemistry of the enediolate was determined by NOE experiments by irradiating benzylic protons (H^a). Irradiating H^a of the major compound, NOE was observed at the cyclohexyl protons (Chart B). Irradiating H^a of the minor compound, however, NOE was not observed at all at the cyclohexyl protons (Chart C). Therefore, stereochemistry of the major and minor enediolates was determined to be E and Z, respectively.
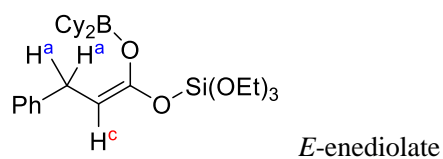
E-enediolate

^{1}H NMR (500 MHz, d_8-toluene): δ = 1.65-1.73 (m, Cy proton), 3.29 (d, *J* = 7.4 Hz, 2H^a), 4.62 (t, *J* = 7.4 Hz, H^c).
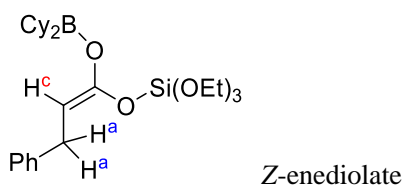
Z-enediolate

^{1}H NMR (500 MHz, d_8-toluene): δ = 1.65-1.73 (m, Cy proton), 3.25 (d, *J* = 7.4 Hz, H^a), 4.39 (t, *J* = 7.4 Hz, H^c).

Chart A. NMR chart of the reaction mixture of enediolate formation from the (EtO)$_3$Si ester and Cy$_2$BOTf.

