キラルリチウムアルコキシドを用いるアキラルホスホネートの

キラルリチウムアルコキシドを用いる アキラルホスホネートのエナンチオ選択的 不斉Horner–Wadsworth–Emmons反応の開発

熊本 卓哉

キラルリチウムアルコキシドを用いるアキラルホスホネートのエナンチオ選択的不斉Horner–Wadsworth–Emmons反応の開発

熊本　卓哉

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熊本　卓哉

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序

我々の身体は，キラルな環境に満ちている．

我々の身体は，キラルな分子.....糖，蛋白質，核酸.....を構成要素に持つ．そのため，外界から侵入する分子でキラリティーを有するものは.....それが生体に必須な栄養分であろうと，難病を克服するために有効な薬剤であろうと.....それぞれ別の分子として認識される．仮に，一方のエナンチオマーが生体に非常に有効であったとしても，そのアンチポードは無効，もしくは重篤な副作用を引き起こす毒物となる可能性がある．よって，医薬品の合成において，一方のエナンチオマーを得ることは非常に重要であり，不斉合成はその有力な手段となりうる．

また，不斉合成は，その立体的な情報を総合することにより，今まで明らかにされなかった反応のメカニズムについて一線の光を与え，それまで不明であった点が明らかにされることがあり，有機合成のツールとしてのみでなく，その反応について，更なる情報を与える方法の一つであると考えられる．

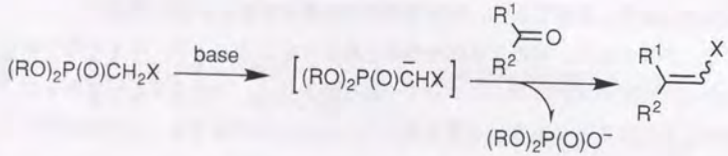
ところで，Horner–Wadsworth–Emmons反応は，Wittig反応と並んで，炭素－炭素２重結合を構築する，有機合成上重要な反応の一つである．この反応を用いた合成の例は膨大な数に上る．よって，本反応のメカニズムの解析は重要な課題の一つであると考えられる．

本反応のメカニズムの考察は，もっぱら生成するオレフィンの(*E*)/ (Z)選択性から議論するものが多かった．そこで，不斉反応としてはそれほど例が多くない Horner–Wadsworth–Emmons反応について，不斉収率というパラメーターから眺めてみようと思い，種々検討を行った．

第１章　背景

第１節　不斉Horner–Wadsworth–Emmons反応の背景

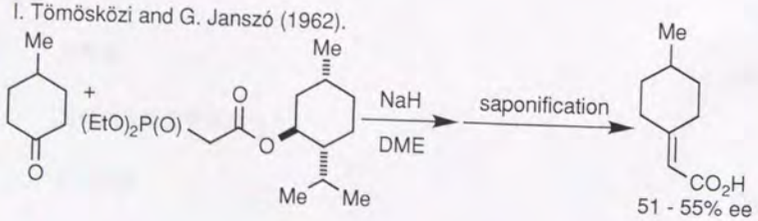
Horner–Wadsworth–Emmons反応は，1961年にWadsworthとEmmonsにより報告されたオレフィンを合成する反応である[1,2]．それまでのオレフィンを合成する反応として代表的なものとしては，リンイリドを用いるWittig反応が知られていた[2c]．しかし，場合によっては加熱の条件が必要なこと，副生するホスフィンオキシドの除去が容易でない，などの問題があった．WadsworthとEmmonsは，ホスホネート誘導体を用いたオレフィン化反応が，ホスホネートカルバニオンが比較的反応性が高く，より緩和な条件で反応が進行すること，およびカルボニル化合物との反応後に生じる副生成物がホスフェートであるため，抽出操作により除去が容易であることなどの点で，Wittig反応よりも優れた面があることを見いだした．以降，Horner–Wadsworth–Emmons反応は，炭素－炭素２重結合を構築する代表的な反応の一つとして用いられてきた．



この反応において，カルボニル化合物としてプロキラルケトンを用いた場合，生成物は軸不斉を有する化合物となるため，本反応を不斉反応としてとらえることができる．この反応を実現する方法として，基質の分子内に不斉源を有するキラルホスホネート誘導体を用いるジアステレオ選択的不斉反応と，アキラルホスホネートをキラル外部配位子で制御するエナンチオ選択的不斉反応に大別される．

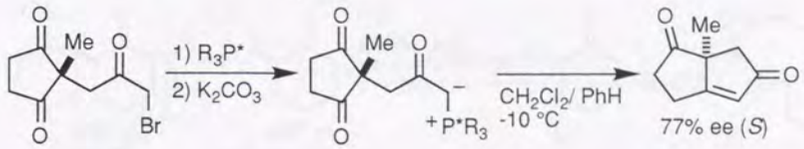
キラルホスホネート誘導体を用いるジアステレオ選択的不斉Horner–Wadsworth–Emmons反応の例はTömösközi らの研究に始まる．彼らは，キラルホスホネートとプロキラルケトンのジアステレオ選択的不斉Horner–Wadsworth–Emmons反応を検討したところ，約50% eeで光学活性オレフィンを得ている[3]．彼らはその後もキラルホスホニウム塩を用いた不斉Wittig反応を報告している[4]．

I. Tömösközi and G. Janszó (1962).



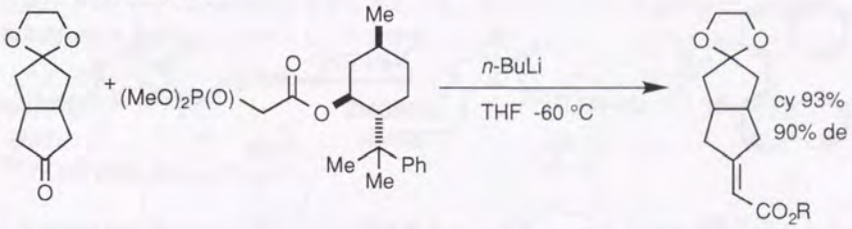
Trostらは，キラルホスホニウム塩を用いた分子内不斉Wittig反応を行い，分子内に存在する２つのジアステレオトピックなケトンを識別することによる，合成中間体として有用なbis–nor–Wieland–Miescher ketoneの光学活性体の合成に成功している[5]．

B. M. Trost and D. P. Curran (1981).



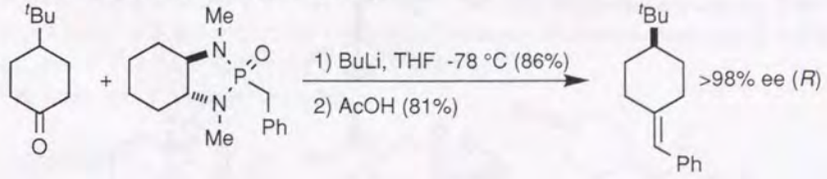
Gaisらは，3-oxa-carbacyclinの前駆体合成の基礎実験の目的で，キラルホスホネートを用いた不斉Horner–Wadsworth–Emmons反応を検討し，高いジアステレオ選択性で光学活性オレフィンを得ている[6]．

H.- J. Gais *et al* (1988).



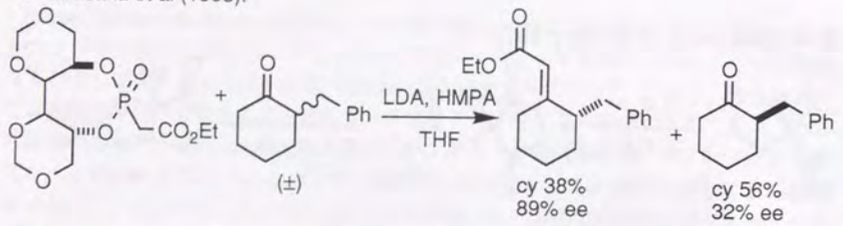
Hanessianらは，1, 2-cyclohexyldiamineを不斉補助基とするキラルホスホナミド誘導体を用いた不斉Horner–Wadsworth–Emmons反応を検討し，高い不斉収率で光学活性オレフィンを得ている[7]．彼らはその前後にも，キラルホスホナミド誘導体を用いた種々の不斉反応を報告している[8]．

S. Hanessian and S. Beaudoin (1990).



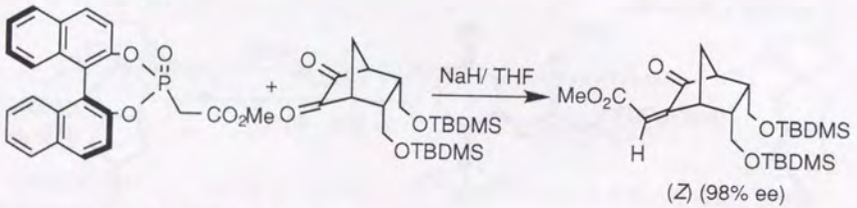
また，奈良坂らはキラルホスホネートを用いたラセミ体のケトンの速度論的光学分割を報告している[9].

K. Narasaka *et al* (1993).



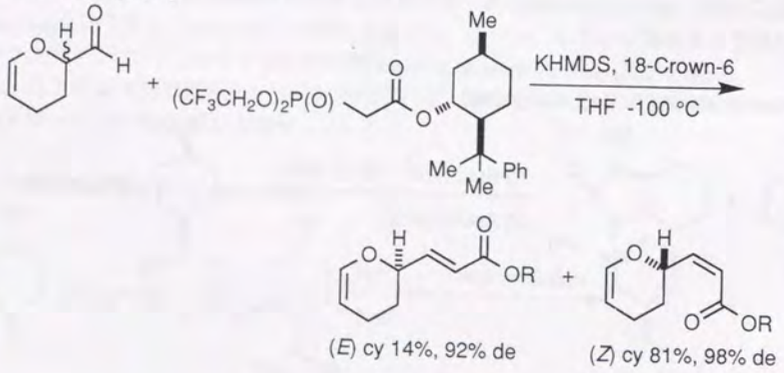
冨士らは，BINOL 誘導体のキラルホスホネートを用い，高い選択性で，エナンチオトピックなケトンの識別に成功している[10].

K. Fuji *et al* (1993).



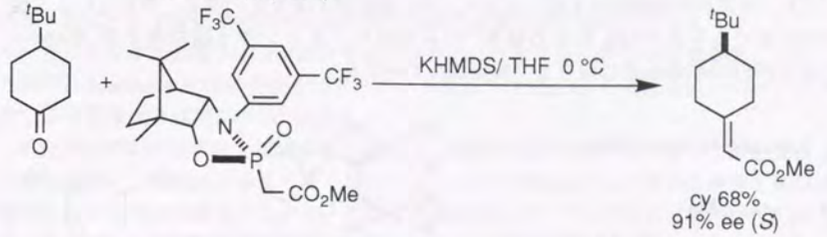
Rein らは，キラルホスホネートを用いたラセミ体のアルデヒドの速度論的光学分割を報告している[11].

T. Rein *et al* (1994).



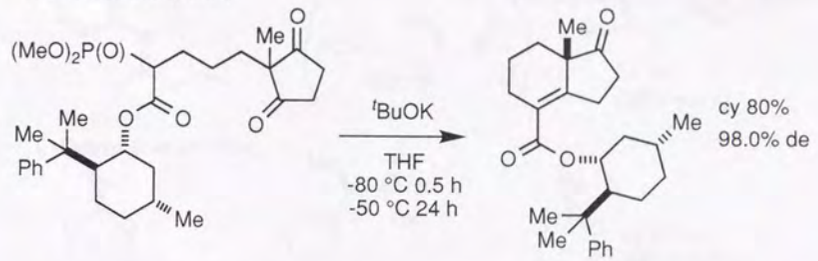
Denmark らは，キラルホスホナミデートを用いた種々の不斉反応を報告している[12]. 不斉Horner–Wadsworth–Emmons反応については，ノルボルナン誘導体のキラルホスホナミデートを用いた例がある[13].

S. E. Denmark and I. Rivera (1994).



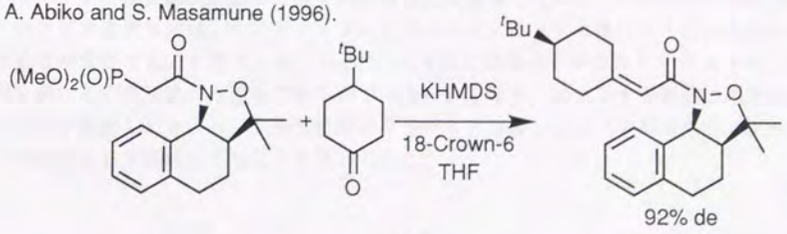
萬代らは，ビタミン D_3 の CD 環構築の合成研究において，先ほどのTrost と同様な，2つのジアステレオトピックなケトンを識別する，ジアステレオ選択的分子内不斉Horner–Wadsworth–Emmons反応を行ったところ，高いジアステレオ選択性で，CD 環の鍵中間体を合成することができたことを報告している[14].

T. Mandai *et al* (1994).



正宗らは，キラル補助剤としてキラルなbenzopyranoisoxazolidine を有する種々の試薬を用いた不斉反応を検討している．その中で，キラルなbenzopyranoisoxazolidine を有するホスホネートを用いたジアステレオ選択的不斉Horner–Wadsworth–Emmons反応を検討し，高いジアステレオ選択性でオレフィンを得ている[15].

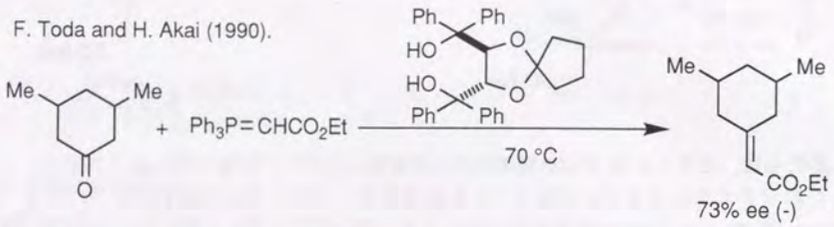
A. Abiko and S. Masamune (1996).



以上，キラルホスホネート誘導体を用いたジアステレオ選択的不斉反応の例を挙げた．これらの反応で得られる化合物の中には，有機合成化学上の有用性が高いものもあるが，その一方で，基質への不斉源の導入，および生成物からの除去などの手間が生じる．

これらの不斉反応をキラル外部配位子でコントロールが可能となり，用いた不斉源を容易に回収できれば，さらに効率よく目的の化合物の光学活性体を合成することが可能となる．キラル外部配位子を用いるエナンチオ選択的不斉反応の例は，戸田らによる固相中における不斉 Wittig 反応の報告[16]のみであり，エナンチオ選択的不斉 Horner–Wadsworth–Emmons反応は現在まで報告されていない．

F. Toda and H. Akai (1990).



73% ee (-)

そこで筆者は，未開拓な分野であると考えられる，キラル外部配位子を用いたアキラルホスホネートとプロキラルケトンのエナンチオ選択的不斉Horner–Wadsworth–Emmons反応の開発を目的とし，本研究に着手した．

第２節　キラルアルコキシドを用いたエナンチオ選択的不斉反応

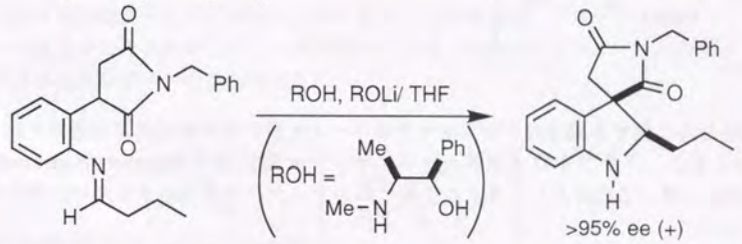
アルコキシドは有機合成化学において汎用される塩基の一つである．しかし，塩基性が十分でないため，アルコキシドを塩基として用いる不斉反応の例は少ない．

近年，柴崎らにより，希土類金属を含むキラルアルコキシドを塩基性触媒として用いた種々のエナンチオ選択的不斉反応に関する研究が精力的に行われている[17]．

一方，アルカリ金属イオンを対カチオンとするキラルアルコキシドを塩基として用いた例は，Speckamp らの不斉分子内アルドール反応[18]，Duhamel らによる脱ハロゲン化水素による脱ラセミ化反応の例[19]がある．

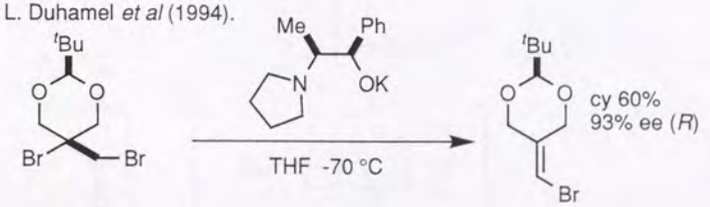
不斉反応で高い選択性を実現するためには、低温で反応を進行させることが必要となることが多く，塩基性があまり高くないアルコキシドを塩基として用いる不斉反応は困難なようにも考えられる．しかし，これらの例を見れば，アルコキシドを不斉反応のキラル塩基として利用できる可能性は十分にあると思われる．

W. N. Speckamp *et al* (1984).



>95% ee (+)

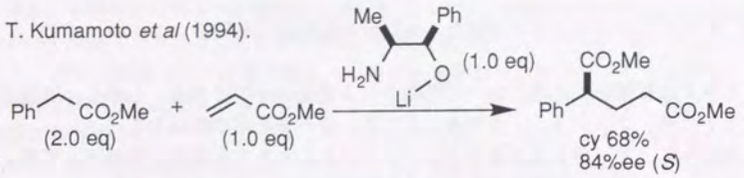
L. Duhamel *et al* (1994).



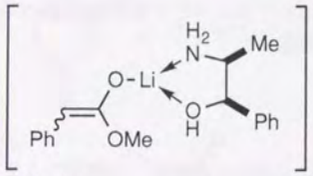
cy 60%
93% ee (*R*)

一方，筆者の研究室において，４座配位型キラルアミンを用いた，リチウムエノラートのエナンチオ面識別に基づく種々の不斉反応を実現している．この反応における高いエナンチオ選択性には，キラルアミン−リチウムエノラート−臭化リチウムの３者の錯体形成が重要であると考えられている[20]．我々はこの概念をキラルリチウムアルコキシドを用いる不斉反応にも適用できるのではないかと考え，エナンチオ選択的不斉マイケル反応を検討したところ，２座配位型のキラルリチウム 2-アミノアルコキシドが有効な不斉塩基として機能しうることを見いだした[21]．

T. Kumamoto *et al* (1994).



この不斉マイケル付加反応は，キラルな外部配位子，すなわちキラルアルコキシドが脱プロトン化した後に生じるキラルアミノアルコールがアキラルなリチウムエノラートに配位して，不斉誘起に有効なキラルな錯体を形成した結果であると考えられる（**Figure**）．

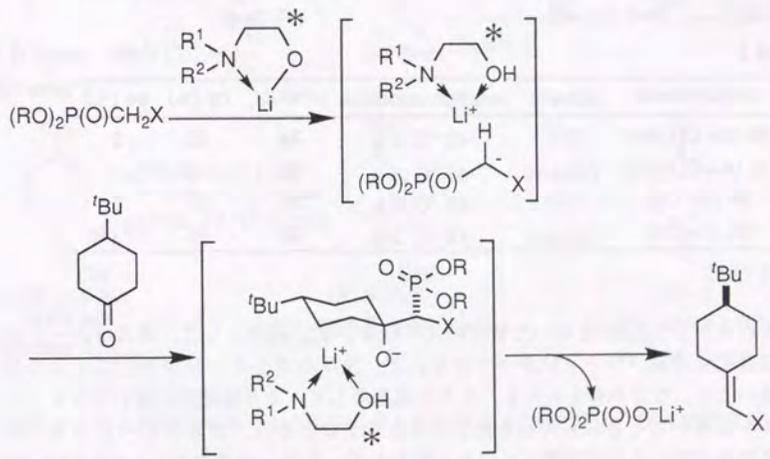


Figure

この錯体形成に関する概念はアキラルホスホネートを用いる不斉反応にも適用可能ではないかと考え，アキラルホスホネートのエナンチオ選択的不斉Horner–Wadsworth–Emmons反応に用いる塩基としてキラルリチウム2-アミノアルコキシドを用い，検討することとした．

Horner–Wadsworth–Emmons反応に用いられるホスホネートのカルバニオンの構造に関する報告が，Seyden-Penne ら[22]，Denmark ら[23]，およびBoche ら[24]によりなされている．特にDenmark らは，X線結晶構造解析や，NMRなどの方法を用い，β位にフェニル基を持つホスホネートのカルバニオンがsp^2様の構造をとるのに対し，β位置換基が脂肪族になるとsp^3性が上昇することを見出した．一方，アルコキシドが適用可能であると思われる酸性度の高い活性メチレンを有するホスホネート，すなわちβ位にエステルやニトリルを有するホスホネートのカルバニオンについても，Seyden-Penne らが，IR，NMRなどを用いた研究から，sp^2構造をとっていることを示唆する結果を得ている．そこで筆者は，ホスホネート カルバニオンがエステルエノラートのような平面な構造をとることを想定し，カルボニル化合物へのアルドール反応の段階でホスホネート カルバニオンのエナンチオ面が識別できれば，この不斉反応は達成できる，と考えた．

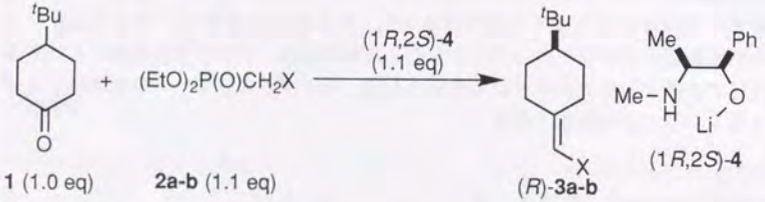
そこで，反応系としては以下のように仮定した．すなわち，リチウムを含むキラル塩基によるアキラルホスホネートの脱プロトン化，生じたホスホネート カルバニオンとキラルな外部配位子とのリチウムイオンを介した錯体形成，プロキラルケトンとのアルドール反応でのキラルなアルドール中間体の生成，およびホスフェートの脱離反応によるキラルなオレフィンの生成である．



第２章　キラルアルコキシドを用いるアキラルホスホネートのエナンチオ選択的不斉 Horner–Wadsworth–Emmons 反応

第１節　アキラルホスホネートの検討

キラル塩基として，２座配位型であるエフェドリンのリチウムアルコキシド（(1*R*,2*S*)-**4**），プロキラルケトンとして 4-*tert*-butylcyclohexanone （**1**）を用い，エナンチオ選択的不斉 Horner–Wadsworth–Emmons 反応を検討した．ホスホネートとして，エステルを有する**2a** を用いると，THF，toluene のいずれの溶媒を用いた場合においても，化学収率は低く，不斉は全く誘起されなかった（run 1, 2）．一方，ニトリルを有する **2b** を用いると，反応は速やかに進行した．溶媒としてTHFを用いると不斉は誘起されなかったが，toluene を用いると，17% eeで (*R*)- **3b** が得られ，わずかではあるが不斉誘起が見られた（run 3, 4）（**Scheme 1**, **Table 1**）．



Scheme 1

run	phosphonate	solvent	reaction condition	product	cy (%)	ee (%)
1	**2a** (X= CO_2Me)	THF	-45 °C 3 h	**3a**	42	0
2	**2a** (X= CO_2Me)	Toluene	-45 °C 3 h	**3a**	18	< 1
3	**2b** (X= CN)	THF	-45 °C 3 h	**3b**	99	0
4	**2b** (X= CN)	Toluene	-78 °C 3 h	**3b**	86	17 (*R*)