88
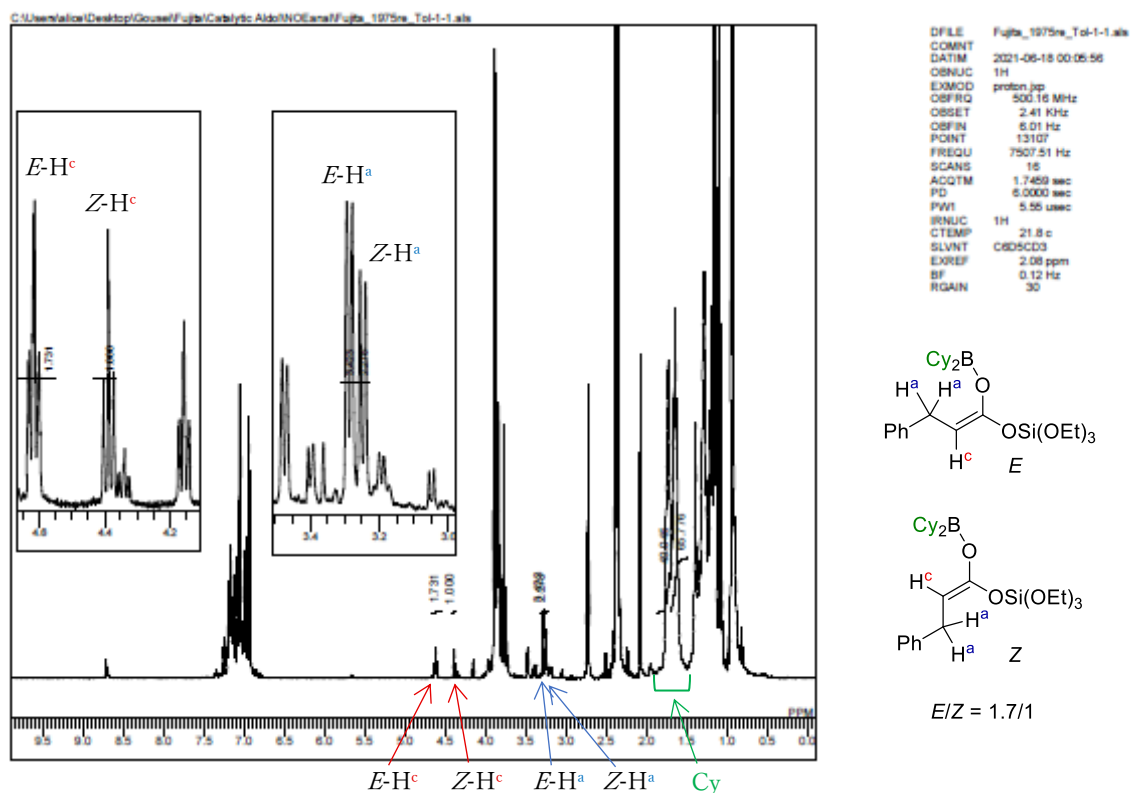
Chart B. NOE measurement by irradiating benzylic protons Hᵃ of the major enediolate.
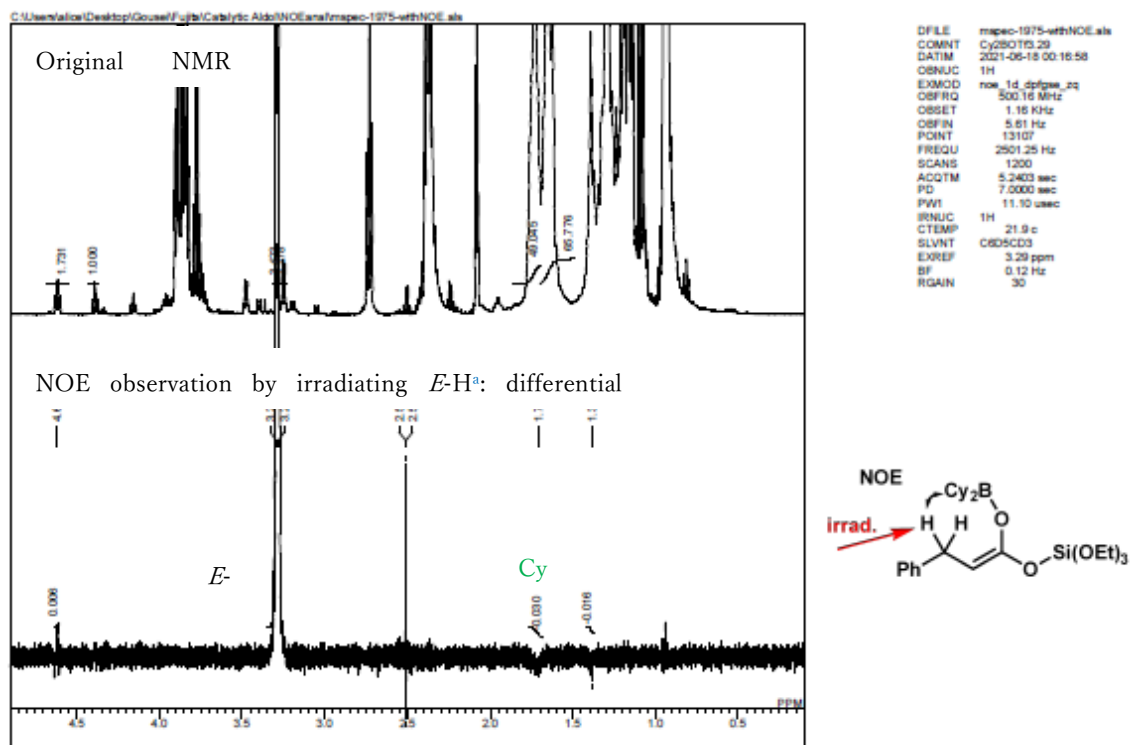
Chart C. NOE measurement by irradiating benzylic protons Hᵃ of the minor enediolate.
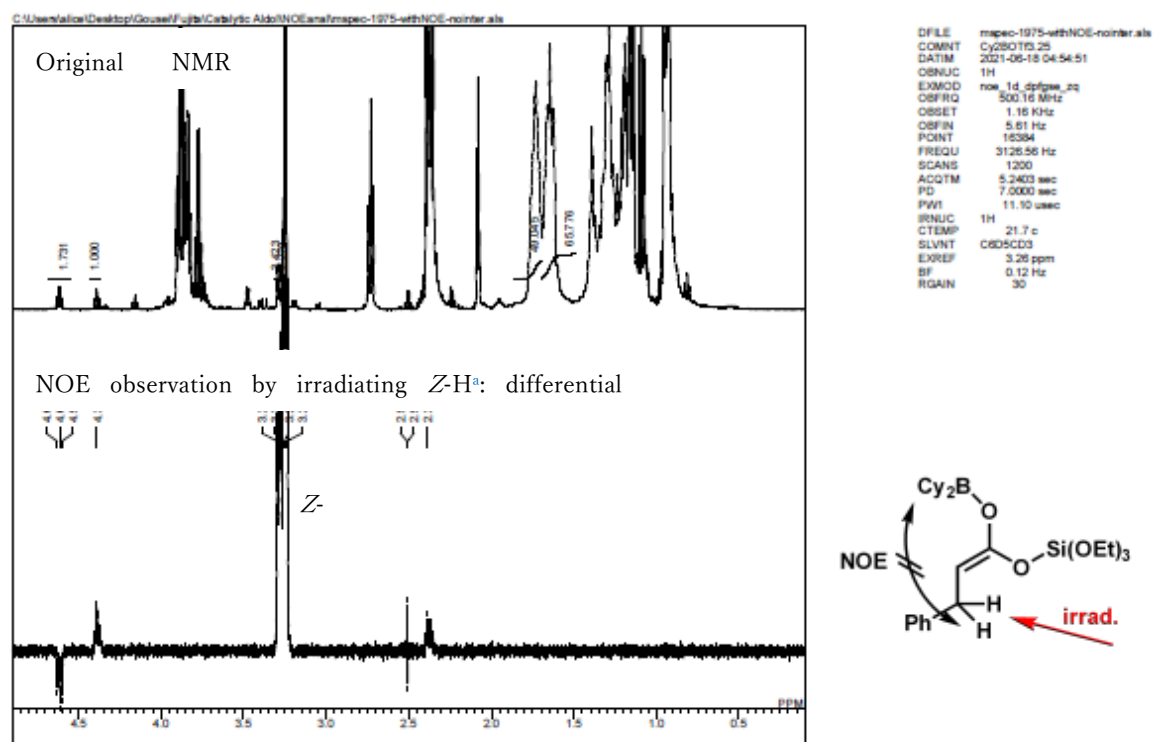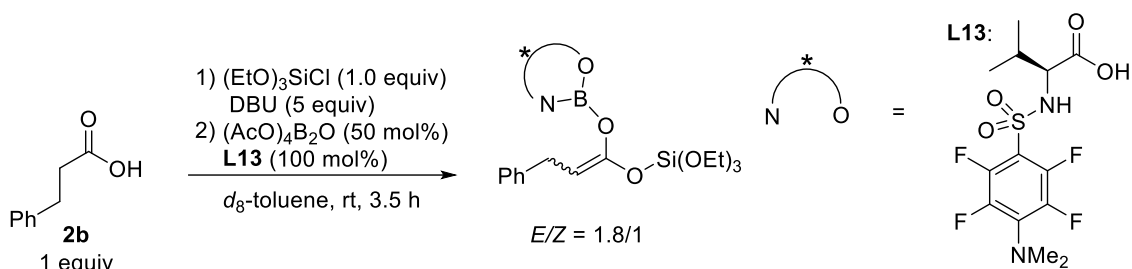
A flame-dried 4 mL test tube A, equipped with a magnetic stirring bar, was charged with propionic acid (**4b**; 15.0 mg, 0.1 mmol), (EtO)$_3$SiCl (19.6 µL, 0.1 mmol) and DBU (74.6 µL, 0.5 mmol) in anhydrous d_8-toluene (125 µL). Another frame-dried 4 mL test tube B, equipped with a magnetic stirring bar, was charged with (AcO)$_4$B$_2$O (13.7 mg, 0.05 mmol), ((4-(dimethylamino)-2,3,5,6-tetrafluorophenyl) sulfonyl)-L-valine (**L6;** 37.2 mg, 0.1 mmol) and anhydrous d_8-toluene (125 µL). After stirring for 0.5 h, a solution of test tube B was added to a test tube A. The reaction mixture was stirred for 3.5 h at room temperature under an argon atmosphere. Subsequently, the reaction mixture was analyzed by ^{1}H NMR. Due to the presence of excess DBU, stereochemistry of the enolate could not be determined by NOE analysis. Based on analogy of the chemical shifts obtained in above experiments using Cy$_2$BOTf, however, we tentatively assigned E-H^c was observed at a greater chemical shift than Z-H^c (E/Z = 1.8/1: Chart D).