Table 1

ホスホネートとして**2a** を用いた場合に化学収率が低い理由として，ホスホネートのキラル塩基による脱プロトン化が不十分なこと，及びホスホネートカルバニオンの反応性が低いこと，などが考えられる．キラル塩基として，より塩基性の高いキラルリチウムアミドを用いたときにも同様な化学収率を示すことから，ホスホネートカルバニオンの反応性が低いことが影響していると思われる．なお，ホスホネートα位のpK_a (in EtOH, 20.0 ℃)は，それぞれ19.75 (**2a**)，18.35 (**2b**)と報告されている[25]．

ホスホネート**2b** では不斉誘起が見られるのに対し，**2a** では不斉は誘起されなかった．**2b** のリチウム塩の構造は不明であるが，**2a** のリチウム塩は環状をとることが予想される[22]．キラル配位子が**2a** のリチウム塩に配位しても単一の錯体を形成できない（**A**若しくは**B**）ために不斉が誘起されないと考えられる（**Figure 1**）．

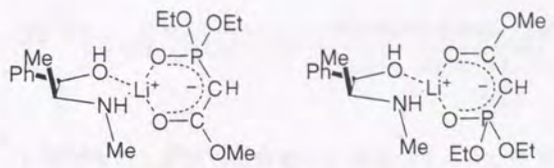
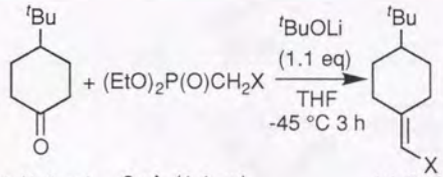


Figure 1

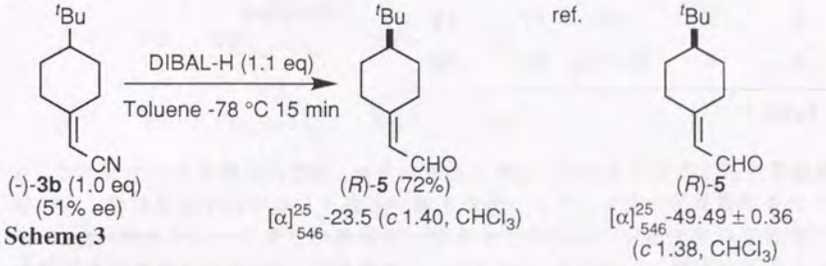
なお，得られた化合物の不斉収率は，光学活性ガスクロマトグラフィー，および光学活性高速液体クロマトグラフィーにより決定した．別途ラセミ体を合成し（**Scheme 2**, **Table 2**），ラセミ体のピークが分離する条件で，それぞれのピークの面積比が1: 1 を示すことを確認した．**3b** の絶対配置は，DIBAL-H還元で文献既知のアルデヒド[26]とし，その旋光度の向きを比較することにより決定した（**Scheme 3**）．



run	phosphonate	product	cy (%)
5	**2a**	**3a**	42
6	**2b**	**3b**	quant

Table 2

Scheme 2



Scheme 3

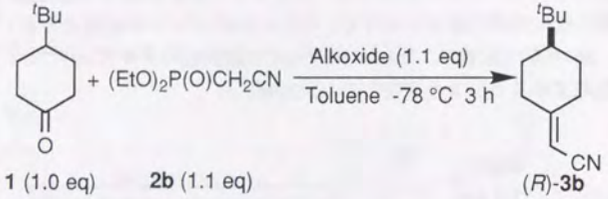
以下，アキラルホスホネートとしてニトリルを有する**2b** を用い，種々検討を行った．

第２節　キラルアルコキシドの検討

前節で設定した反応系について，キラルリチウムアルコキシドのスクリーニングを行った．

1) 窒素上置換基の効果.

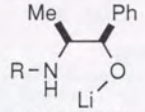
キラルリチウム 2-アミノアルコキシドの窒素上の置換基の効果について調べた（**Scheme 3, Table 3**）．窒素上の置換基をかさ高くするにつれて不斉収率が向上し，ネオペンチル基を有する(1*R*,2*S*)-**8** を用いたときに，化学収率 92%，52% eeで現在までのところ最高の不斉収率で，(*R*)-**3b** が得られた．



1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**

Scheme 3

run	Alkoxide	R	cy (%)	ee (%)
1	**6**	H	98	4
2	**4**	Me	86	17
3	**7**	^{i}Pr	77	19
4	**8**	^{t}BuCH$_2$	92	52

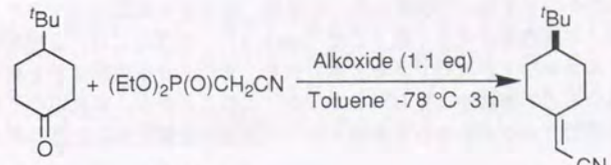


(1*R*,2*S*)-**4-8**

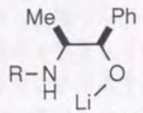
Table 3

窒素置換基上のかさ高さが，α位に必要なのか，β位に必要なのかを調べた．α位に大きな置換基を有し，**7** よりもかさ高いと考えられる**9** を用いたが，不斉収率は改善されなかった（run 3）．**9** のフェニル基のうちの一方をのぞいた**10** を用いると不斉収率は回復する（run 4）．この結果は，β位のかさ高さが重要であることをも示唆する結果であると考えられる．

次に，β位置換基のかさ高さについて検討した．β位をフェニル基，ネオペンチル基とかさ高くするにつれ，不斉収率が向上している．そのほかのβ位がかさ高いアルコキシドを用いて検討したところ，**11**，**12**，**14**を用いたときに**8** に匹敵する不斉収率を実現した（run 5- 6, 8）．これらの結果から，β位を中心とするかさ高さが，本反応の不斉誘起に重要な役割を果たしていると考えられる．一方，β位に *tert*- ブチル基のみを有する**15** では，不斉収率が低下した（**Table 4**）．



1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**



(1*R*,2*S*)- **7-15**

Scheme 3

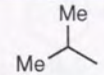
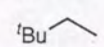
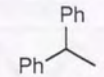
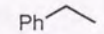
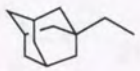
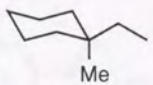
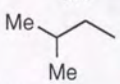
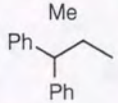
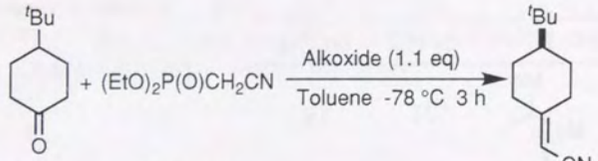
run	Alkoxide	R	cy (%)	ee (%)
1	**7**		77	19
2	**8**		92	52
3	**9**		86	16
4	**10**		84	34
5	**11**		86	51
6	**12**		70	48
7	**13**		87	40
8	**14**		96	49
9	**15**		87	20

Table 4

配座数の異なるアルコキシドを用いて検討した．3座型，および4座型のアルコキシドを用いて検討したが，不斉収率は大きく低下した（run 1, 2）．本反応には，2座配位型のキラルリチウムアルコキシドが有効であると思われる．また，分子内配位子を有しないアルコキシドを用いると不斉誘起は見られなかった．このことから，本反応の不斉誘起には，分子内配位子とリチウムを含む5員環キレート構造が重要であると思われる（run 3, 4）（**Table 5**）．

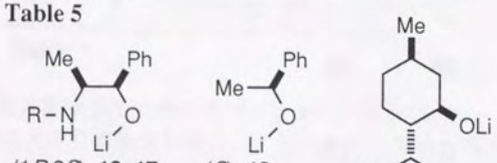


1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**

Scheme 3

run	Alkoxide	R	cy (%)	ee (%)
1	**16**	MeO	95	17
2	**17**	Me, Me_2N	91	4
3	**18**		95	1
4	**19**		75	0

Table 5

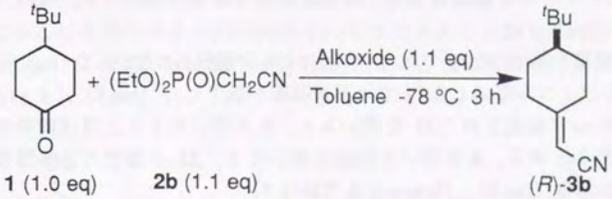


(1*R*,2*S*)- **16**- **17**

(*S*)- **18**

19

分子内配位子として3級アミノ基を有するキラルアルコキシドを用い，検討した．いずれのアルコキシドを用いても，比較的良い結果が得られ，アミノ基が2級でなければならないわけではないことが示された（run 1- 4）．一方，**8** のアミノ基にメチル基を導入した**24** では，全く不斉誘起が見られなかった（run 5）（**Table 6**）．



1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**

Scheme 3

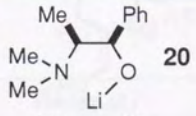
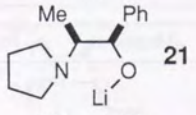
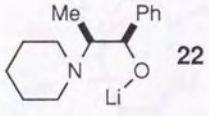
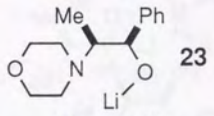
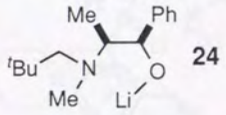
run	Alkoxide	cy (%)	ee (%)
1	 **20**	89	41
2	 **21**	93	29
3	 **22**	92	31
4	 **23**	81	49
5	 **24**	88	0

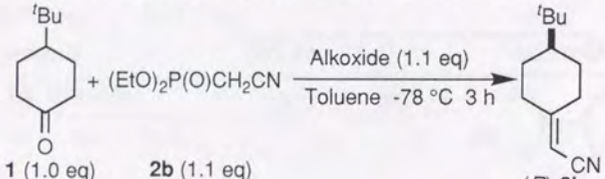
Table 6

2) 炭素上置換基効果

窒素上の置換基をネオペンチル基に固定し，アミノアルコール炭素上の置換基の効果について検討した．**8** の炭素上の置換基をメチル基のみにした**25**，フェニル基のみにした**26** を用い検討したが，不斉収率は低下し，両方の置換基が必要であることがわかった（run 2, 3）．**25** などのアミノ酸誘導体は，置換基のかさ高さに関わらず，ほぼ一定の不斉収率を示した（run 4, 5）．

8 のメチル基の相対配置を逆にした**30** では，不斉はほとんど誘起されなかった（run 7）．また，**8** のメチル基をフェニル基にした**31** では不斉収率が低下した（run 8）．

アミノ基と水酸基が*cis* に固定された**32** を用いると，**8** を用いたときとほぼ同等の不斉収率を示した．このことから，**8** を用いた反応においても，**32** と類似の立体構造をとっているものと思われる（run 9）（**Scheme 3**, **Table 7**）．



Scheme 3

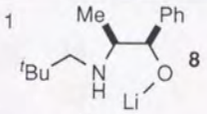
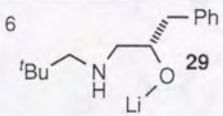
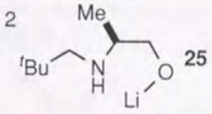
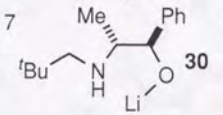
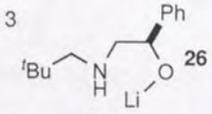
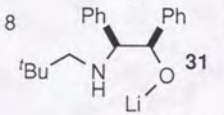
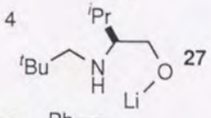
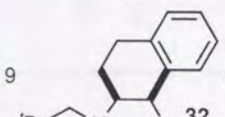
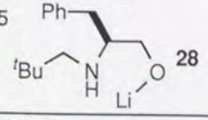
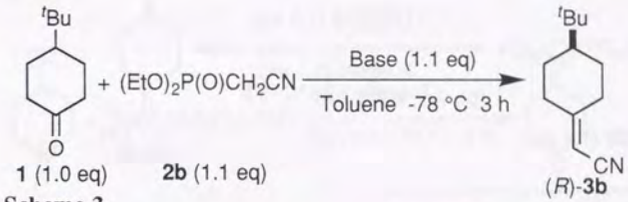
run	Alkoxide	cy (%)	ee (%)	run	Alkoxide	cy (%)	ee (%)
1	 **8**	92	52	6	 **29**	85	16 (*S*)
2	 **25**	81	23	7	 **30**	88	2
3	 **26**	93	14	8	 **31**	65	20
4	 **27**	85	29	9	 **32**	83	46
5	 **28**	77	23				

Table 7

3) リチウムアミドを用いた検討，およびリチウム塩の添加の効果

種々のキラルリチウムアミドを用い，検討を行った．**8** のジアニオン**33**，およびアルコールをメチル基で塞いだリチウムアミド**34** を用いて検討したが，不斉誘起は見られなかった（run 2, 3）．また，我々の研究室で開発された，エナンチオ選択的不斉脱プロトン化反応に有効な**35**，およびエナンチオ選択的不斉アルキル化反応に有効なキラル外部配位子のリチウムアミド**36** とも低い不斉収率を示した（run 4, 5）．また，spartein を用い検討したが，低い不斉収率を示した（**Scheme 3**, **Table 8**）．



Scheme 3

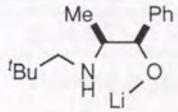
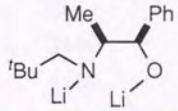
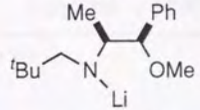
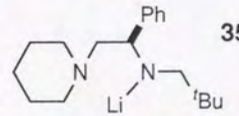
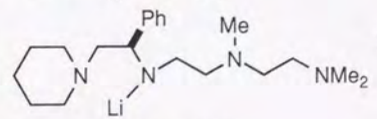
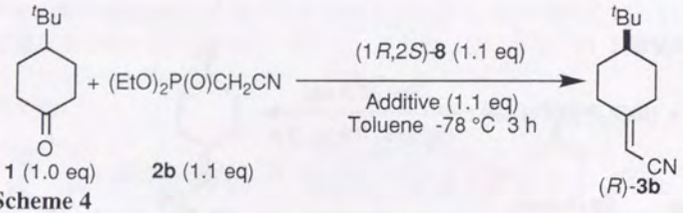
run	Base	cy (%)	ee (%)
1	 **8**	92	52
2	 **33**	71	4
3	 **34**	51	0
4	 **35**	77	0
5	 **36**	85	9 (*S*)
6	(-)-Spartein, *n*-BuLi	88	10 (*S*)

Table 8

また，種々のリチウム塩を添加した系で検討した．

Run 2 では，反応系に1.1 当量のLiBr を添加したが，不斉収率の低下が見られた．しかし，かなりの量のLiBr が溶け残り，LiBr を添加を添加したときの系が実現できなかった．そこで，run 3 では**8-OH** の塩酸塩に対してBuLi を2 当量加えてLiCl を発生させて検討した．反応は均一系となったが不斉収率は大きく低下した．また，Horner–Wadsworth–Emmons 反応の副生成物として生じるホスフェートのリチウム塩を添加すると，不斉収率の低下が見られた（run 4）（**Scheme 4**, **Table 9**）．

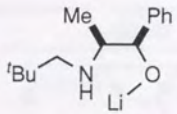


Scheme 4

run	Additive	cy (%)	ee (%)
1	none	92	52
2	LiBr[a]	67	43
3	LiCl	67	7
4	$(EtO)_2P(O)OLi$	80	41

[a] A part of LiBr was insoluble.

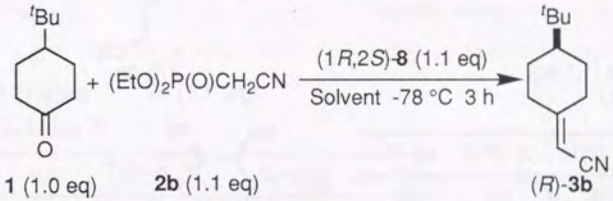
Table 9



(1*R*,2*S*)-**8**

本反応の不斉収率は，用いる溶媒に顕著な影響を受ける．

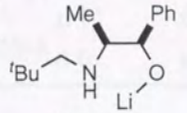
キラルアルコキシドとして**8** を用いた場合，tolueneが最も良い結果を与えた．Et_2Oを用いると不斉収率は低下し，THF，DMEでは不斉は誘起されなかった．また，tolueneを用いたときに，外部配位子としてHMPA 1.0当量を添加すると，不斉収率の低下が見られた．溶媒の配位能が高くなるにつれて不斉収率が低下することから，配位能の高い溶媒中では，ホスホネートのリチウム塩が溶媒和され，不斉誘起に有効な，キラルアミノアルコールとの錯体の形成が妨げられている，と考えることができる（**Scheme 5**, **Table 10**）．



Scheme 5

run	Solvent	cy (%)	ee (%)
1	Toluene	92	52
2	Et_2O	94	34
3	DME	93	1
4	THF	87	0
5	Toluene + HMPA (1.0 eq)	95	28

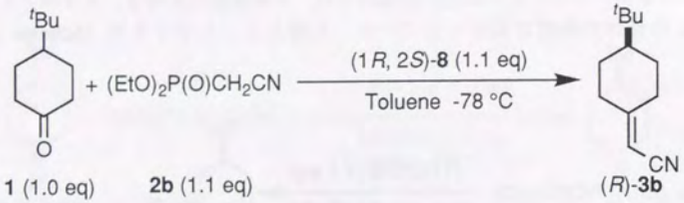
Table 10



(1*R*,2*S*)-**8**

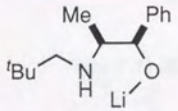
第4節　反応時間の効果

キラルアルコキシドとして(1*R*,2*S*)-**8** を用い，反応時間を変化させて検討した．いずれの反応時間においてもほぼ同等の不斉収率を示した．本反応の生成物が α, β- 不飽和ニトリルであり，アミンなどのマイケル付加－逆マイケル反応によるラセミ化の可能性があるが，反応時間の間では，このようなラセミ化は起きていないと思われる（**Scheme 3, Table 11**）．



1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**

Scheme 3



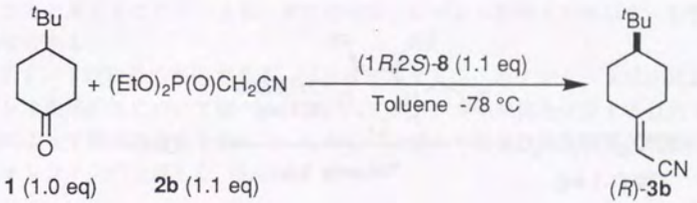
(1*R*, 2*S*)-**8**

run	reaction time	cy (%)	ee (%)
1	10 min	58	49
2	30 min	70	51
3	1 h	84	51
4	3 h	92	52

Table 11

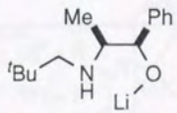
第5節　反応温度の効果

キラルアルコキシドとして (1*R*,2*S*)-**8** を用いて，種々の反応温度における不斉Horner–Wadsworth–Emmons 反応を検討した．反応温度を下げるに従って不斉収率は向上し，-78 ℃のときに 52% eeを示した（run 1- 4）．さらに反応温度を下げることで不斉収率の改善が見込まれたが，予想に反し，-100 ℃では不斉収率は改善されず，むしろ低下した（run 5）．この原因については第5章で議論する（**Scheme 3, Table 12**）．



1 (1.0 eq)　　**2b** (1.1 eq)　　(*R*)-**3b**

Scheme 3

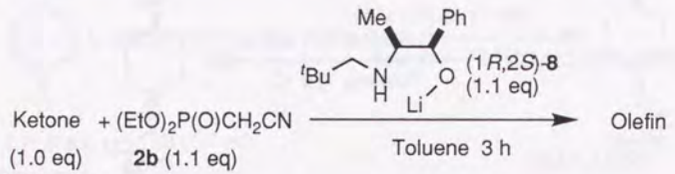


(1*R*, 2*S*)-**8**

run	Temp (°C)	cy (%)	ee (%)
1	–20	90	28
2	–60	79	42
3	–78	92	52
4	–100	85	48

Table 12

キラルアルコキシドとして (1*R*,2*S*)-**8** を用いて，種々のプロキラルケトンとの不斉 Horner–Wadsworth–Emmons 反応を検討した．Cyclohexanone 4 位置換基がメチル基のときに不斉収率の低下が見られるが（run 4），イソプロピル基，およびフェニル基のときは *tert*- ブチル基のときとほぼ同等の不斉収率を示した（run 1- 3）．また，bicyclo[3.3.0]octane-3,7-dione を基本骨格とするプロキラルケトンを用いて検討したが，低い不斉収率を得るにとどまった（run 5）（**Scheme 6**, **Table 13**）．



Scheme 6

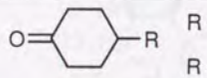
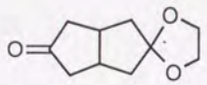
run	Ketone		Temp (°C)	cy (%)	ee (%)
1		R = ^{t}Bu	-78	92	52 (*R*)
2		R = Ph	-78	85	46
3		R = ^{i}Pr	-78	94	47
4		R = Me	-78	84	36
5			-45	98	14

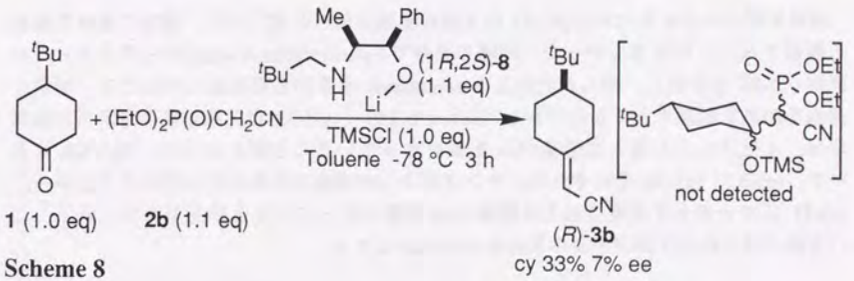
Table 13

前章までにおいて設定した反応系について，反応メカニズムを解析するために，以下のような検討を行った．

第1節　アルドール中間体の合成

Horner–Wadsworth–Emmons 反応は，ホスホネートカルバニオンのカルボニル化合物へのアルドール反応，およびそれに続くホスフェートが脱離する反応の2段階の反応からなると考えることができる．本反応では，いずれの段階も不斉収率に影響を与える可能性がある．

まず，1段階目の反応である，プロキラルケトンへのアルドール反応におけるジアステレオ面選択性について調べる目的と，アルドール中間体を合成する目的で，シリル化剤による中間体の捕捉を試みた．しかし，所望の中間体は得られず，脱離反応が進行したオレフィンが生成した（**Scheme 8**）．



Scheme 8

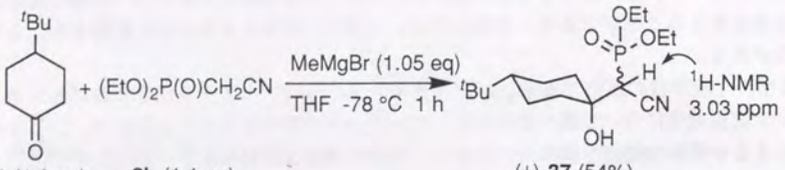
オレフィンの化学収率が低下した理由としては，アルコキシドの窒素がシリル化されて塩酸が発生し，アルコキシドを消費したためであると考えられる．また，不斉収率の低下した理由としては，TMSClやシリル化されたアルコキシド，副生した LiCl が反応に関与したためと思われる．