Chart D. NMR chart of the reaction mixture of enediolate formation from the (EtO)$_3$Si ester and chiral boron complex bearing **L13**.
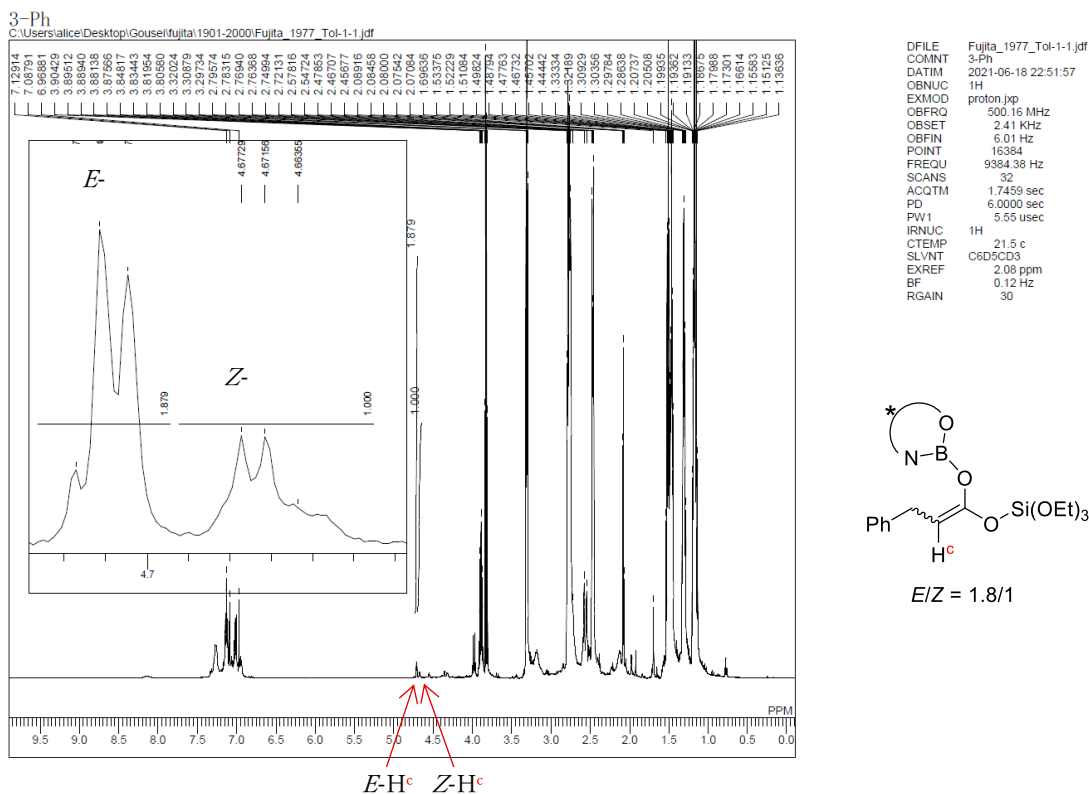
It was previously reported that E/Z ratio dramatically changes depending on the enolization conditions. Therefore,

10. Comparison to Previous Method

To compare our method to previous catalytic asymmetric aldol reaction of carboxylic acids reported by Nakajima group,[4] we conducted the reaction between **1a** and **2p**. While our conditions produced **3ap** in >69% yield with 17/1 dr (see Table 2 in the main text), Nakajima's conditions afforded only 10% yield with 3/1 dr (scheme below). In this comparison, we used BINAPO, which was not the best ligand in Nakajima's work, due to its availability. BINAPO and his best ligand (4,4'-TIPS$_2$-BINAPO) produced **3ab** in 93% and 91% yield, respectively.[4]
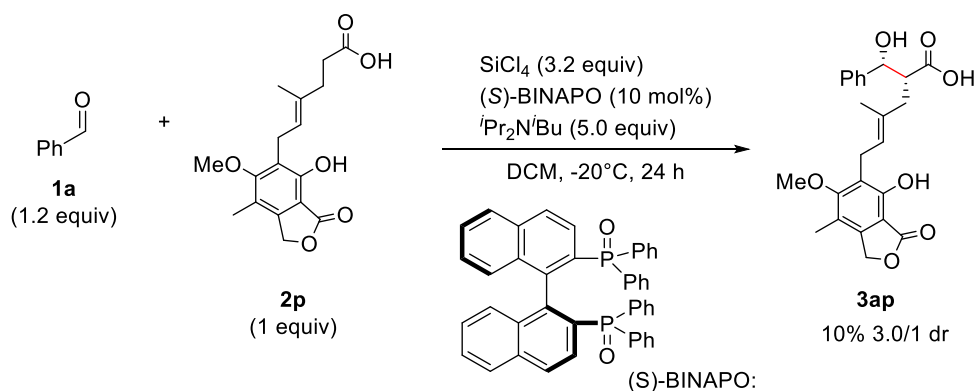
Procedure and amount of the reagents were based on the literature (reaction of 4-hydroxybenzaldehyde and δ-bromocarboxylic acid)[4]. Tetrachlorosilane (36.7 µL, 0.32 mmol) was added dropwise to a solution of carboxylic acid **2p** (32.0 mg, 0.1 mmol) and (*S*)-BINAPO (6.5 mg, 0.01 mmol) in anhydrous dichloromethane (1.0 mL) at –60 °C. *N,N*-Diisopropylisobutylamine (102.5 µL, 0.5 mmol) and aldehyde **1a** (12.3 µL, 0.12 mmol) were successively added dropwise to the solution. After stirring for 24 h at –20 °C, the reaction was quenched with triethylamine trihydrofluoride, and then, aqueous HCl (1 M). Products were extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude product (**3ap**) and analyzed by proton NMR (10% NMR yield, *syn/anti*= 3.0/1).