そこで，2段階目の反応であるアルドール中間体からホスフェートが脱離する反応について，別途合成したアルドール中間体をキラルリチウムアルコキシドで処理することにより検討することとした．

β位に-CN，-CO_2R，-COR などの電子吸引基を有するホスホネートを用いた Horner–Wadsworth–Emmons 反応において，対カチオンにリチウムやナトリウム，カリウムなどの金属を用いた場合，-100 ℃においても速やかに脱離反応が進行し，アルドール中間体は得られないが[1b]，対カチオンにマグネシウムを用いると，アルドール中間体の単離が可能なことが知られている．すなわち，Seyden-Penne らは，ホスホネートと Grignard 試薬から調製したマグネシウム塩を benzaldehyde と反応させると，アルドール中間体が得られることを報告している[26]．

この方法を用い，4-*tert*-butylcyclohexanone とのアルドール中間体の合成を試みた．溶媒としてTHF を用いると，脱離反応が進行した(±)-**3b** も生成するものの，アルドール中間体 (±)-**37** を単離することができた．単離した (±)-**37** は単一のジアステレオマーであった（**Scheme 9**）．

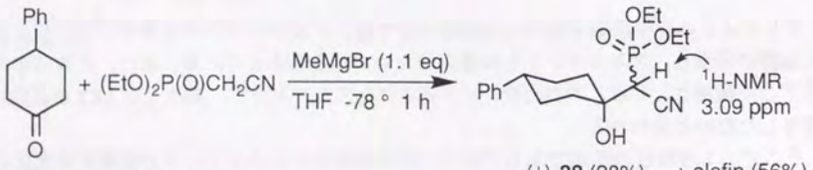
(±)-**37** の合成に際し，反応時間を 3 h に延長しても化学収率に大きな差が見られなかった．このことは，THF 中において(±)-**37** のマグネシウム塩は，低温では比較的安定であることを示していると思われる．



1 (1.0 eq) **2b** (1.1 eq) (±)-**37** (54%) + (±)-**3b** (32%)

Scheme 9

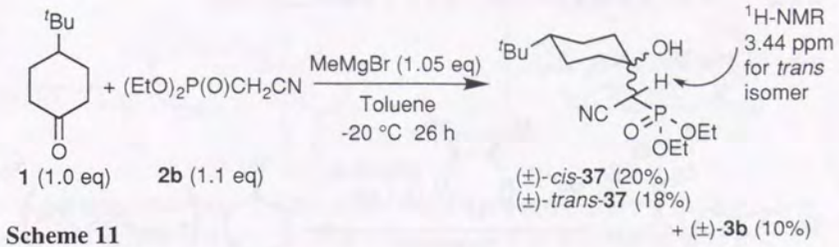
相対配置を決定するために(±)-**37** のX線結晶構造解析を試みたが，測定に適当な結晶を調製することができなかった．同様の条件で4-phenylcyclohexanone からアルドール中間体 (±)-**38** を合成し，得られた結晶をisopropanol–水系から再結晶したところ，測定に適当な結晶を調製することができた（**Scheme 10**）．(±)-**38** はX線結晶構造解析の結果から，4 位フェニル基と水酸基が*cis* 配置をとっていることがわかった．^{1}H-NMR において，(±)-**37**，(±)-**38** それぞれのメチンプロトンが同様の化学シフトを示すことから，(±)-**37** についても 4 位置換基と水酸基が*cis* 配置をとっていると予想された．以下，この方法で得られたアルドール中間体を(±)-*cis*-**37**とする．



(1.0 eq) **2b** (1.1 eq) (±)-**38** (28%) + olefin (56%)

Scheme 10

一方，trans 配置のアルドール中間体 (±)-*trans*-**37** は，溶媒として toluene を用いたときに単離することができた（**Scheme 11**）．化学収率の低下は，toluene 中ではホスホネートのマグネシウム塩が析出したためであると思われる．得られた (±)-*trans*-**37** は不安定で，室温で 2 日放置すると，^{1}H-NMR において 5.03 ppm にオレフィン由来と思われるピークが観察された．

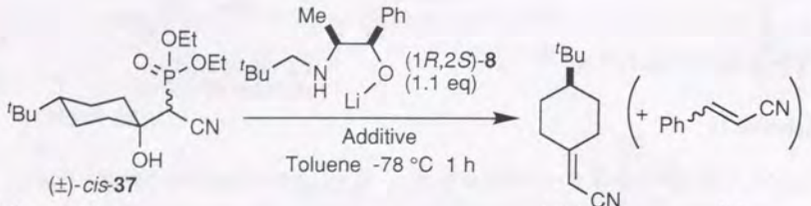


1 (1.0 eq) **2b** (1.1 eq) (±)-*cis*-**37** (20%) (±)-*trans*-**37** (18%) + (±)-**3b** (10%)

Scheme 11

こうして得られたアルドール中間体を用い，種々の条件で脱離反応の検討を行った．

1) (±)-*cis*-**37**を用いた検討



Scheme 12

run	eq of **8**	Additive	**3b** cy (%)	**3b** ee (%)	**39** (*E*)	**39** (*Z*)
1	1.1	none	89	52 (*R*)	——	
2	0.5	none	51	52 (*R*)	——	
3	1.1	PhCHO (1.0 eq)	40	18 (*R*)	31	1

Table 14

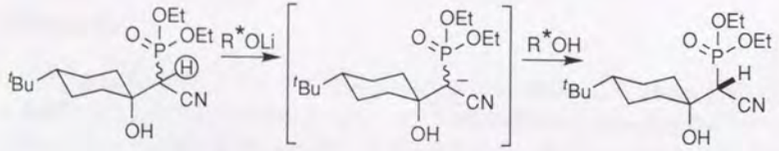
(±)-*cis*-**37** を 1.1 当量の (1*R*,2*S*)-**8** で処理したところ，化学収率 89%，52% eeで元の不斉反応と同じ (*R*)-**3b** が得られた（**Scheme 12**, **Table 14**, run 1）．

(±)-*cis*-**37** の水酸基が脱プロトン化された後，直ちにホスフェートが脱離すれば，ラセミ体の**3b** が生成するはずである．しかし、実際に得られた**3b** は光学活性体であった．この理由として，以下の理由が考えられる．

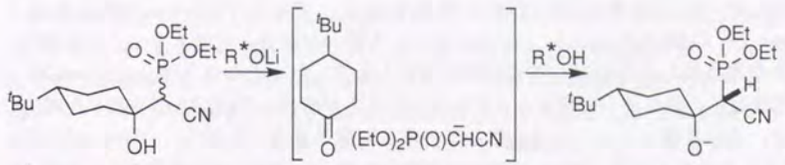
まず，run 1において，得られた**3b** のうち(*R*)-体が 68%，(*S*)-体が 21% 得られたことになり，片方のエナンチオマーの生成が 50%を越えている．このことは，この反応の不斉誘起が直接的な速度論的光学分割によるものではないことを示している．

その他に，以下の可能性が考えられる．

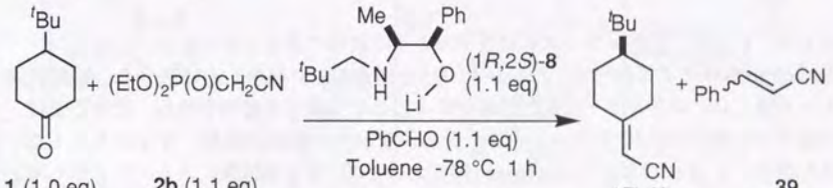
1) (±)-*cis*-**37** の活性メチンの酸性度が高いため，キラルアルコキシドにより脱プロトン化された後，再びプロトン化される際に不斉が誘起される可能性．



2) (±)-*cis*-**37** からは，ホスフェートの脱離反応よりも早くレトロアルドール反応が進行し，いったんケトンとホスホネート カルバニオンに戻った後，キラル外部配位子存在下再び反応が進行し，不斉が誘起される可能性．



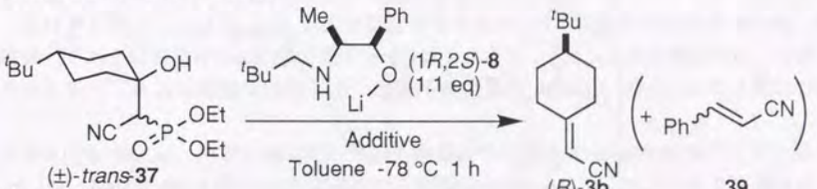
1) の可能性については，この系を評価する適当な系を組むことができていない．一方，2) の可能性については，1.1 当量の benzaldehyde を添加して検討したところ，cinnamonitrile (**39**)の生成が確認された（run 3）．このことから，アルドール中間体からレトロアルドール反応が進行して，一旦ホスホネート カルバニオンが生成していることが示された．なお，この反応における**3b** と**39**の生成比は約１：１であった．また，0.5当量の**8** を用いた検討した結果においても，元の不斉反応と同じ不斉収率を示した（run 2）．なお，(1*R*,2*S*)-**8** をキラル塩基とし，1.1当量の**2b**に対して，それぞれ1当量ずつの**1** と benzaldehyde との混合物を反応させると，得られた**3b**と**39**の比は約１：3.5であった(**Scheme 13**).



1 (1.0 eq)　**2b** (1.1 eq)

Scheme 13

2) (±)-*trans*-**37** を用いた検討．



Scheme 14

run	eq of **8**	additive	**3b** cy (%)	**3b** ee (%)	**39** (*E*)	**39** (*Z*)
1	1.1	none	84	12 (*R*)	——	
2	0.5	none	41	3 (*S*)	——	
3	1.1	PhCHO (1.0 eq)	58	0	16	1

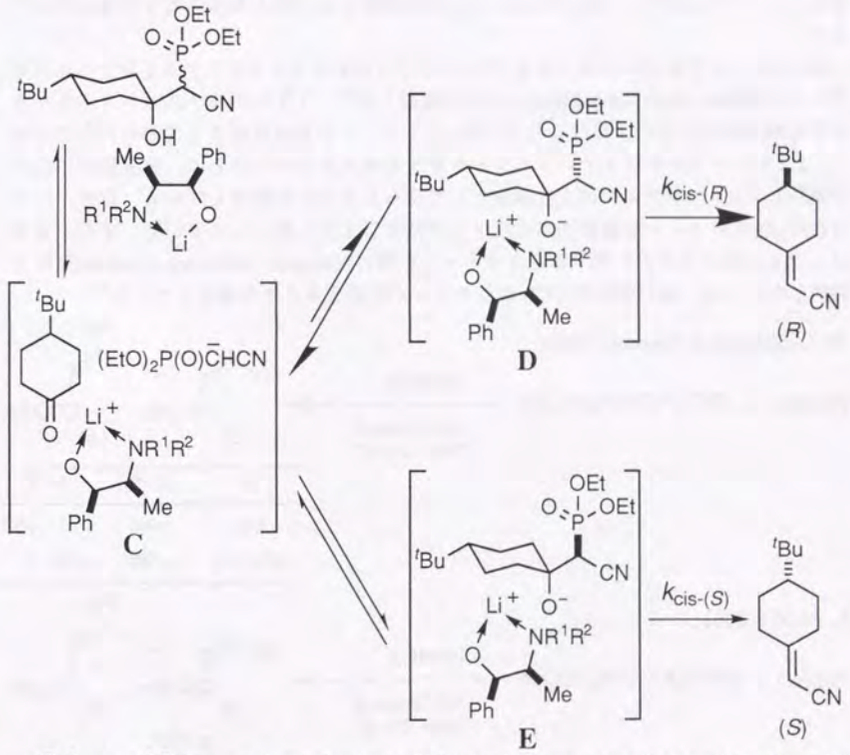
Table 15

(±)-*trans*-**37** を1.1 当量の(1*R*,2*S*)-**8** で処理すると，12% ee で(*R*)-**3b** が得られた（**Scheme 14**, **Table 15**, run 1）．先の(±)-*cis*-**37** を用いた結果と比較すると，化学収率には大きな差は見られないが，不斉収率は大きく低下した．このことは，(±)-*trans*-**37** からの脱離反応の際には一部はレトロアルドール反応が進行して(*R*)-**3b** が有利に生成しているが，その規模は小さいことを示していると解釈される．しかし，(±)-*trans*-**37** を0.5 当量の**8** で処理すると，3% ee で(*S*)-**3b** が得られた（run 2）．1.1 当量の**8** で処理したときに一部はレトロアルドール反応が進行して(*R*)-**3b** が有利に生成していることを考えあわせると，run 2 においては，レトロアルドール反応による(*R*)-**3b** の生成を凌駕するような，(*S*)-**3b** が有利に生成する系が存在していることが予想される．例えば，(±)-*trans*-**37** の水酸基の脱プロトン化，もしくはホスフェートの脱離反応における速度論的光学分割などが考えられる．

一方，benzaldehyde 存在下の脱離反応を検討したところ，**3b** と，benzaldehyde由来のオレフィンの生成比は約３：１で，benzaldehyde由来のオレフィンの生成比は，(±)-*cis*- **37** を用いた結果と比較すると小さくなっている．また，この反応で得られた**3b** は，0% ee であった．（run 3）．

以上のことから，反応メカニズムは以下のように説明できると思われる．
Benzaldehyde存在下において，(±)-*cis*-**37** を1.1 当量の**8** で処理した結果から，脱離反応よりも速くレトロアルドール反応が進行することを示唆する結果を得た．このことは，アルドール体(±)-*cis*-**37** のアニオンが，元の不斉反応の初期の状態，すなわちケトンとホスホネートカルバニオン（**Scheme 15**においてC）と平衡状態にあることを示していると思われる．実際，ホスホネートのpK$_a$（約18）とアルコールのpK$_a$が近い値を取っていることからも支持される．また，アルドール体のアニオンとキラルアミノアルコールの錯体（**D**, **E**）は互いにジアステレオトピックな関係にあるため，錯体の安定度，いいかえれば，アルドール体の脱離反応の速度に差が生じる可能性がある．本反応においては，(*R*)-**3b** を生成する錯体（**D**）のほうが不安定である（$k_{cis\text{-}(R)} > k_{cis\text{-}(S)}$）と考えられる．すると，**D**が消費されるに従い，**C**もしくは**E**から平衡を経由して**D**が供給されて，最終的には得られる(*R*)-**3b** と(*S*)-**3b** の量に差が生じ，不斉誘起が観察される，と考えられる．
その一方で，benzaldehyde 非存在下での脱離反応では(*R*)-**3b** が67%，(*S*)-**3b** が21%得られた計算になるのに対し，benzaldehyde 存在下での脱離反応では(*R*)-**3b** が24%，(*S*)-**3b** が16% 得られた計算になり，(*R*)-**3b** の生成だけが大きく低下している．(*R*)-**3b** の生成に用いられるはずのアニオンがbenzaldehyde に消費されたとすると，**C**と**D** との間の平衡は，**C**側に偏っていると思われる．**C**と**E** との間の平衡状態については不明であるが，全体的に見ると，**C**，**D**，**E**の間では**C**と**E**に平衡が偏っているであろう．Benzaldehyde 存在下では，**E**からの脱離反応は遅いにもかかわらず，**D**が供給されないため，見かけ上，不斉収率が低下する．
一方，(±)-*trans*-**37** については，(±)-*cis*-**37** の場合よりもレトロアルドール反応が起きている程度は小さいと思われる．しかし，0.5 当量の**8** で処理したところ，わずかではあ

るが(*S*)-**3b** が主に生成しているが確認された．一部レトロアルドール反応が進行して*cis*-**37** となり，**D**からの脱離反応を経て(*R*)-**3b** を主に生成する経路の他に，(*S*)-**3b** を主に生成する経路，たとえば(*S*)-**3b** 由来のアルドール体からの速度論的光学分割，などが起きている可能性がある．また，benzaldehyde 存在下での脱離反応では0% ee であった．この反応では，レトロアルドール反応ののち**D** を経由して生じるはずの(*R*)-**3b** が benzaldehyde により消費され，また速度論的光学分割などの別経路により(*S*)-**3b** が優先的に生成した結果，たまたま0% ee であったと解釈している．しかし，プロキラルケトンへのアルドール反応における立体的要因から，*trans*-**37** が実際の不斉反応に対する寄与は，小さいと考えている．



Scheme 15 Proposed mechanism of elimination reaction of phosphate from (±)-*cis*-**37** mediated by chiral lithum alkoxides.

第4章　ホスホネートのエステル置換基の効果

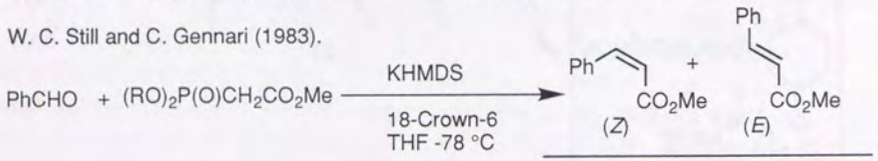
第3章において，本不斉反応の不斉誘起が，レトロアルドール反応を経て生じるアルドール体のアニオンと，キラルアミノアルコールとの錯体の安定性に起因することが示唆された．そこで，レトロアルドール反応を経ずに，速度論的に反応が進行すると考えられるホスホネートを用いた不斉Horner– Wadsworth–Emmons反応を検討した．

第1節　背景

Horner–Wadsworth–Emmons反応では，多くの場合，(*E*)-オレフィンが主生成物として得られる．それに対し，(*Z*)-オレフィンを主生成物として得る反応の開発が進められてきた．

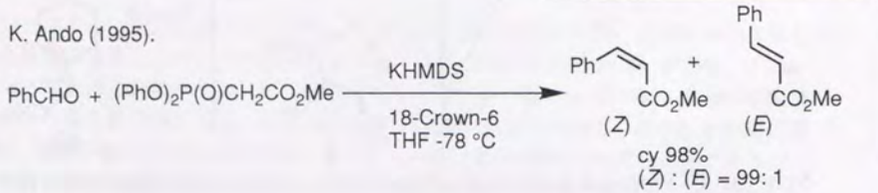
Still らは，メチルエステル，および2,2,2-トリフルオロエチルエステルを有するホスホネートのHorner–Wadsworth–Emmons反応を検討した[28]．メチルエステルのホスホネートからは熱力学的に反応が進行した (*E*)-体のオレフィンが主生成物として得られたのに対し，2,2,2-トリフルオロエチルエステルを有するホスホネートからは，速度論的に反応が進行した(*Z*)-オレフィンが主生成物として得られることを報告している．以後，この方法は(*Z*)-オレフィンを選択的に合成する方法として広く用いられている．また，安藤は，フェニルエステルを有するホスホネートを用いたHorner–Wadsworth–Emmons反応を検討したところ，高い選択性で(*Z*)-オレフィンが生成することを報告している[29]．

W. C. Still and C. Gennari (1983).



R	cy (%)	*Z* / *E*
Me	>95	1 : >50
CF_3CH_2	>95	>50 : 1

K. Ando (1995).



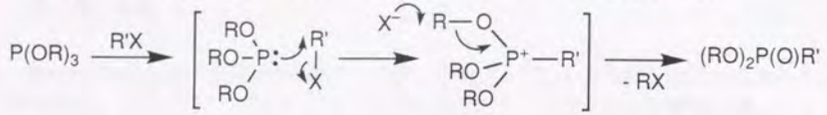
これら2つの反応に共通する点は，ホスホネートのエステル置換基に電子吸引基を有することである．これらの反応における (*Z*)-選択性は，ホスホネートのアルデヒドへのアルドール反応が進行した後，レトロアルドール反応を経ずに速やかに脱離反応が進行

するためであると考えられる．この方法を筆者の反応系に適用した場合，熱力学的なコントロールを受けて反応が進行する場合と，速度論的に反応が進行する場合とで，不斉収率にどのような変化が現れるか，比較検討することができる．

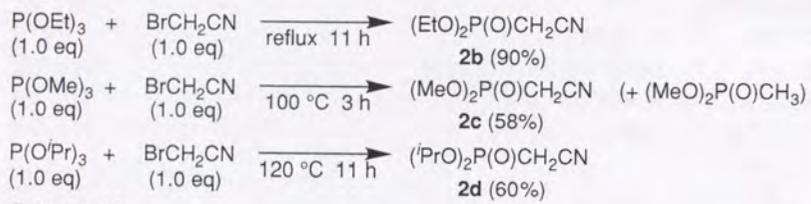
また，一般的な脂肪族エステルを有するホスホネートを用いた場合，立体的なかさ高さを変化させることにより，不斉収率への影響が予想される．そこで，種々のエステル置換基を有するホスホネートを用いた不斉Horner–Wadsworth–Emmons反応を検討した．

第２節　ホスホネートの合成

ホスホネートの一般的な合成方法として，Michaelis–Arbuzov反応が挙げられる[30]．Michaelis–Arbuzov反応は，亜リン酸エステルがハロゲン化アルキルに攻撃し，生じたホスホニウム塩のエステル置換基上の炭素–酸素結合が開裂し，ホスホネートとともに，別のハロゲン化アルキルが生成する反応である．炭素–酸素結合の開裂の段階は，ハロゲン化イオンの炭素原子への攻撃により促進されていることも予想される．

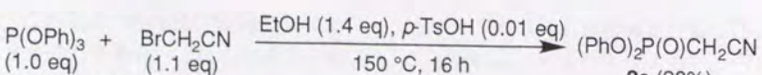


本反応により，エチルエステル **2b**，およびその他の脂肪族エステルを有するホスホネート**2c**，**2d** を合成した．メチルエステル**2c** については，副生するbromomethane がtrimethyl phosphite と反応するために化学収率は低下した（**Scheme 16**）．



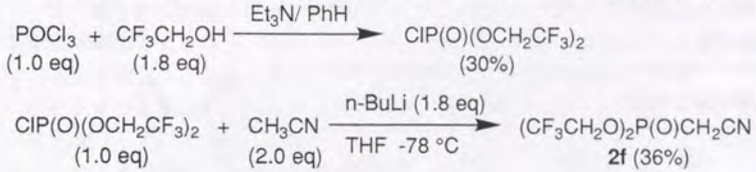
Scheme 16

次に，フェニルエステルを有するホスホネートの合成を検討した．Triphenyl phosphite を用いるMichaelis–Arbuzov反応は，そのままでは相当するホスホネートは得られなかった．そこで，Landauer らは，反応系中にmethanol を1当量加えて検討したところ，反応途中に生じるホスホニウム塩のフェニルエステルからメチルエステルへの置換反応が起こるため，Michaelis–Arbuzov反応が進行することを報告している[31]．これを参考にフェニルエステルのホスホネートの合成を試みたが，目的の化合物を得ることができなかった．Methanolの置換反応が速やかに進行しないこと，副生するbromomethane からも反応が進行すること，などの理由が考えられた．そこで，エステル置換反応を促進する目的で*p*-toluenesulfonic acid を加え，さらに，副生するハロゲン化アルキルの反応性を下げる目的で加えるアルコールを ethanol としたところ，低収率ながらもフェニルエステルのホスホネート**2e** を得ることができた（**Scheme 17**）．