11. Computational methods and Results

Density functional theory (DFT), as implemented in the Gaussian16 program (Version C.01),[11] was used for structure optimizations. The wB97X-D[12] functional and the 6-31G(d)[13] basis sets were employed for all atoms. The polarizable continuum model (PCM)[14] was used as the implicit solvent model, where tetrahydrofuran ($\varepsilon = 7.4257$) was the solvent. Vibrational frequency calculations, at 298.15 K and 1 atm, were performed to confirm that the optimized structures were local minimum

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(i.e., no imaginary frequency) or transition states (i.e., one imaginary frequency). Connectivity between the local minima and transition states were confirmed by performing the Pseudo intrinsic reaction coordinate (IRC)[12] calculations (i.e., 20 steps for forward or reverse IRC followed by optimization). The potential energy of the optimized structures was calculated as the single-point energy, employing the wB97X-D functional, cc-pVTZ[16] basis sets and PCM as the implicit solvent model. The Boltzmann distribution of transition states at 273.15 K and 1 atm was used for calculating the reaction path ratio.[14] Conformational analysis of the local minima was performed using the GMMX method, employing the MMFF force field.[18] Then, ten lowest energy structures were selected and fully optimized using the wB97X-D functional, 6-31G(d) basis sets, and PCM. After that, the lowest energy structure was selected.

Figure S1. Computed free energy barrier for deprotonation of an α-proton of the silyl ester. Among calculated intermediates, **I1** showed the lowest free energy barrier.
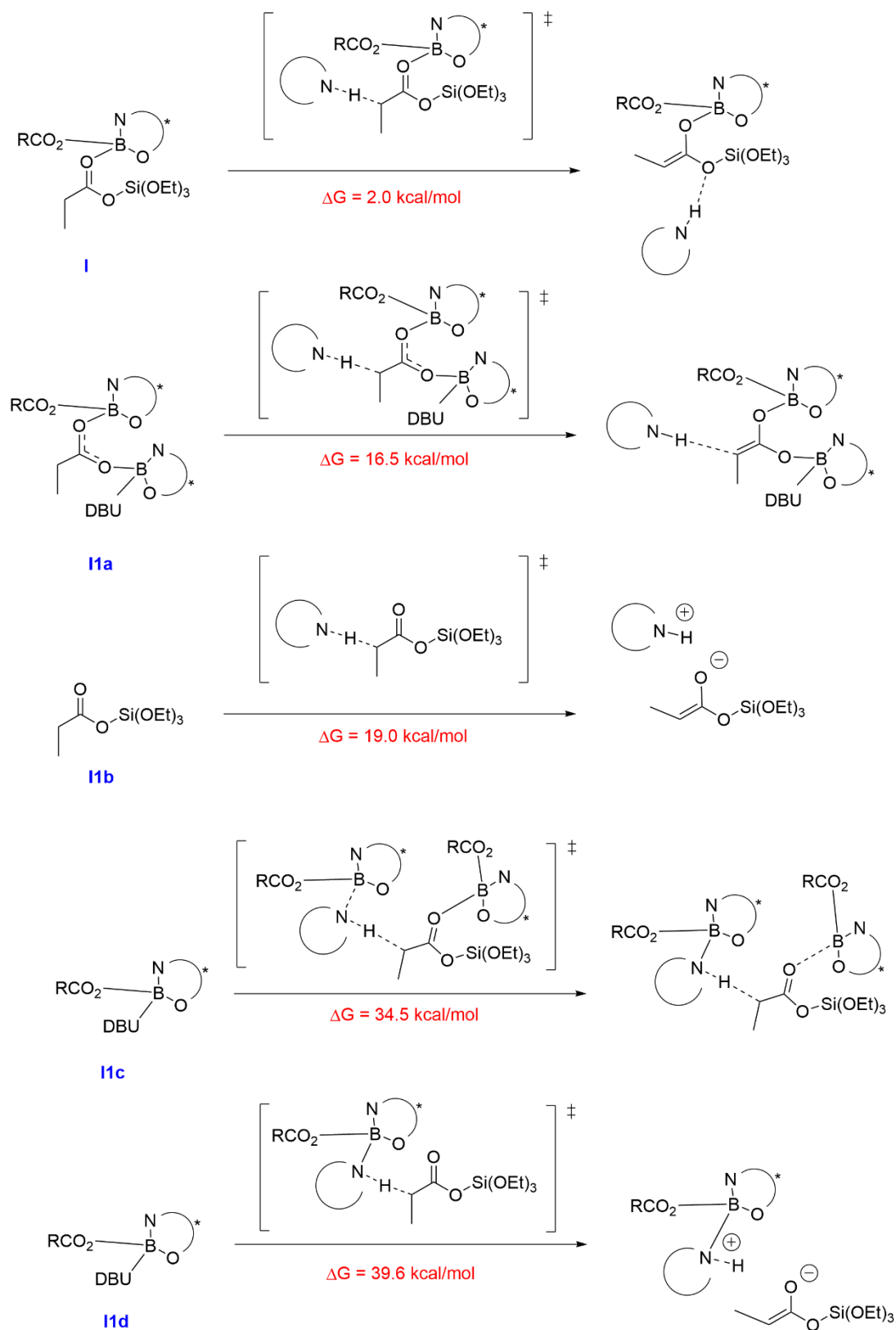
Figure S2. Transition state groups for the asymmetric aldol reaction between I3 and PhC(O)H.

(2S, 3R) anti

(TS_A)
(ΔΔG =2.3, 1.8%)

(2R, 3R) syn

(TS_C = TS2)
(ΔΔG =0.0, 87.7%)

(2S, 3S) syn

(TS_B)
(ΔΔG =1.5, 7.0%)

(2R, 3S) anti

(TS_D)
(ΔΔG =2.0, 3.5%)
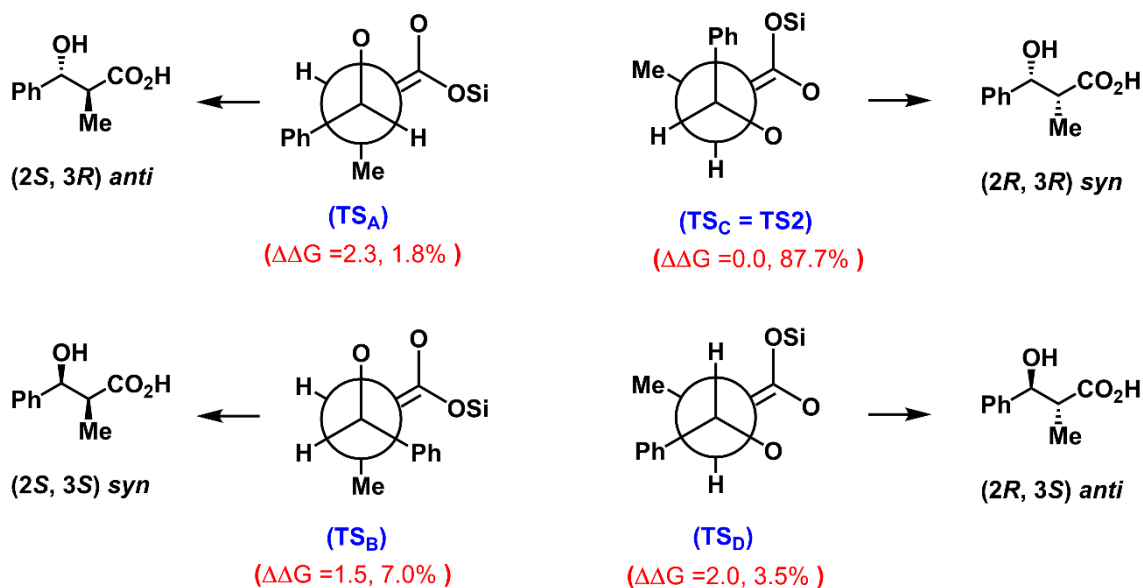
The TS_C (= TS2) leads to the 2R,3R (*syn*) isomer, which is the experimentally observed product. The 2S,3S (*syn*) isomer can be obtained through the TS_B. The TS_A and TS_D transition states give rise to the 2S,3R (*syn*) and 2R,3S (*syn*) isomers, respectively. Relative free energies (ΔΔG in kcal/mol) of the fully optimized transition states and the existing probabilities (%) are shown in the figure.

The observed absolute configuration of the product (i.e., 2R,3R) is obtained from TS_C (= TS2), where the computed existing probability is 87.7%. The TS_B, TS_D, and TS_A give the minor products with the existing probability of 7.0%, 3.5%, and 1.5%, respectively. The calculated *syn*:*anti* ratio is 95:1. In the case of 2R,3R and 2S,3S forms of the products, the computed ee% is 85%.

Figure S3. Computed chair-type(**TS$_D$**) and boat-type(**TS$_C$=TS$_2$**) transition state
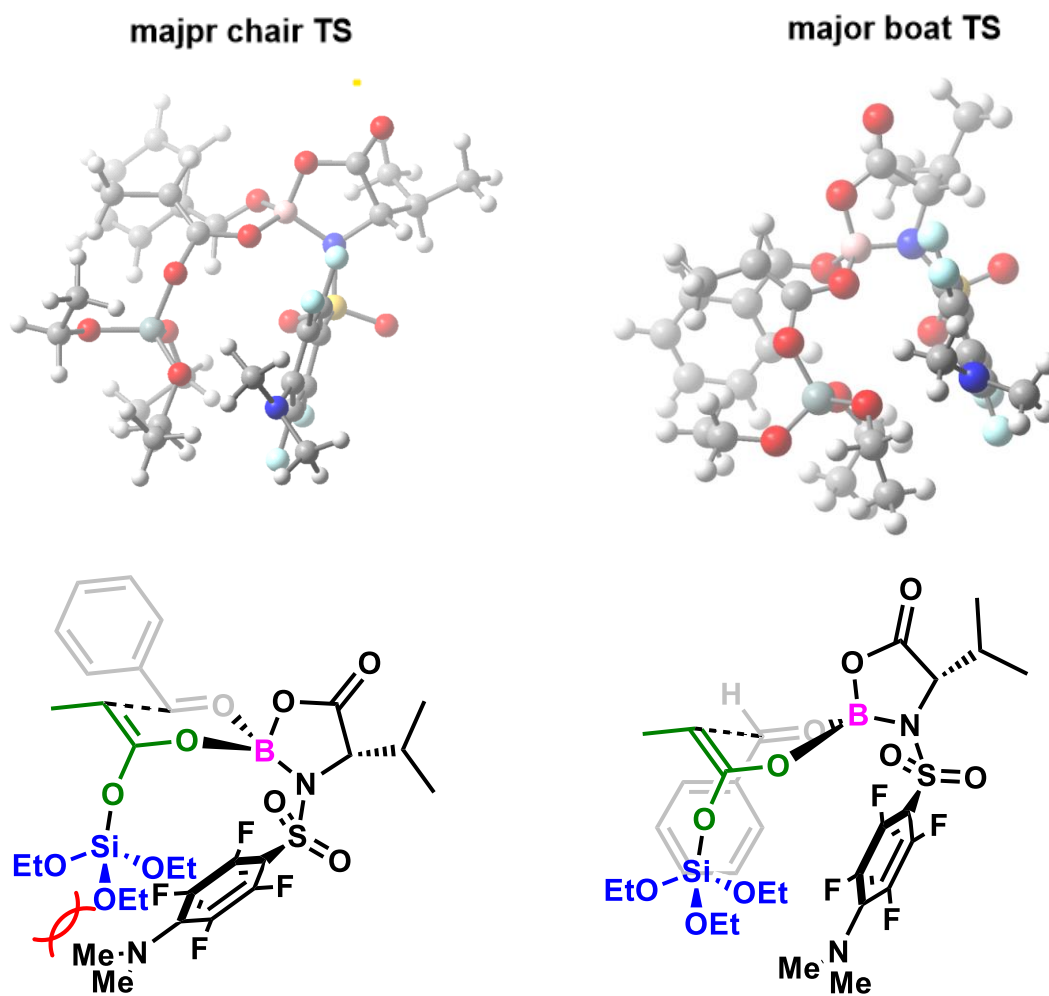
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13. Energies of the Computed Structures