Scheme 17

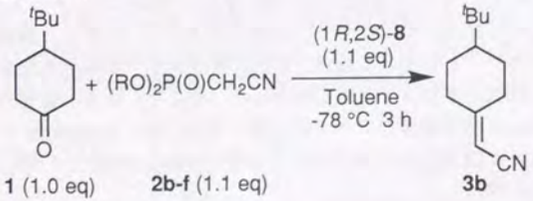
次に，2,2,2-トリフルオロエチルエステルを有するホスホネートの合成を検討した．Tris(2,2,2-trifluoroethyl) phosphite とのMichaelis–Arbuzov反応では，phosphite の求核性が低く，ハロゲン化アルキルへの求核攻撃が進行しにくいため，化学収率が低い．一方 Still らは，ホスホン酸メチルエステルを５塩化リンで処理して酸クロリドとし，2,2,2-trifluoroethanol と反応させて目的のホスホネートを得ている[28, 32]．しかし，置換基としてニトリルを含むホスホネートを合成する場合，目的の酸クロリドが得られなかった．５塩化リンがニトリルと副反応を起こすためと思われる．そこで，オキシ塩化リンと 1.8 当量の 2,2,2-trifluoroethanol から調製したホスホン酸クロリドと，acetonitrile のリチウム塩から目的のホスホネート**2f** を合成することができた（**Scheme 18**）．



Scheme 18

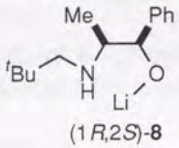
これらのホスホネートを用い，種々検討を行った．

種々のエステル置換基を有するホスホネートを用いて検討を行った（**Scheme 19**, **Table 16**）．



Scheme 19

run	phosphonate	R	cy (%)	ee (%)
1	**2c**	Me	78	11 (*R*)
2	**2b**	Et	92	52 (*R*)
3	**2d**	^{i}Pr	72	31 (*R*)
4	**2e**	Ph	84	23 (*S*)
5	**2f**	CF_3CH_2	90	17 (*S*)

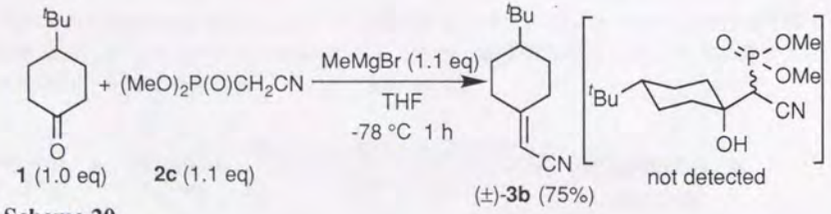


(1*R*,2*S*)-**8**

Table 16

2b を用いたときにもっとも高い不斉収率を与えた（run 2）．脂肪族エステルの範囲内で比較すると，**2c**，および**2d** を用いたときに不斉収率が低下する（run 1, 3）ことは，エステル置換基の立体的なかさ高さだけでは不斉誘起の程度は説明できない．

メチルエステル**2c** を用いた場合：**2c** のマグネシウム塩を用いたアルドール中間体の合成を試みたところ，アルドール中間体は得られず，脱離反応が進行した**3b** が得られた（**Scheme 20**）．**2b** を用いた場合にはアルドール中間体が単離できることから，**2c** 由来のアルドール中間体からは脱離反応が進行しやすいことが予想される．



Scheme 20

一方，第3章において，本不斉反応では，アルドール体のアニオンとキラルアミノアルコールとの錯体の安定度の差が不斉誘起の要因の一つであることが示唆された．よって，脱離反応が比較的進行しやすい**2c** を用いた不斉反応では，錯体の安定度の差が小さいため，不斉収率が低下すると考えられる．

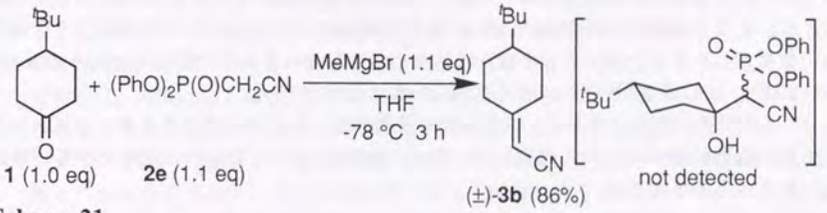
イソプロピルエステル**2d** を用いた場合：**2d** を用いた反応では，**2b** のときと比較すると化学収率の低下が見られる（run 1, 3）．また，薄層クロマトグラフィーで反応を大まかに追跡すると，**2d** を用いた反応の反応速度が，**2b** のそれよりも遅いことが観察された．このことから，基質同士，もしくはリガンドとの間に立体障害が生じていることが予想され，このことが，不斉収率の低下につながっていると考えられる．

一方，電子吸引性基を有するホスホネート**2e**，**2f** では，不斉収率は低いものの，絶対配置の逆転が見られた（run 4, 5）．とくに**2f** は，立体的には**2b** とあまり変わらないかさ高さを有しているにも関わらず，生成物の絶対配置が逆転している．

不斉収率の低下は，脱離反応の進行のしやすさを考慮すると，**2b** を用いた反応において示唆された不斉誘起の要因の一つである，アルドール体のアニオンとキラルアミノアルコールとの錯体の安定度の差が小さいためであると考えられる．

また，生成物の絶対配置の逆転については，あくまでも憶測ではあるが，速度論的アルドール反応により生成した中間体の不斉収率をそのまま反映しているのではないか，と解釈している．

ちなみに，ホスホネート**2e** について，**2b** のときと同様にマグネシウム塩を用いたアルドール中間体の合成を試みたが，所望の中間体は得られず，脱離反応が進行した**3b** が得られた（**Scheme 21**）．



Scheme 21

第5章　考察

これまでに得られた知見についてまとめる．

1)　第2章において，プロキラルケトンとして4-*tert*-butylcyclohexanoneを用いたアキラルホスホネートのエナンチオ選択的不斉Horner–Wadsworth–Emmons反応を検討し，ホスホネートとしてニトリルを有する**2b**を用いたときに収率よくオレフィンが得られることがわかった．そして，キラルリチウム2-アミノアルコキシドが本反応の有用なキラル塩基となりうることを示した．特に，ネオペンチル基を有するノルエフェドリン誘導体(1*R*,2*S*)-**8**を用いたときに，52% eeと，現在までのところ最高の不斉収率で，相当するオレフィンを得た．用いる溶媒はtolueneがもっとも良い結果を与え，他の配位性の溶媒中では不斉収率が低下した．

2)　第3章において，ラセミ体のアルドール中間体を用いた脱離反応を検討したところ，光学活性体で，しかも元の不斉反応と同じ絶対配置のオレフィンが得られた．一方，benzaldehyde存在下での検討から，脱離反応よりも速く，レトロアルドール反応が起きていることが示唆された．このことから，本反応の不斉誘起は，ジアステレオトピックな関係にあるアルドール体のアニオンと，キラルアミノアルコールとの錯体の安定性の差によっている，と解釈した．アルドール体のアニオンから水酸基とP=Oで2座，キラルアミノアルコールから2座，それぞれ配位子が提供されて，対カチオンであるリチウムのtetravalencyが満たされて，ある程度定まった構造の錯体を構築できているのではないかと思われる．また，アルドール体のエナンチオマー間の平衡の関係は，かなり複雑になっている．第2章第5節において，-100 ℃での反応で不斉収率が改善されなかった理由としては，低温ゆえに平衡のバランスが変化し，p.29の**Scheme 15**中の**D**の寄与が低下したためではないかと思われる．

この研究を始めた当初は，本反応の不斉誘起が，ホスホネートアニオンのエナンチオ面の識別に基づくものと想定していたが，実際にはそうではない段階で不斉が誘起されていると思われる．

3)　第4章において，脱離反応が速いとされるホスホネートを用いて検討したところ，不斉収率の低下，および生成物の絶対配置の逆転が見られた．不斉収率の低下については，脱離反応が速いため，ジアステレオトピックな関係にあるアルドール体のアニオンと，キラルアミノアルコールとの錯体の間の安定性の差があまり生じないためであると思われる．絶対配置の逆転については，速度論的に生成するアルドール体由来の生成物が逆の絶対配置を有していたからではないか，と想定している．

反応における立体構造についての情報は，用いたアルコキシドのデザインからしか得られていないが，それに基づいて考えてみる．対カチオンであるリチウムカチオンを介したアルドール体のアニオンとキラルアミノアルコールとの錯体の立体構造について考察する．この錯体は，リチウムを含むアキラルアミノアルコール由来の5員環（**A**環），アルドール体のアニオンの6員環（**B**環），およびシクロヘキサノン由来の6員環（**C**環）がそれぞれスピロでつながった構造が考えられる（**Figure 2**）．ここで，アルドール体アニオンの6員環（**B**環）を，ニトリルをエカトリアル位に配した椅子型のコンフォメーションに固定して考えてみる．

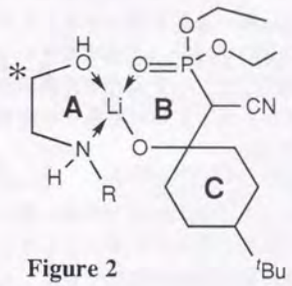


Figure 2

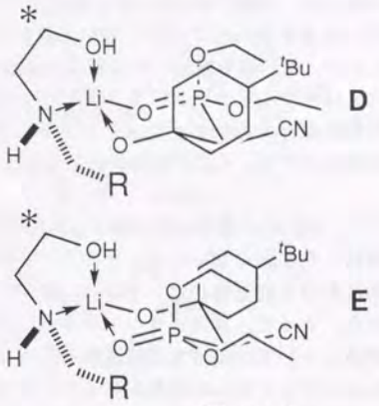
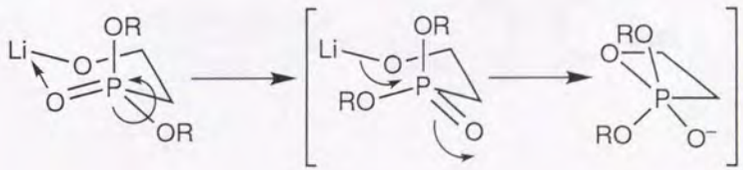


Figure 3

まず，**A**環の接続は，窒素上置換基のかさ高さから，窒素原子がエカトリアル位にあると思われる．これに基づいて考察すると，**D**と**E**の構造が考えられる．しかし，**B**環，**C**環上の置換基と，**A**環上の置換基との相互作用はあまり大きくなように見える．残る可能性は，**A**環上の5員環のひずみに伴う**B**環6員環椅子型構造の不均一化などが考えられる．さらに問題なのは，（確認はされていないものの，想定される[33]）オキサホスフェタン中間体へ転換していく過程がどのように進行しているかである．特に**B**環が構築されると仮定すると，オキサホスフェタン中間体に達するには，一旦P=O上の酸素原子のリチウムへの配位がはずれて，オキシアニオンの攻撃を受けるために隣接するP-C結合が回転することが必要となる．この過程の進行のしやすさが立体選択性の発現に重要であると思われるが，現在までのデータに基づいてこれらを考察することは困難である．

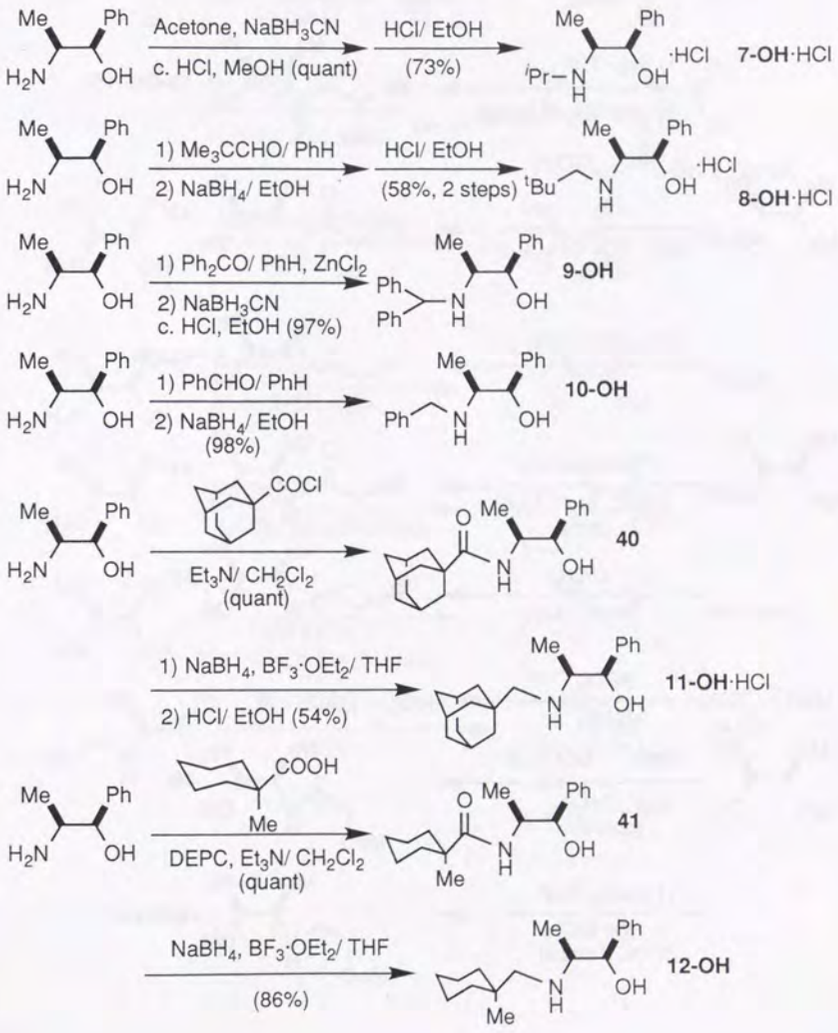


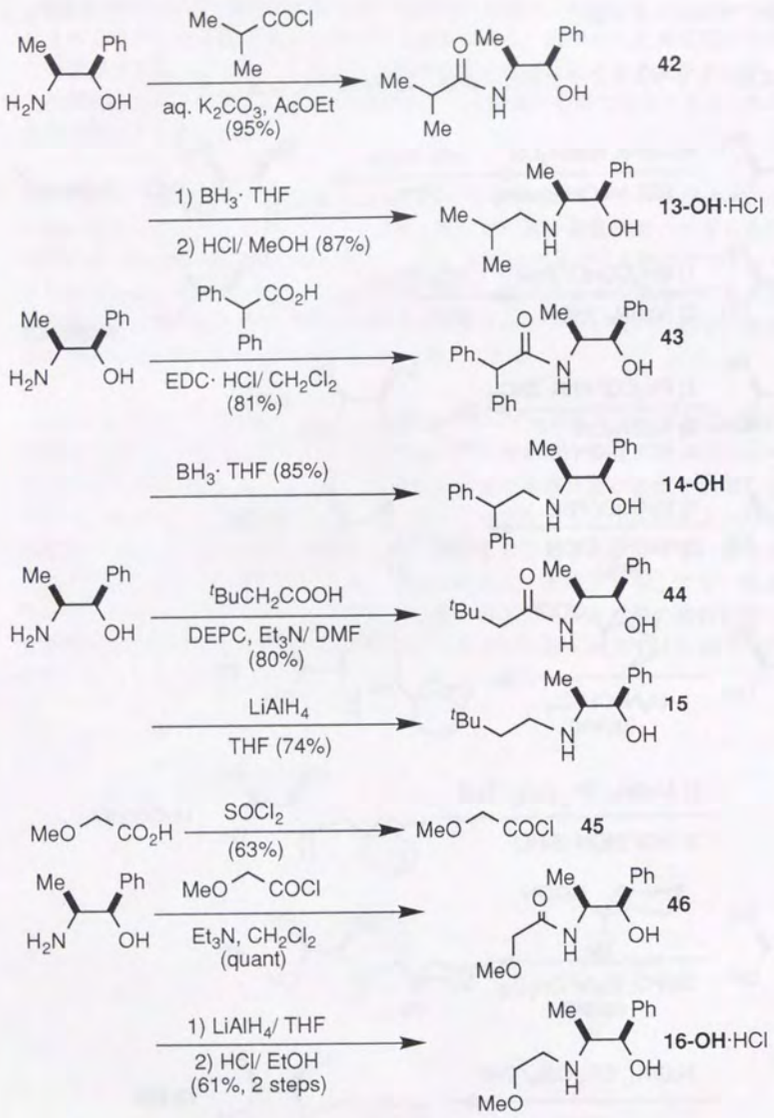
Still らが行った (Z)-選択的オレフィン化反応の条件は，KHMDS/ 18-Crown-6 という，なるべくカチオンを反応系から排除する条件であり，速やかに脱離反応が進行することが予測できる．よって，このような条件を用いれば反応系も考えやすいが，本反応の不斉誘起には，リチウムを含む５員環キレート構造が必須であると考えられるため，実現は難しいと思われる．

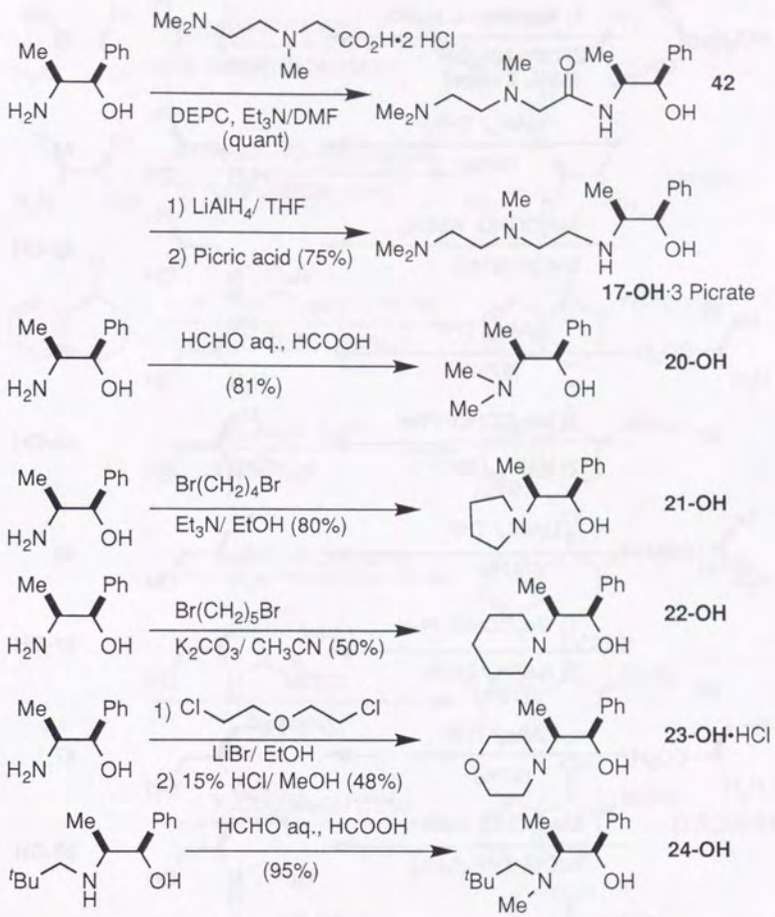
本研究は，出発の時点でキラル塩基としてキラルリチウムアルコキシドという塩基性の低い塩基を選んだために，用いる基質も酸性度の高い基質を用いらざるを得ず，このことが，反応系を複雑にする原因となった．レトロアルドール反応が考えにくい系，たとえばキラルリチウムアミドなどの強塩基と，β位にフェニル基などの置換基を有する比較的酸性度の低い活性メチレンを有するホスホネートを用いた系での検討は，研究の幅を広げていく点で意味のあることと考えられる．

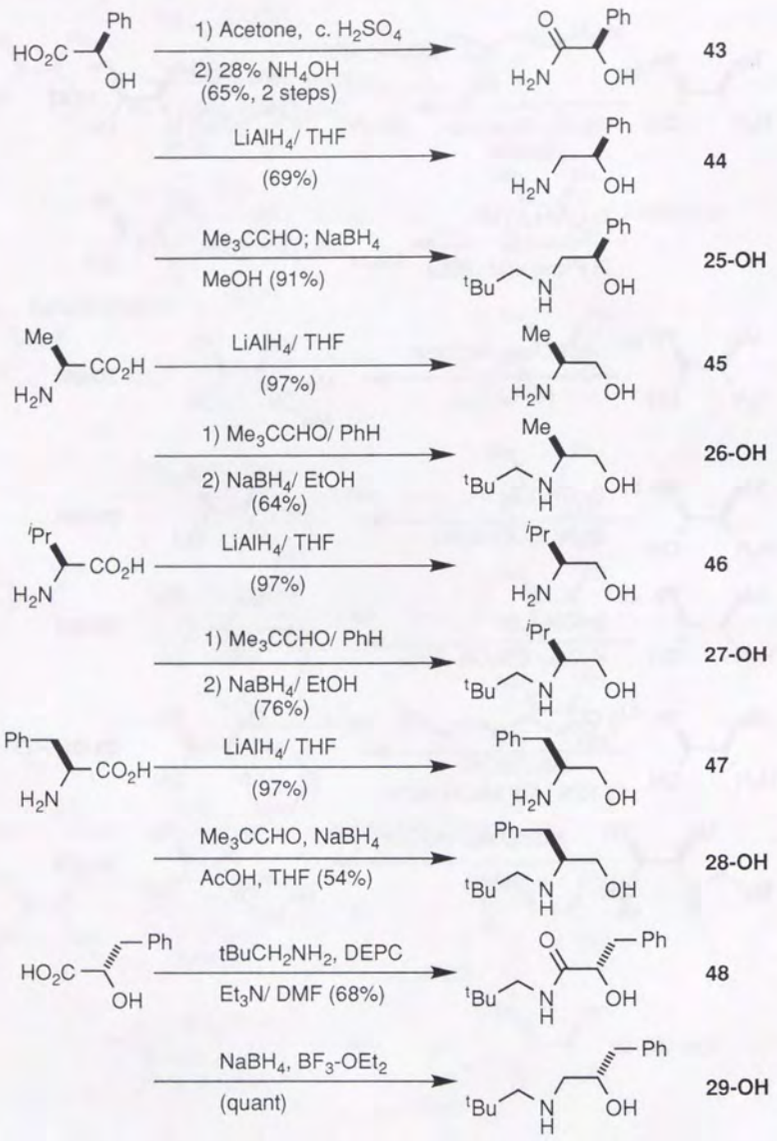
また，本反応の遷移状態における立体構造についても不明のままである．特に，筆者が検討した反応においては，アルドール体のアニオンとキラルアミノアルコールとの錯体における安定性の差，という，非常に不安定な遷移状態が重要であることが示唆された．よって，ホスホネートカルバニオンとキラルアミノアルコールとの錯体の立体構造についてNMRやX線結晶解析などの検討をおこなったとしても，筆者が検討した反応に対して正しい情報を与えない可能性がある．その点からしても，本反応の研究をすすめていくうえでは，より広範な基質，およびキラル塩基の選択を行い，その立体選択性を説明する上での情報を得やすい系での検討が適当ではなかったか，と考えている．