	Thermal correction to Gibbs Free Energy/AU	Potential energy/AU
PhC(O)H	0.080964	-345.574254634
Boron catalyst	0.304056	-2004.60366671
DBU	0.215572	-462.112469478
RCOOH	0.063124	-268.421052544
PhC(O)H bound boron catalyst	0.406944	-2350.18524814
DBU bound boron catalyst	0.548226	-2466.77372587
I	0.823291	-3487.64454179
I1	0.822470	-3487.64506931
TS1	0.817245	-3487.63665856
I2	0.827670	-3487.65493060
I3	0.494286	-2757.03432624
I4	0.740899	-3219.21181007
TS_A	0.604178	-3102.62726473
TS_B	0.605258	-3102.62955302
$TS_C = TS_2$	0.60497	-3102.63170222
TS_D	0.603873	-3102.62738257
I5	0.605218	-3102.67525439
I6	0.599737	-3102.66618643
5aa	0.598798	-3102.66690772

14. Cartesian Coordinates of the Optimized Structures

PhC(O)H

C 3.06187300 0.49033600 0.26109600
O 2.33032500 -0.18858000 -0.43137100
H 2.89564500 0.56058900 1.35543900
C 4.21067800 1.27011300 -0.24556300
C 4.52613800 1.26295100 -1.60862500
C 4.98207500 2.01655500 0.64825900
C 5.60776800 1.99948100 -2.07093200
H 3.91464200 0.67646700 -2.28722900
C 6.06614200 2.75451700 0.18382400
H 4.73144200 2.01779000 1.70645300
C 6.37682700 2.74456900 -1.17440400
H 5.85636700 1.99696600 -3.12755000
H 6.66700600 3.33514200 0.87644900
H 7.22270700 3.31996100 -1.53844900

Boron catalyst

C -0.08505300 0.49696300 -0.08443000
H 0.97224100 0.75550700 0.02575700
N -0.34440500 -0.87552100 0.39057100
O -1.65210200 0.49060600 1.70429000
C -0.90366700 1.32071500 0.90987900
O -0.95569200 2.51166800 1.00453500
B -1.31264800 -0.82276300 1.43375600
S 0.68821200 -2.15076400 0.05378200
O 1.43407200 -1.77018100 -1.13155100
O 1.40227500 -2.51006900 1.26308500
C -0.44053800 -3.45290700 -0.33674000
C -0.66662200 -4.55468400 0.49375800
C -1.19883400 -3.39756600 -1.51084000
C -1.56547400 -5.54798300 0.14872500
C -2.12049000 -4.36862900 -1.83545400
C -2.33130100 -5.51439300 -1.03516400
F -0.02812000 -4.70922100 1.64732900

99

F -1.66188200 -6.58981700 0.98803200
F -2.85837600 -4.17710600 -2.93579400
F -1.09230100 -2.35336800 -2.32763100
N -3.21108700 -6.48978800 -1.38961600
C -3.87406200 -7.35446900 -0.42364100
H -3.94332400 -6.87402400 0.55014700
H -3.35886300 -8.31582700 -0.31335000
H -4.89131100 -7.54020900 -0.78070100
C -3.45517500 -6.83568200 -2.78506500
H -4.40115700 -6.42021400 -3.14864300
H -3.49717700 -7.92647800 -2.86162200
H -2.64261900 -6.48652700 -3.42069000
C -0.54498200 0.74216400 -1.54078600
H -0.05685600 -0.04110300 -2.12674800
C -2.06072700 0.59998100 -1.69388900
H -2.58777100 1.42596000 -1.20113700
H -2.33018800 0.62326500 -2.75386600
H -2.42863600 -0.34329100 -1.27890200
C -0.04617200 2.09775700 -2.04422200
H -0.32676000 2.22618900 -3.09417800
H -0.48242200 2.92167400 -1.47164200
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C -2.91865400 -2.52107100 1.64405200
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O -1.83181300 -1.88119400 2.15311900
C -3.37860400 -3.65040000 2.52120600
H -2.53665000 -4.34311500 2.63558200
H -3.55803800 -3.24014700 3.52130800
C -4.61424000 -4.34701700 1.96908300
H -4.86068900 -5.21850700 2.58097700
H -5.47515500 -3.67347900 1.96449200
H -4.44925700 -4.67675200 0.93929700

DBU
N 4.93677400 0.65364700 0.55689300
N 2.68887400 0.04065200 1.05414500

C 6.33723500 0.34538500 0.81082700
C 6.73119500 0.41835800 2.29334000
C 3.94687100 -0.21811900 0.97630200
C 5.69917700 -0.25483700 3.20495100
C 4.59059500 2.05923500 0.40658500
C 4.41059600 -1.60148900 1.38110400
C 5.21641800 -1.62600500 2.71322000
C 3.18975200 2.16790000 -0.17681200
C 2.22570500 1.37798000 0.70546900
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H 6.94005800 1.04432900 0.22269300
H 6.85418800 1.46440500 2.59861800
H 7.71057700 -0.06276000 2.40899700
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H 5.32796400 2.52625600 -0.25471300
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H 6.07657000 -2.29780500 2.60631400
H 3.19339200 1.75305300 -1.19145100
H 2.88687700 3.21752000 -0.24581700
H 1.25312200 1.28305300 0.20787500
H 2.03805800 1.93434200 1.63555200

RCOOH
C 0.95494600 2.23196900 -2.55166700
O 0.31527100 2.45937600 -3.54935700
C 0.79425000 2.96183700 -1.23273900
H 0.55589300 2.21840700 -0.46124800
H 1.76917900 3.38442100 -0.95842300
O 1.89175900 1.26200800 -2.57432900
C -0.27020400 4.04941200 -1.28422800
H -0.34957700 4.54514600 -0.31293200
H -0.02159800 4.80170600 -2.03740000