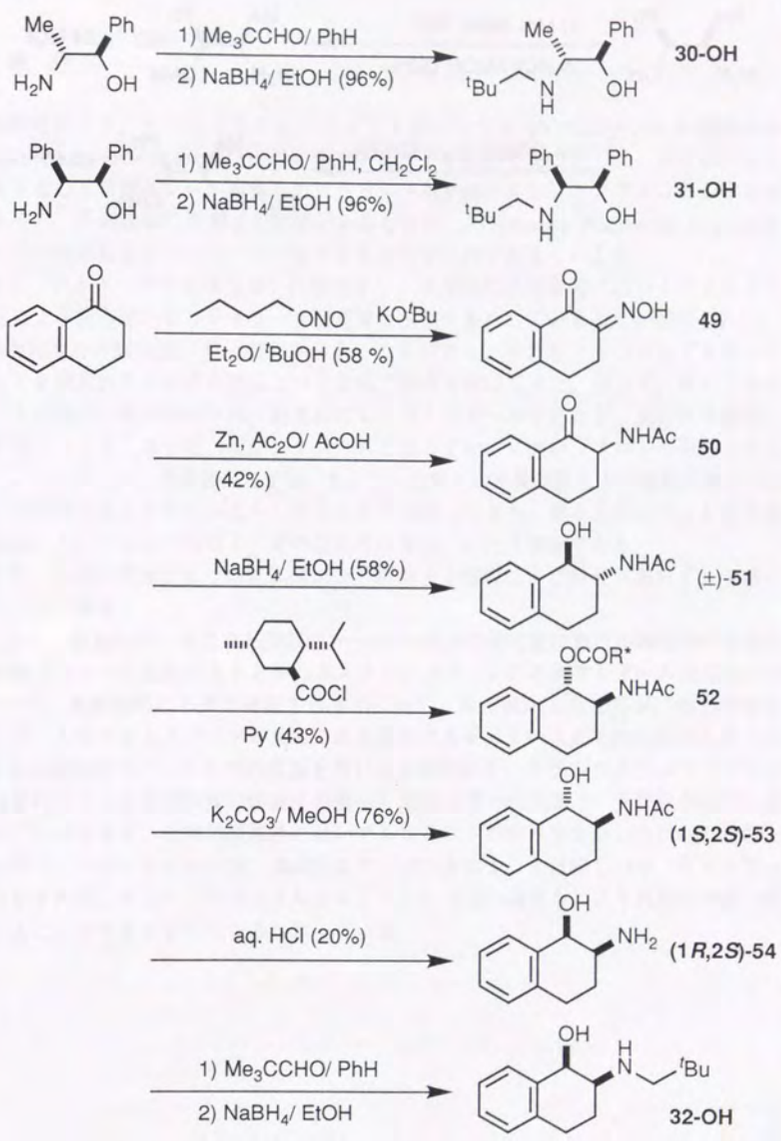
反応に用いたキラルアミノアルコールは，以下のように合成した．

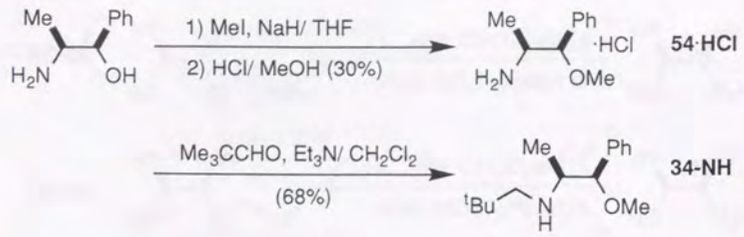



Me
Ph
H2N
OH
Me
COCl
Me
aq. K2CO3, AcOEt
(95%)
O
Me
Ph
Me
N
H
OH
Me
42
1) BH3· THF
2) HCl/ MeOH (87%)
13-OH·HCl
Ph
CO2H
Ph
EDC· HCl/ CH2Cl2
(81%)
43
BH3· THF (85%)
14-OH
tBuCH2COOH
DEPC, Et3N/ DMF
(80%)
44
LiAlH4
THF (74%)
15
MeO
CO2H
SOCl2
(63%)
MeO
COCl
45
MeO
COCl
Et3N, CH2Cl2
(quant)
46
1) LiAlH4/ THF
2) HCl/ EtOH
(61%, 2 steps)
16-OH·HCl


Me2N
N
Me
CO2H•2 HCl
DEPC, Et3N/DMF
(quant)
42
1) LiAlH4/ THF
2) Picric acid (75%)
17-OH·3 Picrate
HCHO aq., HCOOH
(81%)
20-OH
Br(CH2)4Br
Et3N/ EtOH (80%)
21-OH
Br(CH2)5Br
K2CO3/ CH3CN (50%)
22-OH
1) Cl
O
Cl
LiBr/ EtOH
2) 15% HCl/ MeOH (48%)
23-OH•HCl
tBu
HCHO aq., HCOOH
(95%)
24-OH


1) Acetone, c. H2SO4
2) 28% NH4OH
(65%, 2 steps)
43
LiAlH4/ THF
(69%)
44
Me3CCHO; NaBH4
MeOH (91%)
25-OH
LiAlH4/ THF
(97%)
45
1) Me3CCHO/ PhH
2) NaBH4/ EtOH
(64%)
26-OH
LiAlH4/ THF
(97%)
46
1) Me3CCHO/ PhH
2) NaBH4/ EtOH
(76%)
27-OH
LiAlH4/ THF
(97%)
47
Me3CCHO, NaBH4
AcOH, THF (54%)
28-OH
tBuCH2NH2, DEPC
Et3N/ DMF (68%)
48
NaBH4, BF3-OEt2
(quant)
29-OH


1) Me3CCHO/ PhH
2) NaBH4/ EtOH (96%)
30-OH
1) Me3CCHO/ PhH, CH2Cl2
2) NaBH4/ EtOH (96%)
31-OH
ONO
KOtBu
Et2O/ tBuOH (58 %)
49
Zn, Ac2O/ AcOH
(42%)
50
NaBH4/ EtOH (58%)
(±)-51
COCl
Py (43%)
52
K2CO3/ MeOH (76%)
(1S,2S)-53
aq. HCl (20%)
(1R,2S)-54
1) Me3CCHO/ PhH
2) NaBH4/ EtOH
32-OH



結　語

本研究により，キラルリチウムアミノアルコキシドを用いたエナンチオ選択的不斉Horner–Wadsworth–Emmons反応が可能であることを初めて見いだした．本反応にはリチウムを含む５員環キレート構造をとりうるキラルリチウム2-アミノアルコキシドが有効であった．不斉収率の面でまだ問題があるものの，不斉Horner–Wadsworth–Emmons反応をキラル外部配位子でコントロールできた初めての例であるといえる．

また，アルドール中間体を用いた検討から，本反応の不斉誘起にはレトロアルドール反応による熱力学的なコントロールが重要な役割を果たしていることが示唆された．

筆者は現在の研究室に修士課程から入ってきてから，キラルアルコキシドを用いたエナンチオ選択的不斉反応の開発という目的で研究を続けてきた．従って，用いるホスホネートの選択の幅が制限され，結果的にレトロアルドール反応など，反応系を複雑にする原因になってしまった．反応メカニズムを追っていくに従い，アルドール体とキラルアミノアルコールとの錯体の安定性，および，基質との平衡状態などの複数の因子によって不斉収率が決定されているらしいことまでは解ってきた．単なるオレフィンを合成する反応，というものではなく，その反応の中身は，かなり複雑である．

また，反応の遷移状態での立体構造などに関する情報はまだ得られおらず，今後の課題の一つである．

しかし，塩基を用いる主な不斉反応 ――――我々の研究室における例を挙げるなら，不斉脱プロトン化反応であるとか，エステルエノラートの不斉アルドール反応など ――――が，速度論的に不斉が誘起されるのに対し，私の検討した反応が，熱力学的なコントロールを介するステップが重要である反応である，という点は興味深いと思った．

筆者は現在まで，これまでの塩基を用いる不斉反応を，キラルリチウムアミドという（筆者の目から見れば非常に塩基性の強い）塩基を用いた反応という視点からでしか眺めることができず，比較的塩基性の弱いアルコキシドの特性を生かした反応の設計，検討を行うことができなかった．具体的なアイデアを出すことは難しいが，もっと違った見方をすれば，キラルリチウムアルコキシドという弱い塩基も，より汎用性の高い塩基にすることができるようになると思っている．

Experimental Section

General Notes All melting point were determinned by using a Büchi 510 melting point apparatus and are not corrected. Spectra reported herein were recorded on a JASCO Report-100 Infrared spectrometer, a JEOL JNM-EX-270 FT NMR SYSTEM with tetramethylsilane as an internal standard, a JEOL JMS-01 SG-Z MASS Spectrometer, a JEOL DX-303 MASS Spectrometer, a JEOL SX-102 MASS Spectrometer. Optical rotations were measured with a JASCO DIP-370 Digital Polarimeter. The liquid chromatography was performed with a JASCO 880-PU Intelligent HPLC Pump, a JASCO BIP-I-HPLC Pump, a JASCO PU-980 Intelligent HPLC Pump, a JASCO UVIDEC-100-IV UV Spectrophotometer, a JASCO UVIDEC-100-V UV Spectrophotometer, and a JASCO UV-970 Intelligent UV/VIS Spectrophotometer. Elemental analyses were performed by Mrs. R. Hirata at Faculty of Pharmaceutical sciences, University of Tokyo. Fuji Davison BW-200 was used as silica gel for column chromathography. Merck aluminium oxide 90 standardized was used as aluminium oxide for column chromathography. The solvents for asymmetric reaction were distilled from sodium- benzophenone ketyl before use. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, qd = quartet-of-doublets, s = singlet, t = triplet, THF = tetrahydrofuran.

Asymmetric reactions

Table 1, run 1 (ephedrine -OLi, phosphonoacetate, in THF).

Under argon atmosphere, to a solution of **4-OH** (303 mg, 1.83 mmol) in THF (5 mL), BuLi (1.70 N solution in hexane, 1.08 mL, 1.83 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of metyl diethylphosphonoacetate (385 mg, 1.83 mmol) in THF (5 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (257 mg, 1.67 mmol) in THF (5 mL) was added within 2 min, and the resultant mixture was stirred for 1 h at -78 °C and futher 3 h at -45 °C, and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (380 mg), which was purified by column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3a** as a colorless oil (148 mg, 42%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 100 °C, 1 °C/ min) 0% ee.

Table 1, run 2 (ephedrine -OLi, phosphonoacetate, in toluene).

Under argon atmosphere, to a solution of **4-OH** (180 mg, 1.09 mmol) in toluene (4 mL), BuLi (1.70 N solution in hexane, 0.64 mL, 1.09 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -45 °C, and a solution of metyl diethylphosphonoacetate (229 mg, 1.09 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (257 mg, 1.67 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -45 °C, and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (250 mg). The oil was purified by column chromatography (SiO_2 35 g, hexane- ethyl acetate 30:1) to afford **3a** as a colorless oil (37 mg, 18%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 100 °C, 1 °C/ min) <1% ee.

Table 1, run 3 (ephedrine -OLi, cyanomethylphosphonate, in THF).

Under argon atmosphere, to a solution of **4-OH** (212 mg, 1.28 mmol) in THF (4 mL), BuLi (1.70 N solution in hexane, 0.75 mL, 1.28 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -45 °C, and a solution of diethyl cyanomethylphosphonate (227 mg, 1.28 mmol) in THF (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (180 mg, 1.17 mmol) in THF (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -45 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (238 mg). The oil was purified by column chromatography (SiO_2 30 g, hexane-ethyl acetate 10:1) to afford **3b** as a colorless oil (222 mg, quant).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 0% ee.

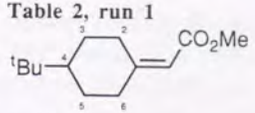
Table 1, run 4 (ephedrine -OLi, phosphonoacetate, in toluene).

Under argon atmosphere, to a solution of **4-OH** (171 mg, 1.04 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.66 mL, 1.04 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (183 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (145 mg, 0.94 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (250 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as a colorless oil (143 mg, 86%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 17% ee (*R*).

SR $[\alpha]_D^{25}$ -18.6 (*c* 1.45, $CHCl_3$).

Table 2, run 1



Under argon atmosphere, to a solution of 2-methyl-2-propanol (109 mg, 1.48 mmol) in THF (5 mL), BuLi (1.70 *N* solution in hexane, 0.87 mL, 1.48 mmol) was added at -78 °C and the mixture was stirred for 10 min at -78 °C. The mixture of metyl diethylphosphonoacetate (263 mg, 1.27 mmol) and 4-*tert*-butylcyclohexanone (207 mg, 1.34 mmol) in THF (8 mL) was added and the resultant mixture was stirred for 3 h at -78 °C and futher 3 h at -45 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (369 mg). The oil (353 mg) was purified by column chromatography (SiO_2 35 g, hexane-ethyl acetate 20:1) to afford **3a** as a colorless oil (108 mg, 42% from phosphate).

IR (neat, cm^{-1}) 2940, 2850, 1710, 1645.

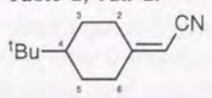
^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.86 (9H, s, CH_3), 1.09-1.30 (3H, m, cyclohexanone C[3]-ax-H, C[4]-H, C[5]-ax-H), 1.86-1.96 (3H, m, C[2]-ax-H, C[3]-eq-H, C[5]-eq-H), 2.15 (1H, m, C[6]-ax-H), 2.29 (1H, m, C[6]-ax-H), 3.68 (3H, s, OMe), 3.84-3.90 (1H, m, C[2]-eq-H), 5.60 (1H, s, vinyl).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 27.53, 28.45, 29.20, 29.56, 34.12, 37.86, 47.75, 50.78, 112.24, 163.92, 167.26.

HRMS Calcd. for $C_{13}H_{22}O_2$: m/z: 210.1620. Found: 210.1586.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 100 °C, 1 °C/ min) 1: 1 peak at 74.99 min and 75.47 min.

Table 2, run 2.



Under argon atmosphere, to a solution of 2-methyl-2-propanol (103 mg, 1.39 mmol) in THF (4 mL), BuLi (1.70 N solution in hexane, 0.82 mL, 1.39 mmol) was added at -45 °C, and the mixture was stirred for 10 min at -45 °C. A solution of diethyl cyanomethylphosphonate (247 mg, 1.39 mmol) in THF (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (196 mg, 1.27 mmol) in THF (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -45 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (259 mg). The ^{1}H-NMR spectrum of the oil showed the yield of the **3b** is quantative.

IR (KBr, cm^{-1}) 2205, 1620, 1450, 1360.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (9H, s, CH_3), 1.10-1.26 (3H, m, cyclohexanone C[3]-ax-H, C[4]-H, C[5]-ax-H), 1.99-2.21 (4H, m, C[2]-ax-H, C[3]-eq-H, C[5]-eq-H, C[6]-ax-H), 2.38-2.46 (1H, m, C[6]-ax-H), 2.96-3.01 (1H, m, C[2]-eq-H), 5.03 (1H, s, vinyl).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 27.51, 28.30, 28.68, 32.42, 33.05, 5.87, 47.29, 91.62, 168.70.

MS m/z: 177 (M^+).

Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found C, 81.36; H, 10.75; N, 7.90.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 1: 1 peak at 92.37 min and 93.04 min.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 1: 1 peak at 13.71 min and 15.16 min.

Scheme 3 (DIBAL-H reduction of nitrile).

DIBAL-H (0.93 M in hexane, 0.80 mL, 0.74 mmol) was added to a solution of 4-*tert*-butylcyclohexylideneacetonitrile (120 mg, 0.68 mmol, 51% ee (-)) in toluene (10 mL) at -78 °C within 2 min. The mixture was stirred for 15 min at -78 °C, then quenched with saturated aquaous ammonium chloride (10 mL). After 10 min, the mixture was diluted with Et_2O (10 mL) and stirred for 1 h. Magesium sulfate was added, and then filtered. The filtrate was concentrated *in vacuo* to leave a yellow oil (120 mg). The oil was purified by column chromatography (SiO_2 15 g, hexane-AcOEt 40: 1) to afford **5** (88 mg, 72%) as a colorless oil.

IR (KBr, cm^{-1}) 1670, 1630.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.79 (9H, s, CH_3), 1.11- 1.24 (3H, m, cyclohexanone C[3]-ax-H, C[4]-H, C[5]-ax-H), 2.16 (4H, m, C[2]-ax-H, C[3]-eq-H, C[5]-eq-H, C[6]-ax-H), 2.31- 2.36 (1H, m, C[6]-ax-H), 3.31- 3.36 (1H, m, C[2]-eq-H), 5.73 (1H, d, J = 8.3 Hz, vinyl), 9,92 (1H, d, J = 8.3 Hz, CHO).

$[\alpha]^{25}_{546}$ -23.5 (*c* 1.40, $CHCl_3$).

Table 3, run 1 (norephedrine Li alkoxide).

Under argon atmosphere, to a solution of **6-OH** (144 mg, 0.95 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.56 mL, 0.95 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (169 mg, 0.95 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (134 mg, 0.87 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (216 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (151 mg, 98%).

mp 47-49 °C.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 4% ee (*R*).

Table 2, run 3 (isopropylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **7-OH** (268 mg, 1.39 mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.88 mL, 1.39 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (246 mg, 1.39 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (194 mg, 1.26 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (323 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (173 mg, 77%).

mp 40-41 °C.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 19% ee (*R*).

SR $[\alpha]_D^{25}$ -19.5 (*c* 1.26, $CHCl_3$).

Table 3, run 4 (neopentylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **8-OH** (254 mg, 1.15 mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.73 mL, 1.15 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (203 mg, 1.15 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (161 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (240 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (170 mg, 92%).

mp 31-33 °C.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 52% ee (*R*).

SR $[\alpha]_D^{25}$ -49.1 (*c* 1.43, $CHCl_3$).

Table 4, run 3 (benzhydrylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **9-OH** (374 mg, 1.18 mmol) in toluene (3 mL), BuLi (1.67 N solution in hexane, 0.71 mL, 1.18 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (209 mg, 1.18 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (165 mg, 1.07 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (602 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (154 mg, 86%).

mp 26- 27 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 16% ee (*R*).

Table 4, run 4 (benzylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **10-OH** (237 mg, 0.98 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.62 mL, 0.98 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (174 mg, 0.98 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (138 mg, 0.89 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (233 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (133 mg, 84%).

mp 26- 27 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 34% ee (*R*).

Table 4, run 5 (1-adamantylmethylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **11-OH** (249 mg, 0.83mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.53 mL, 0.83 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (147 mg, 0.83 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (117 mg, 0.76 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (263 mg). The oil was purified with column chromatography (SiO_2 30 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (131 mg, 97%).

mp 34-35 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 51% ee (*R*).

SR $[\alpha]_D^{25}$ -50.0 (*c* 1.28, $CHCl_3$).

Table 4, run 6 (1-methylcyclohexylmethylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **12-OH** (254 mg, 1.15 mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.73 mL, 1.15 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (203 mg, 1.15 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (161 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (240 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (170 mg, 92%).

mp 31-33 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 1% ee (*R*).

SR $[\alpha]_D^{25}$ -49.1 (*c* 1.43, $CHCl_3$).

Table 4, run 7 (isobutylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **13-OH** (204 mg, 0.98 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.62 mL, 0.98 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (174 mg, 0.98 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (138 mg, 0.89 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (247 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (137 mg, 87%).

mp 24- 25 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 40% ee (*R*).

Table 4, run 8 (2,2-diphenylethylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **14-OH** (304 mg, 0.92 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.58 mL, 0.92 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (162 mg, 0.92 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (129 mg, 0.83 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (312 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (119 mg, 96%).

mp 31- 33 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 49% ee (*R*).

Table 4, run 9 (3,3-dimethylbutylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **15-OH** (238 mg, 1.01 mmol) in toluene (3 mL), BuLi (1.71 N solution in hexane, 0.59 mL, 1.01 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (179 mg, 1.01 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (142 mg, 0.92 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (292 mg). The oil was purified with column chromatography (SiO_2 35 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (141 mg, 87%).

mp 45- 50 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 20% ee (*R*).

Table 5, run 1 (2-methoxyethylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **16-OH** (213 mg, 1.02 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 1.02 mL, 1.02 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (180 mg, 1.02 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (143 mg, 0.93 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (226 mg). The oil was purified with column chromatography (SiO_2 30 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (156 mg, 95%).

mp 44- 46 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 17% ee (*R*).

Table 5, run 2 ([*N*-(dimethylaminoethyl)-*N*-metyl]aminothylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **17-OH** (313 mg, 1.12 mmol) in toluene (3 mL), BuLi (1.61 N solution in hexane, 0.70 mL, 1.12 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (199 mg, 1.12 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (157 mg, 1.02 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (205 mg). The oil was purified with column chromatography (SiO_2 30 g, hexane-ethyl acetate 30:1) to afford **3b** as colorless prisms (164 mg, 91%).

mp 31- 33 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 4% ee (*R*).

Table 5, run 3 (phenetylalcohol Li alkoxide)

To a solution of (*S*)-1-phenyl-1-ethanol **18-OH** (130 mg, 1.06 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.63 mL, 1.06 mmol) was added at -78 °C under argon atmosphere, and the mixture was stirred for 10 min at -78 °C. A solution of diethyl cyanomethylphosphonate (188 mg, 1.06 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (149 mg, 0.97 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (343 mg), which was purifired by column chromatography to give **3b** as colorless needles (164 mg, 95%).

mp 46-47 °C

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 1% ee (*R*).

Table 5, run 4 (menthol Li alkoxide)

To a solution of (-)-mentol **19-OH** (165 mg, 1.06 mmol) in toluene (3 mL), BuLi (1.65 N solution in hexane, 0.64 mL, 1.06 mmol) was added at -78 °C under argon atmosphere, and the mixture was stirred for 10 min at -78 °C. A solution of diethyl cyanomethylphosphonate (187 mg, 1.06 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (148 mg, 0.96 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (343 mg), which was purifired by column chromatography to give **3b** as colorless needles (127 mg, 75%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 0% ee (*R*).

Table 6, run 1 (methylephedrine Li alkoxide).

Under argon atmosphere, to a solution of **20-OH** (218 mg, 1.22 mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.77 mL, 1.22 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (215 mg, 1.22 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (171 mg, 1.11 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (246 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless prisms (176 mg, 89%).

mp 32-33 °C.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 41% ee (*R*).

SR $[\alpha]_D^{25}$ -42.2 (*c* 1.91, $CHCl_3$).

Table 6, run 2 (pyrrolidine-type norephedrine Li alkoxide).

Under argon atmosphere, to a solution of **21-OH** (244 mg, 1.19 mmol) in toluene (3 mL), BuLi (1.61 N solution in hexane, 0.74 mL, 1.19 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (211 mg, 1.19 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (167 mg, 1.08 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (223 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (179 mg, 93%).

mp 30-33 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 29% ee (*R*).

Table 6, run 3 (piperidine-type norephedrine Li alkoxide).

Under argon atmosphere, to a solution of **22-OH** (233 mg, 1.06 mmol) in toluene (4 mL), BuLi (1.58 N solution in hexane, 0.67 mL, 1.06 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (188 mg, 1.06 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (149 mg, 0.97 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (211 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (157 mg, 92%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 31% ee (*R*).

SR $[\alpha]_D^{25}$ -27.0 (*c* 1.60, $CHCl_3$).

Table 6, run 4 (morpholine-type norephedrine Li alkoxide).

Under argon atmosphere, to a solution of **23-OH** (215 mg, 0.97 mmol) in toluene (4 mL), BuLi (1.78 N solution in hexane, 0.55 mL, 0.97 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (172 mg, 0.97 mmol) in toluene (4 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (136 mg, 0.88 mmol) in toluene (4 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (182 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless prisms (127 mg, 81%).

mp 32-33 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 49% ee (*R*).

Table 6, run 5 (N-neopentyl-N-methylnorephedrine Li alkoxide).

Under argon atmosphere, to a solution of **24-OH** (241 mg, 1.03 mmol) in toluene (3 mL), BuLi (1.61 N solution in hexane, 0.53 mL, 1.03 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (183 mg, 1.03 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (145 mg, 0.94 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (233 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (147 mg, 88%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 0% ee.

Table 7, run 2 (N-neopentylalaninol Li alkoxide).

Under argon atmosphere, to a solution of **25-OH** (135 mg, 1.04 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.67 mL, 1.04 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (185 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (146 mg, 0.95 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (233 mg). ^{1}H-NMR spectra of the oil showed yield of **3b** is 81%.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 23% ee (*R*).