H -1.24609200 3.62790800 -1.53892300
H 2.32885200 1.18897300 -1.71367700

PhC(O)H bound boron catalyst
C 3.28329600 0.40166600 0.43447500
O 2.35328000 -0.18766000 -0.15107500
C 0.55701400 -2.04839700 -2.36479300
H 0.56212800 -2.89053700 -1.65521300
N 0.42806600 -0.78356200 -1.63689000
O 2.58282300 -0.82867800 -2.48473400
C 1.98008400 -1.93902200 -2.91934900
O 2.52333900 -2.74038900 -3.63810500
B 1.73681500 -0.04284200 -1.60675200
S -0.92378900 -0.35491600 -0.82985400
O -0.53957000 0.63828100 0.16268900
O -2.00777700 -0.02404900 -1.74230200
C -1.38712600 -1.86526900 0.00385100
C -2.51843900 -2.61936800 -0.31933500
C -0.58046800 -2.37175700 1.02743900
C -2.82784800 -3.78855200 0.35530700
C -0.87102400 -3.55481500 1.67640400
C -2.01996800 -4.31504500 1.37999500
F -3.36814700 -2.24304100 -1.27018900
F -3.97472600 -4.40236900 0.02964600
F 0.00574200 -3.99850200 2.58852900
F 0.54644800 -1.74955000 1.36566000
N -2.31463700 -5.47753600 2.03225500
C -2.01993000 -5.66858400 3.44359200
H -1.13923000 -6.30339900 3.59744000
H -1.85757800 -4.71069700 3.93680800
H -2.88365400 -6.14879500 3.91571600
C -2.98173900 -6.58945800 1.37467800
H -2.52190100 -7.51965800 1.72413600
H -4.05404200 -6.62274800 1.60138800
H -2.84814900 -6.53431300 0.29448800
C -0.51555800 -2.33425700 -3.43805100

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H -1.48266200 -2.19587300 -2.94417700
C -0.44811100 -1.35561200 -4.60812700
H 0.47190900 -1.49851000 -5.18628300
H -1.29714100 -1.51782500 -5.28007100
H -0.47030200 -0.32085100 -4.25955700
C -0.44301100 -3.79257000 -3.89670900
H -0.55134100 -4.48051400 -3.04967600
H -1.25303300 -3.99966300 -4.60347300
H 0.50929700 -4.00437400 -4.38986100
C 1.55852100 1.97343500 -2.97760100
O 1.32699500 1.37831400 -4.00602200
H 3.30288700 0.23175800 1.51530300
C 4.31406900 1.25870800 -0.09570200
C 4.67417500 1.32677600 -1.45561400
C 4.99235700 2.04850500 0.85062500
C 5.67160700 2.20104100 -1.85163300
H 4.20550100 0.67511800 -2.18215500
C 5.97393900 2.93785600 0.44026700
H 4.73014900 1.97542100 1.90212800
C 6.30861300 3.01410200 -0.91027300
H 5.96107200 2.24967400 -2.89563500
H 6.48225300 3.56157200 1.16704900
H 7.08334300 3.70214200 -1.23368100
C 1.70130000 3.47282400 -2.85872400
H 2.69602400 3.67041900 -2.43982300
H 0.98681700 3.81135300 -2.09943300
O 1.73950400 1.37930100 -1.79190300
C 1.49917400 4.20260000 -4.17899900
H 1.60948500 5.28133600 -4.03627500
H 2.23140400 3.87705900 -4.92321200
H 0.50198100 4.00916300 -4.58393100

DBU bound boron catalyst
C -0.15871500 0.25964400 -0.19050800
H 0.92705000 0.37355200 -0.29655400
N -0.51729500 -1.15203000 0.06424500

O -1.03062000 0.09997300 1.99359000
C -0.53264800 0.95686500 1.11638700
O -0.37833400 2.13500400 1.35061100
B -1.27684100 -1.24635500 1.41304700
S 0.56744200 -2.23703300 -0.52222900
O 1.07406500 -1.72005900 -1.78886200
O 1.56910500 -2.63658200 0.46083400
C -0.42761300 -3.66652900 -0.86926900
C -0.40811300 -4.82600700 -0.09390700
C -1.30583900 -3.64617300 -1.94980900
C -1.21726500 -5.90257600 -0.40413700
C -2.12646700 -4.72119800 -2.24545500
C -2.12094200 -5.89342500 -1.47860500
F 0.35839000 -4.94509700 0.98980800
F -1.14987100 -6.97732300 0.39564500
F -2.98997600 -4.57117200 -3.25692900
F -1.43622900 -2.55596700 -2.69484000
N -2.91317400 -7.00907000 -1.71872000
C -3.86743400 -7.37626600 -0.67785600
H -3.42011300 -7.26800500 0.31000600
H -4.15086600 -8.42428400 -0.81138800
H -4.77669400 -6.75831000 -0.72643200
C -3.39236900 -7.27484700 -3.06662900
H -4.30245100 -6.71599400 -3.32132700
H -3.61193800 -8.34470000 -3.13748700
H -2.61448900 -7.03874200 -3.79444300
C -0.81633700 0.85386200 -1.45294800
H -0.49713600 0.19353800 -2.26590100
C -2.34261900 0.82272500 -1.39292800
H -2.72358100 1.36371100 -0.51711300
H -2.76463900 1.29910500 -2.28404500
H -2.70429400 -0.20733300 -1.36423600
C -0.28721400 2.25938300 -1.74866100
H -0.66140800 2.59932900 -2.72008400
H -0.60658600 2.97360200 -0.98523700
H 0.80806100 2.27292200 -1.78630500

C -3.59942200 -1.69292900 0.42396200
O -3.34511300 -2.48622100 -0.46249200
N -1.01557600 -3.82907300 4.14162100
N -0.71399500 -2.29022100 2.42905600
C -1.60757800 -5.06682800 4.67156300
C -3.06828500 -4.91340300 5.10475600
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H 2.77679700 2.87655800 -4.44529200
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H 7.33995600 -1.02741800 2.56534600
C 6.29573900 2.03758500 -2.41530700
H 6.76860900 2.80407300 -3.04196200
H 6.67471200 2.15288200 -1.39585000
H 6.61767200 1.06215800 -2.79325500
H 4.26748500 1.75036000 -3.31075700

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O 4.23469600 0.13034100 -1.32260100
Si 4.68951200 0.88383200 0.10314900
O 5.88109400 -0.06601400 0.68987300
O 5.12172800 2.38503800 -0.33839600
O 3.48911400 0.90342200 1.20130900
C 6.82935200 -0.79079600 -0.09193900

H 7.42880900 -1.36717700 0.61794400
H 6.29611300 -1.50015400 -0.73566900
C 3.53218200 0.29037500 2.49304200
H 3.95642100 -0.71554100 2.41101700
H 2.49445300 0.20147500 2.82492400
C 5.40341400 3.44733400 0.57293400
H 5.26489500 4.37280900 0.01140400
H 4.66434800 3.44436400 1.38169800
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H 8.23394400 0.84335300 -0.29176300
H 8.46695000 -0.47945100 -1.45647500
H 7.13535000 0.66859100 -1.66989800
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H 4.29189900 0.68308700 4.47085400
H 5.37732400 1.19965500 3.16701300
H 3.90782000 2.14007800 3.53304500
C 6.81710900 3.34008500 1.11680000
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H 6.95190300 2.41912300 1.69349100
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N 1.62851800 3.67665500 -2.86468800
O 1.79814200 1.98341600 -4.45420500
C 0.66012700 2.63372400 -4.70839500
O -0.11344300 2.29404400 -5.56999500
B 2.50871600 2.53062400 -3.30034400
S 1.64757900 4.42853000 -1.42818100
O 3.01909100 4.77761400 -1.09999300
O 0.62640400 5.46995500 -1.44882200
C 1.11903300 3.23234400 -0.19828000
C 1.45489400 3.42919300 1.14122600
C 0.30874900 2.13762900 -0.47873100
C 1.03927200 2.55521000 2.12560900
C -0.11257000 1.26405500 0.51216500
C 0.25255900 1.42682200 1.85360200

F 2.21482500 4.45806800 1.51582700
F 1.45834100 2.77656100 3.37869100
F -0.92122100 0.26301000 0.14046000
F -0.14167300 1.89862900 -1.71356100
N -0.06036200 0.53970600 2.87702400
C -0.30647700 -0.85920900 2.56323500
H -1.33785300 -1.05806300 2.24376400
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H -0.55491100 2.05858700 4.24863600
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C 0.60120700 5.17485900 -4.61189900
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H -0.62810200 6.38347000 -5.91892200
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O 3.89117100 2.96624400 -3.66064100
H 4.31445000 1.77600400 -5.27000400
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C 6.61250100 3.05717700 -3.05969200
C 6.97113100 1.48646600 -4.87825600
C 7.98356800 3.12493600 -2.85828300
H 5.92645500 3.62218200 -2.44072800
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H 6.56981600 0.86066400 -5.67038500
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H 9.01455000 0.95585400 -5.27097100

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O 4.06181000 0.92327100 -0.75138700
Si 4.56363300 2.15877000 0.24055500
O 6.03566800 1.81552100 0.85894600
O 4.72723100 3.47807500 -0.70566700
O 3.41582500 2.27401800 1.39053700
C 6.34655400 0.82491000 1.83940400
H 7.43560300 0.73171700 1.83512100
H 6.05126600 1.19990500 2.82690000
C 3.61179300 2.87642200 2.67454900
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130

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O 1.97759800 4.21923500 -2.23233400
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C 0.31938400 2.73396900 1.53619500
C -0.08197700 0.66883600 0.45163200
C 0.03451400 1.36628200 1.65937500
F 0.80653500 4.64404200 0.30778300
F 0.46866200 3.47789700 2.64012600
F -0.42302200 -0.62593400 0.44509800
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C 4.31976200 2.74364000 -3.74371100
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H 4.13313000 3.16489600 -2.75614400
C 5.55873500 3.09975000 -4.40879800
C 5.77356600 2.80837900 -5.76233000
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C 6.34659400 0.41674800 -2.49703300
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H 6.51705600 0.74337600 -1.46865100
H 6.63056500 -0.63982700 -2.56899500
H 4.67751500 0.33270000 -3.94758800

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H 5.68866000 1.78265300 -1.33023800
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O 6.64888300 3.06228000 0.39573400

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134

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H 6.29971800 -3.88231500 -3.73232800

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H 5.33655500 0.06487700 -3.59895000
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5aa
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S 5.75819000 3.93511500 -0.41552000
O 6.33893900 3.09282500 -1.44499200
O 5.22326500 5.23934900 -0.74447400
C 6.93890600 4.12305300 0.89473900
C 7.37410300 5.35650900 1.38615000
C 7.49633100 2.98323900 1.48349400

C 8.31647700 5.43207900 2.39737800
C 8.40308100 3.05752200 2.51731500
C 8.87012600 4.29369000 3.01633400
F 6.94286700 6.50226600 0.87593000
F 8.74045700 6.65277500 2.75040400
F 8.80878400 1.91166500 3.07750500
F 7.09416200 1.76880600 1.09457100
N 9.78185200 4.37507500 4.02443500
C 10.83950800 3.38956900 4.19597100
H 10.60256400 2.66391100 4.98233100
H 11.02782700 2.85834700 3.26345900
H 11.75680700 3.91889300 4.47210000
C 9.77429000 5.46019400 4.99453500
H 10.00435500 5.03843600 5.97794300
H 10.51901700 6.22901400 4.75907900
H 8.78894000 5.92190400 5.04956400
C 2.61101400 4.45811800 1.03265100
H 3.05041600 5.25170100 0.41966100
C 1.61597900 3.67799100 0.17107500
H 1.12946400 2.87844600 0.74402000
H 0.82973400 4.34860800 -0.18757000
H 2.10060300 3.23577700 -0.70576300
C 1.94039100 5.10228900 2.24686100
H 2.66071800 5.67050700 2.84544300
H 1.16102000 5.79324400 1.91159000
H 1.47597800 4.35223100 2.89364400
H 5.05917200 -1.58631600 -1.67020800
C 6.39885200 -2.24260100 -3.18399100
C 6.49213800 -2.66778200 -4.50910900
C 7.37353400 -2.64434700 -2.26899800
C 7.54399800 -3.48633800 -4.91289300
H 5.73323600 -2.35930600 -5.22013200
C 8.42759100 -3.45898400 -2.67170300
H 7.30240600 -2.32417000 -1.23178400
C 8.51405000 -3.88371300 -3.99597000
H 7.60493300 -3.81358900 -5.94658000

H 9.17630700 -3.76954900 -1.94916500
H 9.33232200 -4.52441700 -4.31047400