Table 7, run 3 (manderic acid derivative Li alkoxide).

Under argon atmosphere, to a solution of **26-OH** (203 mg, 0.98 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.62 mL, 0.98 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (173 mg, 0.98 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (137 mg, 0.89 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (183 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (146 mg, 93%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 14% ee (*R*).

Table 7, run 4 (valinol derivative Li alkoxide).

Under argon atmosphere, to a solution of **27-OH** (182 mg, 1.05 mmol) in toluene (3 mL), BuLi (1.67 N solution in hexane, 0.63 mL, 1.05 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (186 mg, 1.05 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (147 mg, 0.94 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (226 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (144 mg, 85%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 29% ee (*R*).

Table 7, run 5 (phenylalaniol derivative Li alkoxide).

Under argon atmosphere, to a solution of **28-OH** (197 mg, 0.89 mmol) in toluene (3 mL), BuLi (1.67 N solution in hexane, 0.55 mL, 0.89 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (158 mg, 0.89 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (125 mg, 0.81 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (268 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (111 mg, 77%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 23% ee (*R*).

Table 7, run 6 (phenyllactic acid derivative Li alkoxide).

Under argon atmosphere, to a solution of **29-OH** (224 mg, 1.01 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.64 mL, 1.01 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (179 mg, 1.01 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (142 mg, 0.92 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (185 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless oil (138 mg, 85%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 16% ee (*S*).

Table 7, run 7 (pseudoephedrine derivative Li alkoxide).

Under argon atmosphere, to a solution of **30-OH** (250 mg, 1.13 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.71 mL, 1.13 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (200 mg, 1.13 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (158 mg, 1.03 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (253 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (138 mg, 88%).

mp 51-53 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 2% ee (*R*).

Table 7, run8 (2-amino-1,2-diphenylethanol derivative Li alkoxide).

Under argon atmosphere, to a solution of **31-OH** (292 mg, 1.04 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.66 mL, 1.13 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (183 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (145 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (253 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (108 mg, 65%).

mp 45- 49 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 20% ee (*R*).

Table 7, run9 (tetralone derivative Li alkoxide).

Under argon atmosphere, to a solution of **32-OH** (110 mg, 0.471 mmol) in toluene (2 mL), BuLi (1.65 N solution in hexane, 0.29 mL, 0.471 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (83 mg, 0.471mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (66 mg, 0.43 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (150 mg). ^{1}H-NMR spectra of the oil showed yield of the oil is 83%.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 46% ee (*R*).

Table 8, run 2 (BuLi 2 eq).

Under argon atmosphere, to a solution of **8-OH** (160 mg, 0.72 mmol) in toluene (3 mL), BuLi (1.65 N solution in hexane, 0.86 mL, 1.44 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (183 mg, 0.72 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (101 mg, 0.66 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (177 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (83 mg, 77%).

mp 48- 51 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 4% ee (*R*).

Table 8, run 3 (methyl ether Li amide).

Under argon atmosphere, to a solution of **34-NH** (230 mg, 0.98 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.62 mL, 0.98 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (173 mg, 0.98 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (137 mg, 0.89 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (227 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as a colorless oil (80 mg, 51%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 0% ee.

Table 8, run 4 (chiral Li amide neopentyl).

Under argon atmosphere, to a solution of **35-NH** (282 mg, 1.03 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.65 mL, 1.03 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (182 mg, 1.03 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (144 mg, 0.93 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (261 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (127 mg, 77%).

mp 48- 51 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 0% ee.

Table 8, run 6 (chiral Li amide tetradentate).

Under argon atmosphere, to a solution of **36-NH** (305 mg, 0.92 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.58 mL, 0.92 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (164 mg, 0.92 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (130 mg, 0.84 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (177 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (127 mg, 85%).

mp 48- 51 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 9% ee (*S*).

Table 8, run 7 (spartein+ BuLi).

Under argon atmosphere, to a solution of (-)-spartein (260 mg, 1.11 mmol) in toluene (6 mL) and diethyl cyanomethylphosphonate (197 mg, 1.11 mmol), BuLi (1.58 N solution in hexane, 0.70 mL, 1.11 mmol) was added at -78 °C and the mixture was stirred for 30 min at -78 °C. A solution of 4-*tert*-butylcyclohexanone (156 mg, 1.01 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (229 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as a colorless oil (158 mg, 88%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 10% ee (*S*).

Table 9, run 2 (LiBr added).

Under argon atmosphere, to a mixture of **8-OH** (229 mg, 1.04 mmol) and lithium bromide (90 mg, 1.04 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.61 mL, 1.04 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature (lithum bromide insoluble). The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (183 mg, 1.04 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (145 mg, 0.94 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave cololess oil (231 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (139 mg, 67%).

mp 41- 45 °C

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 7% ee (*R*).

Table 9, run 3 (LiCl added).

Under argon atmosphere, to a suspension of **8-OH hydrochloride** (210 mg, 0.81 mmol) in toluene (2 mL), BuLi (1.61 N solution in hexane, 1.02 mL, 0.81 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (144 mg, 0.81 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (114 mg, 0.74 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a yellow oil (217 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as a colorless oil (88 mg, 67%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 7% ee (*R*).

Table 9, run 4 (Li phosphate added).

Under argon atmosphere, to a mixture of **8-OH** (195 mg, 0.88 mmol) and phosphonic acid diethyl ester (136 mg, 0.88 mmol) in toluene (2 mL), BuLi (1.65 N solution in hexane, 1.06 mL, 0.88 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (156 mg, 0.88 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (124 mg, 0.80 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a yellow oil (251 mg). ^{1}H-NMR spectrum of the oil showed that yield of **3b** is 80%.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 41% ee (*R*).

Table 10, run 2 (solvent Et_2O).

Under argon atmosphere, to a solution of **8-OH** (180 mg, 0.81 mmol) in Et_2O (2 mL), BuLi (1.69 N solution in hexane, 0.48 mL, 0.81 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (144 mg, 0.81 mmol) in Et_2O (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (114 mg, 0.74 mmol) in Et_2O (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (161 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane- ethyl acetate 40:1) to afford **3b** as a colorless oil (123 mg, 94%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 34% ee (*R*).

Table 10, run 3 (solvent 1,2-dimethoxyethane).

Under argon atmosphere, to a solution of **8-OH** (177 mg, 0.80 mmol) in 1,2-dimethoxyethane (2 mL), BuLi (1.69 N solution in hexane, 0.47 mL, 0.80 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (142 mg, 0.80 mmol) in 1,2-dimethoxyethane (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (112 mg, 0.73 mmol) in 1,2-dimethoxyethane (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (162 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane- ethyl acetate 40:1) to afford **3b** as a colorless oil (120 mg, 90%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 1% ee (*R*).

Table 10, run 4 (solvent THF).

Under argon atmosphere, to a solution of **8-OH** (179 mg, 0.81 mmol) in THF (2 mL), BuLi (1.69 N solution in hexane, 0.48 mL, 0.81 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (143 mg, 0.81 mmol) in THF (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (113 mg, 0.74 mmol) in THF (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (180 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as a colorless prisms (114 mg, 87%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 0% ee.

Table 10, run 5 (solvent toluene, HMPA added).

Under argon atmosphere, to a solution of **8-OH** (200 mg, 0.90 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.53 mL, 0.90 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (160 mg, 0.90 mmol) in toluene (3 mL) was added within 2 min. After 20 min, hexamethylphosphoric triamide (0.16 mL, 162 mg, 0.90 mmol) was added and The whole was stirred for further 20min. A solution of 4-*tert*-butylcyclohexanone (127 mg, 0.82 mmol) in toluene (3 mL) was added within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (251 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane- ethyl acetate 40:1) to afford olefin as a colorless prisms (138 mg, 95%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 28% ee (*R*).

Table 11, run 1 (reaction time 10 min).

Under argon atmosphere, to a solution of **8-OH** (229 mg, 0.88 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.56 mL, 0.88 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (181 mg, 0.88 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (124 mg, 0.80 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 10 min at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (218 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless oil (87 mg, 58%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 49% ee (*R*).

Table 11, run 2 (reaction time 30 min).

Under argon atmosphere, to a solution of **8-OH** (188 mg, 0.85 mmol) in toluene (3 mL), BuLi (1.61 N solution in hexane, 0.53 mL, 0.85 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (150 mg, 0.85 mmol) in toluene (2 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (119 mg, 0.77 mmol) in toluene (2 mL) was aded within 2 min and the resultant mixture was stirred for 30 min at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (174 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless oil (96 mg, 70%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 51% ee (*R*).

Table 11, run 3 (reaction time 1 h).

Under argon atmosphere, to a solution of **8-OH** (226 mg, 1.02 mmol) in toluene (3 mL), BuLi (1.61 N solution in hexane, 0.60 mL, 1.02 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (181 mg, 1.02 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (143 mg, 0.93 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil. The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless prisms (138 mg, 84%).

mp 41- 45 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 51% ee (*R*).

Table 12, run 1 (reaction temperature -20 °C).

Under argon atmosphere, to a solution of **8-OH** (223 mg, 1.01 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.64 mL, 1.01 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (178 mg, 1.01 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (141 mg, 0.92 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -20 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (221 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless prisms (172 mg, 98%).

mp 32- 35 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 22% ee (*R*).

Table 12, run 2 (reaction temperature -60 °C).

Under argon atmosphere, to a solution of **8-OH** (223 mg, 1.01 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.64 mL, 1.01 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (178 mg, 1.01 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (141 mg, 0.92 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -60 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil . The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless prisms (142 mg, 87%).

mp 32- 35 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 44% ee (*R*).

Table 12, run 4 (reaction temperature -100 °C).

Under argon atmosphere, to a solution of **8-OH** (278 mg, 1.26 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.74 mL, 1.26 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (223 mg, 1.26 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (176 mg, 1.14 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -60 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil . The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless prisms (171 mg, 85%).

mp 32- 35 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 48% ee (*R*).

Table 13 run 2 (4-phenylcyclohexanone).

Under argon atmosphere, to a solution of **8-OH** (237 mg, 1.07 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.68 mL, 1.07 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (190 mg, 1.07 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-phenylcyclohexanone (170 mg, 0.97 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (257 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless oil (169 mg, 88%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 300: 1, 0.6 mL/ min, 254 nm) 46% ee.

IR (neat, cm^{-1}) 2200, 1630.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.54- 1.73 (2H., m), 2.07- 2.22 (2H, m), 2.27- 2.54 (2H, m), 2.49- 2.54 (1H, m), 2.79 (1H, dddd, J = 12.2 Hz, 12.2 Hz, 3.2 Hz, 3.2 Hz), 3.05- 3.10 (1H, m), 5.13 (1H, s), 7.31 (15H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 32.87, 34.39, 34.84, 35.68, 43.38, 92.77, 126.44, 126.67, 128.52, 145.11.

MS m/z: 198 [$(M+1)^+$], 197 (M^+).

SR $[\alpha]_D^{25}$ -74.2 (*c* 1.49, $CHCl_3$).

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found C, 85.23; H, 7.85; N, 6.91.

Table 13 run 3 (4-isopropylcyclohexanone).

Under argon atmosphere, to a solution of **8-OH** (213 mg, 0.96 mmol) in toluene (3 mL), BuLi (1.71 N solution in hexane, 0.56 mL, 0.96 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (171 mg, 0.96 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-(1-methylethyl)cyclohexanone (123 mg, 0.87 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (260 mg). ^{1}H-NMR spectrum of the oil showed yield of olefin is 94%.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 47% ee.

Table 13 run 4 (4-methylcyclohexanone).

Under argon atmosphere, to a solution of **8-OH** (221 mg, 1.00 mmol) in toluene (3 mL), BuLi (1.67 N solution in hexane, 0.60 mL, 1.00 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (177 mg, 1.00 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-methylcyclohexanone (102 mg, 0.91 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (405 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless oil (103 mg, 88%).

HPLC (DAICEL CHIRALCEL OD-H x 2, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 36% ee.

IR (neat, cm^{-1}) 3070, 2200.

Table 13 run 5 (biciclo[3.3.0]octanone).

Under argon atmosphere, to a solution of **8-OH** (217 mg, 0.98 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.58 mL, 0.98 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diethyl cyanomethylphosphonate (174 mg, 0.98 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 7,7-ethylenedioxy-bicyclo[3.3.0]octane-3-one (162 mg, 0.89 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -45 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (251 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford olefin as colorless oil (186 mg, 98%).

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 100: 1, 0.5 mL/ min, 238 nm) 14% ee.

IR (neat, cm^{-1}) 2210, 1630.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.60-1.67 (2H., m), 2.04- 2.10 (2H, m), 2.37- 2.90 (6H, m), 3.89 (4H, m), 5.21 (1H, dd, J = 2.0 Hz, 2.0 Hz).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 39.26, 41.15, 40.34, 41.86, 41.95, 64.01, 64.55, 91.39, 117.06, 118.27, 173.21.

HRMS Calcd for $C_{12}H_{15}NO_2$, m/z: 205.1103. Found: 205.1145.

SR $[\alpha]_D^{25}$ -16.0 (*c* 1.87, $CHCl_3$).

Table 16 run 1 (dimethyl cyanomethylphosphonate).

Under argon atmosphere, to a solution of **8-OH** (214 mg, 0.97 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.61 mL, 0.97 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of dimethyl cyanomethylphosphonate (144 mg, 0.97 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (136 mg, 0.87 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (260 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (122 mg, 78%).

mp 49- 52 °C

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 11% ee (*R*).

SR $[\alpha]_D^{25}$ -10.7 (*c* 1.23, $CHCl_3$).

Table 16 run 3 (diisopropyl cyanomethylphosphonate).

Under argon atmosphere, to a solution of **8-OH** (222mg, 1.01 mmol) in toluene (3 mL), BuLi (1.58 N solution in hexane, 0.64 mL, 1.01 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of bis(1-methylethyl) cyanomethylphosphonate (208 mg, 1.01 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (141 mg, 0.91 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (294 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (116 mg, 78%).

mp 30- 34 °C

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 31% ee (*R*).

SR $[\alpha]_D^{25}$ -30.7 (*c* 0.97, $CHCl_3$).

Table 16 run 2 (diphenyl cyanomethylphosphonate).

Under argon atmosphere, to a solution of **8-OH** (274 mg, 1.24 mmol) in toluene (3 mL), BuLi (1.69 N solution in hexane, 0.73 mL, 1.24 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of diphenyl cyanomethylphosphonate (300 mg, 1.10 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (174 mg, 1.13 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (671 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (163 mg, 84%).

mp 29- 30 °C

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 23% ee (*S*).

SR $[\alpha]_D^{25}$ +24.0 (*c* 1.19, $CHCl_3$).

Table 16 run 5 (bis(2,2,2-trifluoroethyl) cyanomethylphosphonate).

Under argon atmosphere, to a solution of **8-OH** (194 mg, 0.88 mmol) in toluene (3 mL), BuLi (1.67 N solution in hexane, 0.52 mL, 0.88 mmol) was added at 0 °C and a mixture was stirred for 30 min at room temperature. The whole was cooled to -78 °C, and a solution of bis(2,2,2-trifluoroethyl) cyanomethylphosphonate (223 mg, 0.88 mmol) in toluene (3 mL) was added within 2 min. After 30 min, a solution of 4-*tert*-butylcyclohexanone (123 mg, 0.80 mmol) in toluene (3 mL) was aded within 2 min and the resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aqueous citric acid (2 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (243 mg). The oil was purified by column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (128 mg, 90%).

mp 29- 33 °C

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 17% ee (*S*).

SR $[\alpha]_D^{25}$ +17.4 (*c* 1.15, $CHCl_3$).

Synthesis of aldol intermediates

Scheme 9 (synthesis of aldol intermediate in THF).

Under argon atmosphere, to a solution of diethyl cyanomethylphosphonate (1.77 g, 10.0 mmol) in THF (20 mL), methylmagnesiumbromide (2.23 M in Et_2O, 4.48 mL, 10.0 mmol) was added within 10 min. The resultant suspension was stirred for 1 h, and a solution of 4-*tert*-butylcyclohexanone (1.46 g, 9.50 mmol) in THF (10 mL) was added within 4 min and the resultant mixture was stirred for 1 h at -78 °C, and then quenched with 10% aqueous citric acid (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with water (2 x 20 mL) and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (3.19 g). The oil was purified by column chromathography (SiO_2 120 g, hexane-ethyl acetate 10:1) to afford olefin (yellow oil, 0.54 g, 32%) and aldol (*cis* isomer) as colorless prisms (1.69 g, 54%). The solid was recrystalized from hexane to give authentic sample.

mp 77-78 °C.

IR (KBr, cm^{-1}) 3400, 2230, 1240.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (9H, s, CH_3), 1.39 (3H, t, J = 7.0 Hz, CH_3 in ester), 1.42 (3H, t, J = 7.0 Hz, CH_3 in ester), 1.42- 1.48 (2H, m, C[3]-ax-H, C[5]-ax-H), 1.60- 1.80 (5H, m, C[2]-ax-H, C[3]-eq-H, C[4]-H, C[5]-eq-H, C[6]-ax-H), 1.95 (1H, m, C[2]-eq-H), 2.05 (1H, m, C[6]-eq-H), 3.03 (1H, d, J = 23.0 Hz, CH), 4.21 (2H, dq, J = 8.3 Hz, 7.0 Hz, CH_2), 4.31 (2H, dq, J = 8.3 Hz, 7.0 Hz, CH_2).

Anal. Calcd for $C_{16}H_{30}NO_4P$: C, 57.97; H, 9.12; N, 4.23. Found C, 57.84; H, 8.98; N, 4.11.

Scheme 10 (synthesis of aldol intermediate in THF, 4-Ph).

Under argon atmosphere, to a solution of diethyl cyanomethylphosphonate (1.70 g, 11.2 mmol) in THF (80 mL), methylmagnesiumbromide (2.23 M in Et_2O, 5.00 mL, 11.2 mmol) was added within 10 min. The resultant suspension was stirred for 20 min, and a solution of 4-phenylcyclohexanone (1.43 g, 10.1 mmol) in THF (20 mL) was added within 5 min and the resultant mixture was stirred for 1 h at -78 °C, and quenched with 10% aqueous citric acid (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with water (2 x 20 mL) and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (3.82 g). The oil was purified by column chromathography (SiO_2 60 g, hexane-ethyl acetate 5:1) to afford olefin (colorless solid, 1.12 g) and aldol (*cis* isomer) as colorless solid (989 mg, 28%). The solid was recrystalized from water- isopropanol (5: 3) to give authentic sample as colorles prisms.

mp 99- 100 °C (dec.).

IR (nujol, cm^{-1}) 3330, 2230, 1595, 1250.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 6.8 Hz, CH_3 in ester), 1.43 (3H, t, J = 6.8 Hz, CH_3 in ester), 1.76- 2.04 (7H, m, C[2]-ax-H, C[6]-ax-H ,C[3]-H_2, C[4]-H, C[5]-H_2), 2.16- 2.21 (1H, m, C[2]-eq-H), 2.46- 2.56 (1H, m, C[6]-eq-H), 3.09 (1H, d, J = 22.4 Hz, CH), 3.30 (1H, br, OH), 4.22 (2H, dq, J = 8.4 Hz, 6.8Hz, CH_2), 4.31 (2H, dq, J = 8.4 Hz, 6.8Hz, CH_2), 7.17 (5H, m, Ph).

MS m/z: 351 (M^+), 350 [$(M+1)^+$].

Anal. Calcd for $C_{18}H_{26}NO_4P$: C, 61.53; H, 7.46; N, 3.99. Found C, 61.31; H, 7.26; N, 3.73.

Scheme 11 (synthesis of aldol intermediate in toluene).

Under argon atmosphere, to a solution of diethyl cyanomethylphosphonate (167 mg, 0.94 mmol) in toluene (3 mL), methylmagnesiumbromide (2.23 M in Et_2O, 0.42 mL, 0.94 mmol) was added within 3 min. The resultant suspension was stirred for 1 h, and a solution of 4-*tert*-butylcyclohexanone (132 mg, 0.86 mmol) in toluene (2 mL) was added within 2 min and the resultant mixture was allowed to stand for 26 h at -20 °C, and then quenched with 10% aqueous citric acid (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with water (2 x 20 mL) and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (299 mg). 1H-NMR spectra of the oil showed that yield of **3b** is 10%. The oil was purified by column chromathography (SiO_2 50 g, hexane-ethyl acetate 15:1- 1: 1) to afford (±)-*cis*-**37** (56 mg, 20%) and (±)-*trans*-**37** (51 mg, 18%) as a colorless oil.

(±)-*trans*-**37**:

IR (neat, cm^{-1}) 3420, 2230, 1240.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (9H, s, CH_3), 0.90- 1.10 (2H, m, C[3]-ax-H, C[5]-ax-H), 1.39 (3H, t, J = 7.0 Hz, CH_3 in ester), 1.42 (3H, t, J = 7.0 Hz, CH_3 in ester), 1.50- 1.65 (3H, m, C[3]-eq-H, C[4]-H, C[5]-eq-H), 1.70- 1.85 (2H, m, C[2]-ax-H, C[6]-ax-H), 2.10- 2.30 (3H, m, C[2]-eq-H, C[6]-eq-H), 3.44 (1H, d, J = 24.1 Hz, CH), 4.23 (2H, dq, J = 7.3 Hz, 7.3 Hz, CH_2), 4.38 (2H, dq, J = 7.3 Hz, 7.3 Hz, CH_2).

Elimination reactions of aldol intermediates

Table 14, run 1 (cis aldol 1.1 eq base).

Under argon atmosphere, to a solution of **8-OH** (156 mg, 0.71 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.41 mL, 0.71 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*cis*-**37** (212 mg, 0.64 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (129 mg). ^{1}H-NMR spectrum of the oil showed that yield of **3b** is 89%.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 52% ee (*R*).

Table 14, run 2 (cis aldol 0.5 eq base).

Under argon atmosphere, to a solution of **8-OH** (106.5 mg, 0.48 mmol) in toluene (5 mL), BuLi (1.66 N solution in hexane, 0.29 mL, 0.48 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*cis*-**37** (319 mg, 0.91 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (210 mg). The oil was purified with column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (88 mg, 51% from aldol).

mp 28- 32 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 52% ee (*R*).

Table 14, run 3 (cis aldol 1.0 eq base wih benzaldehyde).

Under argon atmosphere, to a solution of **8-OH** (153 mg, 0.69 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.41 mL, 0.69 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*cis*-**37** (209 mg, 0.63 mmol) and benzaldehyde (67.0 mg, 0.63 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (205 mg). ^{1}H-NMR spectrum of the oil showed yield of **3b** (40%), (*E*)- cinnamate (18%) and (*Z*)- cinnnamate (2%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 18% ee (*R*).

Scheme 13

Under argon atmosphere, to a solution of **8-OH** (187 mg, 0.85 mmol) in toluene (3 mL), BuLi (1.65 N solution in hexane, 0.51 mL, 0.85 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The solution was cooled at -78 °C, and a solution of diethyl cyanomethylphosphonate (150 mg, 0.85 mmol) was added within 1 min. The whole was stirred for 30 min, and a mixture of 4-*tert*-butylcyclohexanone (119 ng, 0.77 mg) and benzaldehyde (81.5 mg, 0.77 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 3 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (240 mg). ^{1}H-NMR spectrum of the oil showed yield of **3b** (17%), (*E*)- cinnamate (50%) and (*Z*)- cinnnamate (11%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 25% ee (*R*).

Table 15, run 1 (trans aldol 1.1 eq base).

Under argon atmosphere, to a solution of **8-OH** (141 mg, 0.64 mmol) in toluene (5 mL), BuLi (1.57 N solution in hexane, 0.41 mL, 0.64 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*trans*-**37** (192 mg, 0.58 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (115 mg). The oil was purified with column chromatography (SiO_2 20 g, hexane-ethyl acetate 40:1) to afford **3b** as colorless needles (84 mg, 84%).

mp 41- 44 °C.

HPLC (DAICEL CHIRALCEL OD-H, hexane-isopropanol 1000: 1, 0.6 mL/ min, 238 nm) 12% ee (*R*).

Table 15, run 2 (trans aldol 0.5 eq base).

Under argon atmosphere, to a solution of **8-OH** (106 mg, 0.46 mmol) in toluene (5 mL), BuLi (1.57 N solution in hexane, 0.30 mL, 0.46 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*trans*-**37** (317 mg, 0.96 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless oil (268 mg). ^{1}H-NMR spectrum of the oil showed that yield of **3b** is 41%.

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 3% ee (*S*).

Table 15, run 3 (*trans* aldol 1.0 eq base wih benzaldehyde).

Under argon atmosphere, to a solution of **8-OH** (132 mg, 0.60 mmol) in toluene (3 mL), BuLi (1.57 N solution in hexane, 0.35 mL, 0.60 mmol) was added at room temperature, and the mixture was allowed to stand for 30 min at room temperature. The whole was added to a solution of (±)-*trans*-**37** (180 mg, 0.54 mmol) and benzaldehyde (57.6 mg, 0.54 mmol) in toluene (3 mL) within 2 min at -78 °C. The resultant mixture was stirred for 1 h at -78 °C, and then quenched with saturated aquerous ammonium chloride (10 mL). The organic layer was separated and the aquerous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed successively with 10% aquerous citric acid (2 x 10 mL), saturated aquerous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (268 mg). ^{1}H-NMR spectrum of the oil showed yield of **3b** (58%), (*E*)- cinnamate (16%) and (Z)- cinnnamate (3%).

GC (CHROMPAK CP-Cyclodextrin-β-236-m-19, 50 m, carrier gas: N_2 85 ml/ min, H_2 1.2 kgf/ cm^2, air 0.8 kgf/ cm^2, temp. inj. 200 °C, det. 200 °C, column 80 °C, 1 °C/ min) 0% ee.

Syntheses of Chiral Alcohols

(1*R*,2*S*)-2-(1-Methylethylamino)-1-phenyl-1-propanol (7-OH)

To a solution of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (2.27 g, 15 mmol) in methanol (30 mL), 36% hydrochloric acid (1.40 mL, 16.5 mmol), acetone (11.0 mL, 8.71 g, 150 mmol), and sodium cyanoborohydride (95%, 1.09 g, 16.5 mmol) were added in this order at 0 °C, and the mixture was stirred for 11 h at room temperature. The solvent was evaporated *in vacuo*, and 10% aqueous potassium hydroxide (20 mL) was added to the residue. The whole was extracted with benzene (1 x 50 mL, 1 x 30 mL, 2 x 20 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to give colorless needles (2.90 g, quant) .

IR (KBr, cm^{-1}) 3400, 1600.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, d, *J* = 6.6 Hz, CH_3(ephedrine)), 1.08 (3H, d, *J* = 4.3 Hz, CH_3 (isopropyl)), 1.10 (3H, d, *J* = 4.3 Hz, CH_3 (isopropyl)), 2.97 (1H, dq, *J* = 4.3 Hz, 4.3 Hz, CH (isopropyl)), 3.04 (1H, qd, *J* = 6.6 Hz, 4.0 Hz, CHN), 4.68 (1H, d *J* = 4.0 Hz, PhCH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.00, 24.68, 46.72, 56.15, 74.12, 127.24, 128.03, 129.06.

MS m/z: 194 [$(M+1)^+$].

SR $[\alpha]_D^{25}$ +4.5 (*c* 5.00, EtOH).

To a solution of the salt (2.31 g, 12.0 mmol) in ethanol (30 mL), 15% hydrochloric acid (1.5 mL in ethanol) was added. The whole was concentrated *in vacuo* to leave colorless needles (2.75 g), which was recrystalized from ethanol (10 mL), concentrated to 5 mL to give colorless needles (2.00 g, 73%).

mp 222- 225 °C.

IR (KBr, cm^{-1}) 3260, 1600, 1565.

SR $[\alpha]_D^{25}$ -13.4 (*c* 5.30, H_2O).

Anal. Calcd for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77; N, 6.10. Found C, 62.64; H, 8.89; N, 6.01.

(1*R*,2*S*)-2-(2,2-Dimethylpropylamino)-1-phenyl-1-propanol (8-OH)

Trimethylacetaldehyde (2.06 mL, 1.64 g, 19 mmol) was added to a solution of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (2.27 g, 15 mmol) in benzene (30 mL), and the mixture was stirred for 1 h at room temperature. Anhydrous sodium sulfate (10 g) was added and the mixture was stirred for 30 min, then filtered. The filtrate was concentrated *in vacuo* to give a colorless oil (3.73 g). The oil was dissolved in ethanol (30 mL), and sodium borohydride (1.13 g, 30 mmol) was

added. The mixture was stirred for 11 h at room temperature. The whole was concentrated *in vacuo*, and 10% aqueous potassium hydroxide (20 mL) was added to the residue. The whole was extracted with benzene (1 x 50 mL, 1 x 30 mL, 2 x 20 mL). The organic layer was washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to give a colorless oil (3.26 g, quant).

IR (neat, cm^{-1}) 3420, 1475, 700.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, d, *J* = 6.6 Hz, CH_3(ephedrine)), 0.93 (9H, s, ^{t}Bu), 2.37 (1H, d, *J* = 11.2 Hz, CH_2), 2.53 (1H, d, *J* = 11.2 Hz, CH_2), 2.86 (1H, qd, *J* = 6.6 Hz, 3.6 Hz, CHN), 4.72 (1H, d *J* = 3.6 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.00, 27.63, 31.38, 58.89, 59.50, 72.48, 125.97, 126.84, 127.96.

MS m/z: 222 [$(M+1)^+$], 220 (M^+).

SR $[\alpha]_D^{25}$ +12.2 (*c* 2.55, EtOH).

To a solution of the oil (2.63 g, 11.9 mmol) in ethanol (50 mL), 15% hydrochloric acid in ethanol (1.5 mL) was added, and the solution was evaporated *in vacuo*. The residue was recrystalized from ethanol (50 mL). The whole was concentrated to 20 mL to give colorless plates (1.82 g, 58%, 2 steps).

mp 222-224 °C.

IR (KBr, cm^{-1}) 3260, 1600.

SR $[\alpha]_D^{25}$ -21.6 (*c* 5.50, H_2O).

Anal. Calcd for $C_{14}H_{24}ClNO$: C, 65.23; H, 9.38; N, 5.43. Found C, 65.20; H, 9.34; N, 5.43.

(1*R*,2*S*)-2-(Diphenylmethylamino)-1-phenyl-1-propanol (9-OH)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (3.02 g, 20 mmol), benzophenone (3.64 g, 20 mmol) and zinc chloride (100 mg) in toluene (100 mL) was refluxed for 48 h with Dean- Stark apparatus, and the whole was concentrated *in vacuo* to leave imine as yellow oil. To the solution of the imine in methanol (60 mL), aqueous hydrochloric acid (28%, 1.5 mL) and sodium cyanoborohydride (2.51 g) were added at 0 °C. The mixture was stirred for 12 h at room temperature and concentrated *in vacuo*, and aqueous sodium hydroxide (50 mL) was added to the residue. The whole was extracted with methylene chloride (1 x 100 mL, 2 x 50 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil (6.72 g), which was purified by column chromatography (SiO_2 150 g, hexane- AcOEt 20: 1) to give a yellow oil (6.18 g, 98%).

IR (neat, cm^{-1}) 3420, 3320, 1590, 1485.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 6.9 Hz, CH_3), 1.62 (1H, br, NH), 2.91 (1H, qd, J = 6.9 Hz, 4.0 Hz, CHN), 3.42 (1H, br, OH), 4.70 (1H, d J = 4.0 Hz, PhC*H*), 5.02 (1H, s, Ph_2CH), 7.31 (15H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.81, 55.76, 63.97, 73.87, 126.13, 127.05, 127.14, 127.19, 127.43, 128.03, 128.54, 128.64, 141.32, 143.49, 143.89.

MS m/z: 210 [$(M\text{-}PhCHOH)^+$], 223 [$(Ph_2CH)^+$].

SR $[\alpha]_D^{25}$ +34.6 (*c* 1.10, EtOH).

Anal. Calcd for $C_{22}H_{23}NO$: C, 83.25; H, 7.30; N, 4.41. Found C, 83.14; H, 7.47; N, 4.38.

(1*R*,2*S*)-2-(Phenylmethylamino)-1-phenyl-1-propanol (10-OH)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (6.05 g, 40 mmol) and benzaldehyde (4.6 mL, 4.78 g, 45 mmol) in benzene (80 mL) was heated to reflux for 1 h with Dean- Stark apparatus, and the whole was concentrated *in vacuo* to leave imine as a yellow oil. To the solution of the imine in ethanol (100 mL), sodium borohydride (3.02 g, 80 mmol) was added at 0 °C. The mixture was stirred for 12 h at room temperature and concentrated *in vacuo*, and water (50 mL) was added to the residue. The whole was extracted with methylene chloride (4 x 50 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a slightly yellow oil (11.52 g), which was purified by column chromatography to give a colorless oil (9.48 g, 98%).

IR (neat, cm^{-1}) 3300- 3400, 1600, 1485, 740.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 6.6 Hz, CH_3), 3.00 (1H, qd, J = 6.6 Hz, 3.6 Hz, CHN), 3.88 (2H, s, CH_2), 4.79 (1H, d J = 3.6 Hz, PhCH), 7.31 (10H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.62, 51.22, 57.50, 73.07, 126.04, 126.98, 127.09, 128.01, 128.26, 128.47, 140.06, 141.27.

HRMS Calcd. for $C_{16}H_{19}NO$: m/z: 241.1467. Found: 241.1432.

SR $[\alpha]_D^{25}$ +15.6 (*c* 5.04, EtOH).

(1*R*,2*S*)-2-(1-Adamantylcarboxamido)-1-phenyl-1-propanol (40)

To the solution of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (3.08 g, 20 mmol) in ethyl acetate (100 mL), the solution of potassium carbonate (5.53 g, 40 mmol) in water (50 mL) was added. The solution of 1-adamantanecarboxyl chloride (4.37 g, 22 mmol) in ethyl acetate (20 mL) was added at 0 °C and the mixture was stirred for 5 min, then filtered off. The precipitate was dried to give crude product (4.34 g), which was recrystalized from benzene (30 mL) and hexane (15 mL) to give colorless needles (3.76 g, 60%). mp 147- 149 °C. The filtrate was separated, and the organic layer was washed successively with 10% hydrochrolic acid (1 x 30 mL), water (1 x 30 mL),

saturated aqueous sodium bicarbonate (1 x 30 mL), water (1 x 30 mL) and brine (1 x 30 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless solid (2.89 g), which was recrystalized from benzene (20 mL) and hexane (15 mL) to give colorless needles (2.73 g, 44%).mp 147- 149 °C.

IR (neat, cm^{-1}) 3300- 3400, 1600, 1485, 740.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 7.0 Hz, CH_3), 1.65- 1.83 (12 H, m, CH_2 at adamantyl), 2.04 (3H, br, CH at adamantyl), 4.17 (1H, d, J = 4.3 Hz, OH), 4.37 (1H, ddq, J = 7.0 Hz, 7.0 Hz, 2.6 Hz, CH_3CH), 4.81 (1H, dd J = 3.0 Hz, 3.0 Hz, PhC*H*), 7.25- 7.38 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.53, 28.05, 36.44, 39.21, 40.52, 50.86, 126.63, 127.53, 127.99, 140.49, 179.30.

MS m/z: 314 [$(M+1)^+$], 296 [$(M\text{-}H_2O+1)^+$].

SR $[\alpha]_D^{25}$ -89.2 (*c* 2.01, $CHCl_3$).

(1*R*,2*S*)-2-(1-Adamantylmethylamino)-1-phenyl-1-propanol (11-OH)

To a suspension of (1*R*,2*S*)-2-(1-adamantylcarboxamido)-1-phenyl-1-propanol (3.54 g, 11.3 mmol) and sodium borohydride (4.27 g, 110 mmol) in THF (200 mL), boron trifluoride etherate (15.7 mL, 18.2 g, 128 mmol) was added at 0 °C. The whole was heated to reflux for 11 h, then added water (20 mL) and hydrochloric acid (10%, 30 mL). The whole was heated to reflux for 1.5 h. Sodium hydroxide (93%, *ca.* 15 g) was added, and the whole was extracted with Et_2O (1 x 50 mL, 2 x 30 mL). The organic layers were combined, washed successively with water (1 x 20 mL) and brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (3.87 g), which was purified by column chromatography (SiO_2 50 g, hexane- AcOEt 4: 1) to give a colorless oil (3.33 g).

IR (neat, cm^{-1}) 3400, 1595, 1445, 695.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.77 (3H, d, J = 6.6 Hz, ^{t}Bu), 1.47- 1.76 (12H, m, 6 x CH_2), 1.98 (3H, brs, 3 x CH), 2.28 (1H, d, J = 11.2 Hz, $CH_2{}^t$Bu), 2.42 (1H, d, J = 11.2 Hz, $CH_2{}^t$Bu), 2.83 (1H, qd, J = 6.6 Hz, 4.0 Hz, CHN), 4.00 (2H, br, NH, OH), 4.72 (1H, d, J = 4.0 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.92, 28.39, 33.32, 37.18, 40.77, 58.89, 59.93, 72.35, 125.95, 126.77, 127.92, 141.40.

MS m/z: 298 [$(M+1)^+$], 280 [$(M\text{-}H_2O)^+$].

The oil was dissolved in ethanol (10 mL), and hydrochloric acid (17% EtOH solution, 10 mL)was added. The solvent was evaporated *in vacuo*. The residue was recrystalized from ethanol (45 mL) to give colorless needles (2.02 g, 54%).

mp >250 °C.

IR (nujol, cm^{-1}) 3270, 1565.

SR $[\alpha]_D^{25}$ -21.9 (*c* 1.99, MeOH).

Anal. Calcd for $C_{20}H_{30}ClNO$: C, 71.51; H, 9.00; N, 4.17. Found C, 71.72; H, 9.09; N, 4.34.

(1*R*,2*S*)-2-(1-Methylcyclohexylcarboxamido)-1-phenyl-1-propanol (41)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (3.20 g, 20 mmol), 1-methylcyclohenanecarboxylic acid (3.13 g, 22 mmol), diethyl cyanophosphonate (93%, 3.51 mL, 3.78 g, 22 mmol), triethylamine (3.07 mL, 22 mmol) in *N*,*N*-dimethylformamide (100 mL) was stirred for 12 h at room temperature. The solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and washed with water (1 x 30 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The organic layers were combined, washed successively with aqueous hydrochloric acid (5%, 1 x 10 mL), water (1 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a yellow oil (7.12 g), which was purified by column chromatography (SiO_2 200 g, hexane-AcOEt 7:1) to give a colorless oil (5.53 g, quant.)

IR (neat, cm^{-1}) 3400, 1750, 1640.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.13 (3H, s, CH_3), 1.25-1.86 (10H, m, cyclohexyl), 4.00 (1H, br, OH), 4.36 (1H, qdd, *J* = 7.0 Hz, 7.0 Hz, 3.0 Hz, CHN), 4.81 (1H, d *J* = 3.0 Hz, PhC*H*), 5.64 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.37, 22.73, 22.79, 25.70, 26.32, 35.46, 35.55, 42.57, 50.95, 77.14, 126.52, 127.51, 128.03, 140.59, 178.92.

SR $[\alpha]_D^{25}$ -13.4 (*c* 1.40, EtOH).

MS m/z: 276 [$(M+1)^+$], 258 [$(M-H_2O+1)^+$].

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found C, 73.95; H, 8.86; N, 4.81.

(1*R*,2*S*)-2-(1-Methylcyclohexylmethylamino)-1-phenyl-1-propanol (12-OH)

To a suspension of (1*R*,2*S*)-2-(1-methylcyclohexylcarboxamido)-1-phenyl-1-propanol (4.53 g, 16.4 mmol) and sodium borohydride (3.12 g, 82 mmol) in THF (100 mL), boron trifluoride etherate (13.5 mL, 15.56 g, 109 mmol) was added at 0 °C. The whole was refluxed for 11 h, then added water (10 mL) and hydrochloric acid (10%, 20 mL). The whole was heated to reflux for 1.5 h. The slolvent was concentrated *in vacuo* to a small volume, and aqueous potassium hydroxide (20%, 50 mL) was added. The whole was extracted with hexane (3 x 50 mL). The organic layers were combined, washed successively with water (1 x 20 mL) and brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (3.80 g), which was purified

by column chromatography (SiO_2 100 g, hexane- isopropylamine 10: 1) to give a colorless oil (3.68 g, 86%).

IR (neat, cm^{-1}) 3420, 3350, 1595, 1485.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.78 (3H, d, *J* = 6.6 Hz, CH_3), 0.93 (3H, s, CH_3), 1.31-1.48 (6H, m, cyclohexyl), 2.46 (1H, d, *J* = 11.5 Hz, NCH_2), 2.55 (1H, d, *J* = 11.5 Hz, NCH_2), 2.86 (1H, qd, *J* = 7.3 Hz, 4.0 Hz, CHN), 4.01 (1H, br, OH), 4.73 (1H, d *J* = 4.0 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.07, 21.88, 23.65, 26.49, 33.79, 35.84, 36.01, 58.12, 58.91, 72.46, 125.99, 126.84, 127.98, 141.37.

SR $[\alpha]_D^{25}$ +12.7 (*c* 2.00, EtOH).

MS m/z: 262 [$(M+1)^+$], 260 [$(M-1)^+$].

Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found C, 78.09; H, 10.31; N, 5.40.

(1*R*,2*S*)-2-(1-Methylpropionamido)-1-phenyl-1-propanol (42)

A soluion of isobutyl chloride (3.46 mL, 3.52 g, 33 mmol) in ethyl acetate (25 mL) was added to a solution of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (4.53 g, 30 mmol) in ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (100 mL) under ice- water bath. The mixture was stirred for 1 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed successively with aqueous hydrochloric acid (5%, 2 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless solid (5.96 g), which was recrystalized from benzene (50 mL) and hexane (20 mL) to give colorless needles (5.94g, 95%).

mp 120- 122 °C.

IR (KBr, cm^{-1}) 3360, 3280, 1635.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.01 (3H, d, *J* = 6.9 Hz, C*H*$_3$CHN), 1.13 (3H, d, *J* = 6.9 Hz, C*H*$_3$CHCH$_3$), 1.14 (3H, d, *J* = 6.9 Hz, C*H*$_3$CHCH$_3$), 2.33 (1H, ddq, *J* = 6.9 Hz, 6.9 Hz, 6.9 Hz, CH$_3$C*H*CH$_3$), 4.05 (1H, d, *J* = 4.1 Hz, OH), 4.31 (1H, qdd, *J* = 6.9 Hz, 4.1 Hz, 2.7 Hz, CH$_3$C*H*N), 4.80 (1H, dd, *J* = 4.1 Hz, 4.1 Hz, PhC*H*), 5.62 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.97, 19.40, 19.63, 35.53, 50.89, 76.93, 126.39, 127.46, 128.03, 140.59, 178.01.

MS m/z: 222 [$(M+1)^+$], 204 [$(M-H_2O+1)^+$].

SR $[\alpha]_D^{25}$ -34.9 (*c* 1.73, MeOH).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found C, 70.60; H, 8.95; N, 6.27.

(1*R*,2*S*)-2-(2-Methyl-1-propylamino)-1-phenyl-1-propanol (13-OH)

To a solution of (1*R*,2*S*)-2-(1-methylpropionamido)-1-phenyl-1-propanol (3.12 g, 15 mmol) in THF (100 mL), borane- THF complex (1 M soluion in THF, 36.0 mL, 36.0 mmol)was added under ice- water bath. The mxture was heated to reflux for 10 h, then quenched with methaol (25 mL) after cooling with ice- water bath. The solvent was evaporated *in vacuo*. Methanol (20 mL) was added, and the whole was concentrated *in vacuo* to leave colorless oil (3.53 g). The oil was disolved in methanol (20 mL), and hydrochloric acid (20% solution in MeOH, 40 mL) was added. The solution was concentrated *in vacuo* to leave colorless solid, which was recrystalized from ethanol (20 mL) and Et_2O (5 mL) to give colorless needles (3.18 g, 87%. 2nd crop 0.21 g, 6%).

mp >200 °C.

IR (KBr, cm^{-1}) 3280, 1460.

SR $[\alpha]_D^{25}$ -28.5 (*c* 5.31, MeOH).

Anal. Calcd for $C_{13}H_{22}ClNO$: C, 64.05; H, 9.10; N, 5.75. Found C, 63.99; H, 8.91; N, 5.74.

A solution of **13-OH** hydrochloride (1.41 g) in aqueous sodium hydroxide (20%, 30 mL) was extracted from hexane (1 x 50 mL, 2 x 20 mL). The organic layers were combined, washed successively with water (1 x 20 mL) and brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (1.18 g).

IR (neat, cm^{-1}) 3300, 1595.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 6.3 Hz, C*H*$_3$CHN), 0.92 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_3$), 0.94 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_3$), 1.71 (1H, ddq, *J* = 6.6 Hz, 6.6 Hz, 6.6 Hz, CH$_3$C*H*CH$_3$), 2.44 (1H, d, *J* = 11.2 Hz, 6.6 Hz, CH$_2$), 2.56 (1H, d, *J* = 11.2 Hz, 6.6 Hz, CH$_2$), 2.88 (1H, qd, *J* = 6.3 Hz, 4.0 Hz, CH$_3$C*H*N), 3.80 (2H, br, NH, OH), 4.71 (1H, d, *J* = 4.0 Hz, PhC*H*), 5.62 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.86, 20.61, 28.74, 55.22, 58.42, 72.80, 126.02, 126.90, 128.00, 141.46.

MS m/z: 208 [(M+1)$^+$], 206 [(M-1)$^+$], 190 [(M-H$_2$O+1)$^+$].

SR $[\alpha]_D^{25}$ +10.4 (*c* 3.54, EtOH).

(1*R*,2*S*)-2-(Diphenylacetamido)-1-phenyl-1-propanol (43)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.33 g, 33 mmol) was added to a suspension of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (4.53 g, 30 mmol) and diphenylacetic acid (7.00 g, 33 mmol) in methylene chloride (80 mL) at 0 °C. The mixture was stirred for 3 h at room temperature. The mixture was diluted with Et_2O (50 mL), and aqueous hydrochloric acid (5%, 50 mL) was added. The precipitate was filtered, washed with Et_2O and dried. The organic layer was separated from the filtrate, washed successively with aqueous

hydrochloric acid (5%, 1 x 50 mL), water (1 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless solid (5.96 g), which was combined with the former precipitate, and recrystalized from chloroform (150 mL) and hexane (50 mL) to give colorless needles (8.38g, 81%).

mp 143- 145 °C.

IR (KBr, cm^{-1}) 3370, 1640.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 7.6 Hz, C*H*$_3$CHN), 2.63 (1H, br, OH), 4.38 (1H, m,, CH$_3$C*H*N), 4.77 (1H, m, PhC*H*), 4.89 (1H, s, C*H*Ph$_2$), 5.77 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.01, 51.14, 59.03, 76.53, 126.34, 127.24, 127.30,127.55, 128.16, 128.73, 128.82, 129.04, 139.16, 140.27, 172.54.

MS m/z: 345 (M$^+$), 326 [(M-H$_2$O-1)$^+$], 238 [(M-PhOH)$^+$].

SR $[\alpha]_D^{25}$ -24.6 (*c* 2.40, MeOH).

(1*R*,2*S*)-2-(2,2-Diphenylethylamino)-1-phenyl-1-propanol (14-OH)

To a solution of (1*R*,2*S*)-2-(diphenylacetamido)-1-phenyl-1-propanol (5.00 g, 14.5 mmol) in THF (100 mL), borane- THF complex (1 M soluion in THF, 36.0 mL, 36.0 mmol) was added under ice- water bath. The mixture was heated to reflux for 10 h, then quenched with methanol (25 mL) after cooling with ice- water bath. The solvent was evaporated *in vacuo*. Methanol (20 mL) was added, and the whole was concentrated *in vacuo* to leave colorless needles (4.83 g), which was recrystalized from benzene (10 mL) and hexane (25 mL) to give colorless needles (4.10 g, 85%).

mp 107- 109 °C.

IR (KBr, cm^{-1}) 3400, 1590, 1485.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 6.3 Hz, C*H*$_3$CHN), 2.94 (1H, qd, *J* = 6.3 Hz, 4.0 Hz, CH$_3$C*H*N), 3.29 (1H, dd, *J* = 11.9 Hz, 7.5 Hz, CH$_2$), 3.36 (1H, dd, *J* = 11.9 Hz, 7.5 Hz, CH$_2$), 4.15 (1H, dd, *J* = 7.5 Hz, 7.5 Hz, C*H*Ph$_2$), 4.71 (1H, d, *J* = 4.0 Hz, PhC*H*), 5.62 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.60, 51.47, 51.80, 58.45, 73.09, 125.97, 126.56, 126.65, 127.00, 127.89, 127.96, 128.03, 128.61, 128.69.

MS m/z: 331 (M$^+$), 313 [(M-H$_2$O)$^+$].

(1*R*,2*S*)-2-(3,3-Dimethylbutanamido)-1-phenyl-1-propanol (44)

(1*R*,2*S*)-2-Amino-1-phenyl-1-propanol (3.02 g, 20 mmol), diethyl cyanophosphonate (93%, 3.58 mL, 22 mmol), triethylamine (3.07 mL, 22mmol) were added to a solution of 2,2-

dimethylbutanoic acid (2.56 g, 22 mmol) in *N,N*-dimethylformamide (50 mL) under ice- water bath. The whole was stirred for 2 h. The solvent was evaporated *in vacuo*. Water (30 mL) was added to the residue, and whole was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed successively with saturated aqueous sodium bicarbonate (1 x 30 mL), water (1 x 20 mL) and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a yellow oil (5.83 g). The oil was purified by column chromatography (SiO_2 100 g, hexane-AcOEt 10: 1- 1: 1) to afford colorless needles (4.60 g, mp 56- 57.5 °C). The solid was recrystalized from benzene and hexane to afford colroless needles (4.31 g, 86%).

mp 57- 58 °C.

IR (nujol, cm^{-1}) 3270, 1625.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.02 (3H, d, *J* = 6.8 Hz, C*H*$_3$CHN), 1.04 (9H, s, CH3), 2.03 (1H, d, *J* = 13.8 Hz, CH_2), 2.08 (1H, d, *J* = 13.8 Hz, CH_2), 3.59 (1H, br, OH), 4.33 (1H, qdd, *J* = 6.8 Hz, 6.8 Hz, 3.0 Hz, CHN), 4.84 (1H, d, *J* = 3.0 Hz, PhC*H*), 5.51 (1H, br, NH), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.83, 29.80, 30.89, 50.55, 50.96, 76.73, 126.36, 127.53, 128.14, 140.68, 172.54.

MS m/z: 250 [$(M+1)^+$], 233 [$(M-H_2O)^+$].

SR $[\alpha]_D^{25}$ -95.1 (*c* 1.56, $CHCl_3$).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found C, 72.37; H, 9.26; N, 5.34.

(1*R*,2*S*)-2-(3,3-Dimethyl-1-butanamino)-1-phenyl-1-propanol (15-OH)

A solution of (1*R*,2*S*)-2-(3,3-dimethylbutylamido)-1-phenyl-1-propanol (4.10 g, 16.4 mmol) in THF (10 mL) was added to a suspension of lithium aluminum hydride (1.52 g, 40 mmol) in THF (40 mL) under ice- water bath. The whole was heated to reflux for 8 hr. After cooling, water (1.5 mL), 15% aqueous sodium hydroxide (1.5 mL) and water (4.5 mL) were added successively to the reaction mixture. Potassium carbonate was added, and the mixture was filtered off. The precipitate was washed with Et_2O. The filtrate and washings were combined and concentrated *in vacuo* to leave colorless needles (4.06 g), which was recrystalized from hexane (50 mL) to afford colorless needles (2.85 g, 74%).

mp 107-109 °C.

IR (KBr, cm^{-1}) 3280, 1595.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 6.5 Hz, CH_3), 0.92 (9H, s, ^{t}Bu), 1.29-1.51 (2H, m, C*H*$_2{}^t$Bu), 2.64- 2.74 (2H, m, C*H*$_2$CH$_2{}^t$Bu) 2.92 (1H, qd, *J* = 6.5 Hz, 4.1 Hz, CHN), 4.73 (1H, d, *J* = 4.1 Hz, C*H*Ph), 7.22- 7.33 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.81, 29.63, 29.89, 43.43, 44.55, 58.64, 73.10, 126.07, 126.95, 128.03, 141.49.

MS m/z: 236 [$(M+1)^+$], 220 [$(M-CH_3)^+$].

SR $[\alpha]_D^{25}$ +9.9 (*c* 6.30, EtOH).

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.54; H, 10.71; N, 5.95. Found C, 76.65; H, 10.53; N, 5.76.

Methoxyacetylchloride (45)

Methoxyacetic acid (4.60 mL, 5.04 g, 60 mmol) was added to thionyl chloride (18.24 mL, 29.74 g, 250 mmol). The mixture was refluxed for 1 h and concentrated *in vacuo* to leave a colorless oil (4.16 g, 63%).

IR (neat, cm^{-1}) 1800.

(1*R*,2*S*)-2-(Methoxyacetamido)-1-phenyl-1-propanol (46)

To a solution of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (4.10 g, 27 mmol) in methylene chloride (40 mL), a solution of methoxyacetylchloride (4.16 g, 38 mmol) in methylene chloride (12 mL) and triethylamine (5.58 mL, 4.05 g, 40 mmol) were added successively at 0 °C. The mixture was stirred for 2 h and diluted with methylene chloride (40 mL). The whole was washed successively with water (1 x 20 mL), 10% aqueous citric acid (1 x 20 mL), water (1 x 20 mL), saturated aqueous sodium bicarbonate (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to leave a yellow oil (7.96 g, quant).

IR (neat, cm^{-1}) 3400, 1750, 1655.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.6 Hz, CH_3), 3.20 (1H, br, OH), 3.38 (3H, s, OCH_3), 3.89 (2H, s CH_2), 4.33 (1H, m, CHN), 4.86 (1H, d, *J* = 2.9 Hz, CHPh), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.25, 50.35, 59.09, 71.74, 126.22, 127.49, 128.12, 140.70, 169.94.

MS m/z: 224 [$(M+1)^+$], 206 [$(M-H_2O+1)^+$].

SR $[\alpha]_D^{25}$ -14.3 (*c* 1.08, EtOH).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.67; N, 6.27. Found C, 64.60; H, 7.66; N, 6.05.

(1*R*,2*S*)-2-(2-Methoxyethylamino)-1-phenyl-1-propanol (16-OH)

To a suspension of lithium alminum hydride (3.17 g, 75 mmol) in THF (100 mL), a solution of (1*R*,2*S*)-2-(methoxyacetamido)-1-phenyl-1-propanol (7.66 g) in THF (40 mL) was added. The mixture was heated to reflux for 1 h. Water (3.1 mL), 15% aqueous sodium hydroxide (3.1 mL), water (9.3 mL) was added successively to the reaction mixture . Potassium carbonate was added

and filtered. The precipitate was washed with Et_2O. The filtrtate and the washing were combined and concentrated *in vacuo* . The residue was dissolved in ethanol (30 mL) and 15% hydrochloric acid in ethanol (5 mL) was added to the solution. The whole was concentrated *in vacuo* to leave colorless solid, which was recrystalized from ethanol to give colorless plates (2.46 g, 40%. 2nd crop: 1.28 g, 21%).

mp 185-186 °C.

IR (nujol, cm^{-1}) 3320, 1595, 1555.

SR $[\alpha]_D^{25}$ -28.4 (*c* 1.98, MeOH)

The salt was dissolved in 5% aqueous potassium hydroxide (20 mL). The whole was extracted with benzene (3 x 20 mL). The organic layer was washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil, which was distilled (bulb-to-bulb, 190-200 °C/ 0.9 mmHg) to give colorless needles (981 mg, 94%).

IR (KBr, cm^{-1}) 3400, 3120, 1600.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, d, *J* = 6.3 Hz, CH_3), 2.90 (3H, m, CHN , CH_2N), 3.36 (3H, s, OCH_3), 3.51 (2H, m, OCH_2), 4.75 (1H, d, *J* = 4.0 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.33, 46.65, 58.42, 58.77, 72.09, 72.93, 125.99, 126.91, 128.01, 141.41.

MS m/z: 210 $[(M+1)^+]$.

SR $[\alpha]_D^{25}$ -23.8 (*c* 3.74, EtOH)

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found C, 68.89; H, 9.22; N, 6.81.

(1*R*,2*S*)-2-[(*N'*,*N'*-Dimethylaminoethyl)-*N*-methylanimoacetylamido]-1-phenyl-1-propanol (47)

Triethylamine (13.9 mL, 99 mmol) was added to a suspension of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (4.54 g, 30 mmol) and *N'*,*N'*-dimethylaminoethyl)-*N*-methylglycine hydrochloride (7.69 g, 33mmol) in *N*,*N*-dimethylformamide (100 mL) at room temperature. After cooling with ice- water bath, diethyl cyanophosphonate (7.69 g, 33 mmol) was added. The whole was stirred at room temperature for 7 h. The mixture was poured into ice- water (200 mL) and extracted with ethyl acetate (3 x 100 mL, 2 x 50 mL). Basified with 10% sodium hydroxide (pH 10), the aqueous layer was extracted with methylene chloride (2 x 200 mL). The organic layers were combined, washed with brine (1 x 50 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil (10.98 g), which was purified by column chromatography (SiO_2 100 g, hexane- isopropylamine 5: 1) to afford a yellow oil (9.77 g, quant).

IR (neat, cm^{-1}) 3350, 3050, 1650.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 7.0 Hz, CH_3), 2.20 (6H, s, Me_2N), 2.31 (3H, s, NMe), 2.30- 2.54 (4H, m, NCH_2CH_2N), 3.00 (1H, d, *J* = 16.5 Hz, CH_2CO), 3.10 (1H, d, *J* = 16.5 Hz, CH_2CO), 4.31 (1H, m, CHN), 4.82 (1H, d, *J* = 4.0 Hz, CHPh), 7.31 (5H, m, Ph).

MS m/z: 293 (M^+).

(1*R*,2*S*)-2-[[*N*-(*N'*,*N'*-Dimethylaminoethyl)-*N*-methylanimo]ethylamino]-1-phenyl-1-propanol (17-OH)

A solution of (1*R*,2*S*)-2-[(*N'*,*N'*-dimethylaminoethyl)-*N*-methylanimoacetylamido]-1-phenyl-1-propanol in THF (25 mL) was added to the suspension of lithium aluminum hydride (2.36 g, 58 mmol) at 0 °C within 5 min. The whole was heated to reflux for 1 h. After cooling, water (2.5 mL), 15% sodium hydroxide (2.5 mL), and water (7.5 mL) were added successively. Potassium carbonate was added and filtered, and the precipitate was washed with Et_2O. The filtrate and the washings were combined and concentrated *in vacuo* to leave a yellow oil (7.72 g). A part of the oil (3.03 g) was purified by column chlomatography (SiO_2 160 g, Et_2O- isopropylamine 10: 1) to afford a slightly yellow oil (2.66 g). The oil was dissolved in ethanol (20 mL), and a solution of picric acid (80%, 8.2 g) in ethanol (100 mL) was added. The whole was digested to afford yellow needles (8.28 g, 75%).

mp 133- 135 °C (dec).

IR (KBr, cm^{-1}) 3425, 3020, 1605, 1560, 1310.

SR $[\alpha]_D^{25}$ +5.6 (*c* 1.30, acetone)

Anal. Calcd for $C_{34}H_{35}N_{12}O_{22}$: C, 42.37; H, 3.66; N, 17.44. Found C, 42.10; H, 3.88; N, 17.25.

The salt (3.25 g) was suspended in aqueous ammonia (28%, 50 mL), and extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (1 x 50 mL) and dried over potassium carbonate. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2 20 g, Et_2O- isopropylamine) to afford a colorless oil (0.79g, 80%).

IR (neat, cm^{-1}) 3300, 2940, 1450.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 6.9 Hz, CH_3), 2.24 (6H, s, Me_2N), 2.26 (3H, s, NMe), 2.37- 2.51 (6H, m, $NCH_2CH_2NCH_2$), 2.79 (2H, d, *J* = 5.4 Hz, CH_2N), 2.88 (1H, m, CHN), 4.78 (1H, d, *J* = 3.2 Hz, C*H*Ph), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 14.52, 42.48, 44.31, 45.64, 55.40, 57.21, 57.38, 58.56, 73.08, 125.98, 126.62, 127.79, 142.05.

SR $[\alpha]_D^{25}$ +2.7 (*c* 2.82, EtOH)

(1*R*,2*S*)-2-Pyrrolidyl-1-phenyl-propanol (21-OH)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (3.02 g, 20 mmol), 1,4-dibromobutane (5.40 g, 25 mmol) and triethylamine (6.97 mL, 60 mmol) in ethanol (20 mL) was heated to reflux for 24 h. The solvent was evaporated *in vacuo*. The residue was dissolved in 15% aqueous sodium hydroxide (30 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil (3.30 g), which was purified by column chromatography (SiO_2 100 g, CH_2Cl_2- MeOH 10: 1- 3: 1) to afford a colorless oil (3.28 g, 80%).

IR (neat, cm^{-1}) 3400, 1595.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, d, J = 6.6 Hz, CH_3), 1.82 (4H, m, 2 x CH_2CH_2N), 2.48 (1H, qd, J = 6.6 Hz, 3.0 Hz, CHN), 2.63 (2H, m, 2 x CH_2CH_2N), 2.80 (2H, m, 2 x CH_2CH_2N), 3.61 (1H, br, OH), 5.50 (1H, d, J = 3.0 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 12.03, 27.49, 51.80, 65.28, 72.63, 125.67, 127.96, 141.78.

SR $[\alpha]_D^{25}$ -1.4 (*c* 5.25, EtOH).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06, H, 9.33; N, 6.82. Found C, 75.80 ; H, 9.57; N, 6.72.

(1*R*,2*S*)-2-Piperidyl-1-phenyl-propanol (22-OH)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (4.54 g, 30 mmol), 1,5-dibromopentane (6.90 g, 30 mmol) and potassium carbonate (8.29 g, 60 mmol) in acetonitrile (30 mL) was heated to reflux for 24 h. The reaction mixture was filtered, and the precipitate was washed with acetonittrile. The filtrate and the washing were combined and concentrated *in vacuo* to leave colorless solids (4.70 g), which was recrystalized from benzene (8 mL) to afford colorless needles (2.65 g, 36%, 2nd crop 1.00 g, 14%).

mp 97- 98 °C.

IR (KBr, cm^{-1}) 3130, 1600, 1440, 1350.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6.9 Hz, CH_3), 1.44- 1.62 (6H, m, 3 x CH_2), 2.45- 2.55 (4H, m, 3 x CH_2), 2.69 (1H, qd, J = 6.9 Hz, 4.3Hz, CHN), 4.83 (1H, d, J = 4.3 Hz, CHPh), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 10.91, 24.57, 26.58, 51.75, 64.58, 72.18, 126.00, 126.07, 127.65, 142.26.

MS m/z: 220 [$(M+1)^+$], 219 (M^+).

SR $[\alpha]_D^{25}$ -3.7 (*c* 6.00, EtOH).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66, H, 9.65; N, 6.39. Found C, 76.92 ; H, 9.43; N, 6.41.

(1*R*,2*S*)-2-Morphonyl-1-phenyl-propanol (23-OH)

A mixture of (1*R*,2*S*)-2-amino-1-phenyl-1-propanol (2.27 g, 15 mmol), bis(2-chloroethyl)ether (2.14 g, 15 mmol), lithium bromide (1.30 g, 15 mmol) and potassium carbonate (4.15 g, 30 mmol) in ethanol (30 mL) was heated to reflux for 24 h. The reaction mixture was filtered off. The precipitate was washed with ethanol. The filtrate and the washing were combined and concentrated *in vacuo* to leave a colorless oil (3.53 g), which was purified by column chromatography (Al_2O_3 70 g, hexane- AcOEt 1: 1) to afford a colorless oil (2.35 g). The oil was dissolved in methanol (10 mL), and hydrochloric acid (15% in MeOH, 20 mL) was added. The solvent was evaporated *in vacuo*. The residue was recrystalized with ethanol to afford colorless needles (1.51 g, 39%, 2nd crop 0.35 g, 9%)

mp >200 °C.

IR (KBr, cm^{-1}) 3130, 1600, 1440, 1350.

SR $[\alpha]_D^{25}$ -23.5 (*c* 2.57, EtOH).

The salt (0.61 g) was dissolved in 20% potassium hydroxide (20 mL). The whole was extracted with benzene (3 x 20 mL). The organic layers were combined, and dried over potassium carbonate. The solvent was evaporated *in vacuo*. The residue was distilled (220 °C, 3mmHg) to give a colorless oil

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 6.9 Hz, CH_3), 2.54- 2.70 (5H, m, 2 x CH_2, CHN), 3.52 (1H, br, OH), 3.73 (4H, t, J = 4.6 Hz, CH_2OCH_2), 4.92 (1H, d, J = 3.6 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 9.87, 50 .95, 64.82, 67.42, 71.70, 125.86, 126.94, 128.05, 141.71.

SR $[\alpha]_D^{25}$ -5.4 (*c* 1.43, EtOH)

MS m/z: 222 [$(M+1)^+$], 221 (M^+).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.36, H, 8.85; N, 6.33. Found C, 70.32 ; H, 3.88; N, 6.41.

(1*R*,2*S*)-2-[*N*-Methyl-*N*-(2,2-dimethylpropyl)amino]-1-phenyl-1-propanol (24-OH)

A mixture of (1*R*,2*S*)-2-(2,2-dimethlpropylamino)-1-phenyl-1-propanol (1.54 g, 6.0 mmol), formalin (34%, 1.8 mL, 24 mmol), and formic acid (2.0 mL, 48 mmol) was heated to reflux for 9 h. After cooling, the mixture was basified with 10% aqueous sodium hydroxide (pH 11) and extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with brine (1 x 30 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (1.48 g), which was purified by column chromatography (SiO_2 45 g, CH_2Cl_2- MeOH 20: 1) to afford a colorless oil (1.34 g, 95%).

IR (neat, cm^{-1}) 3400, 2940, 1450.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, s, ^{t}Bu), 0.94 (3H, d, J = 6.9 Hz, CH_3), 2.19 (1H, d, J = 13.8 Hz, CH_2), 2.28 (3H, s, NCH_3), 2.30 (1H, d, J = 13.8 Hz, CH_2), 2.77 (1H, qd, J = 6.9 Hz, 4.9 Hz, CHN), 4.78 (1H, d, J = 4.9 Hz, PhC*H*), 7.31 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 10.04, 28.21, 30.03, 40.94, 66.43, 74.36, 126.20, 126.83, 127.87, 143.04.

SR $[\alpha]_D^{25}$ -4.4 (*c* 1.21, EtOH)

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55, H, 10.71; N, 5.95. Found C, 76.33 ; H, 10.91; N, 5.72.

(*R*)-α-Hydroxyphenylacetamide (43)[34, 35]

98% Sulfric acid (2.20 mL, 40 mmol) was added to a solution of (*R*)-manderic acid (3.04 g, 20 mmol) in acetone (20 mL) at -5 °C within 10 min. The mixture was stirred at room temperature for 10 min. The whole was poured into aqueous sodium carbonate (8.4 g, 80 mmol in 50 mL water), then filtered. The precipitate was dried *in vacuo* and dissolved in methanol (25 mL). 28% Aqueous ammonia (10 mL) was added to the solution, and the mixture was stirred at room temperature for 4 h. The solvent was concentrated *in vacuo* to a small volume and the residue was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo*. The residue was recrystalized from ethanol to give colorless needles (2.00 g, 65%).

mp 117-119 °C.

IR (KBr, cm^{-1}) 3695, 3200, 1645, 1590, 690.

^{1}H-NMR (270 MHz, acetone-d_6) 5.01 (1H, s, CH), 7.31 (5H, m, Ph).

MS m/z: 151 (M^+).

SR $[\alpha]_D^{25}$ -74.6 (*c* 1.70, acetone).

(*R*)-2-Amino-1-phenylethanol (44)[35]

To a suspension of lithium aluminum hydride (0.80 g, 20 mmol) in THF (10 mL), a solution of (*R*)-α-hydroxyphenylacetamide (1.00 g, 6.62 mmol) in THF (5 mL) was added. The mixture was heated to reflux for 5 h. After cooling, water (0.8 mL), 15% aqueous sodium hydroxide (0.8 mL) and water (2.4 mL) was added successively to the reaction mixture. Potassium carbonate was added and filtered. The precipitate was washed with Et_2O. The filtrate and the washing were combined and concentrated *in vacuo*. The residue was recrystalized from Et_2O to give colorless needles (623 mg, 69%).

mp 55-57 °C.

IR (KBr, cm^{-1}) 3300, 1630.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.20 (3H, br, NH_2, OH), 2.81 (1H, dd, J = 12.9 Hz, 7.9 Hz, CH_2), 3.00 (1H, dd, J = 12.9 Hz, 4.0 Hz, CH_2), 4.63 (1H, dd, J = 7.9 Hz, 4.0 Hz, CH), 7.35 (5H, m, Ph).

MS m/z: 137 (M^+).

SR $[\alpha]_D^{25}$ -47.4 (*c* 2.30, EtOH).

(*R*)-2-(2,2-Dimethylpropylamino)-1-phenylethanol (25-OH)

To a solution of (*R*)-2-amino-1-phenylethanol (2.56 g, 18.6 mmol) in methanol (40 mL), trimethylacetaldehyde (1.72 g, 20 0 mmol) was added at room temperature. The whole was stirred for 20 min. Sodium borohydride (1.53 g, 40. 5 mmol) was added at room temperature. The

mixture was stirred for 24 hr at room temperature. The solvent was evaporated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with methylene chloride (4 x 20 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a slightly yellow oil (3.99 g). The oil was purified by column chromathography (SiO_2, 100 g, CH_2Cl_2- MeOH 30: 1- 10: 1) to give colorless needles (3.52 g, 91%).

mp 55-57 °C.

IR (KBr, cm^{-1}) 3300, 1630.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.92 (9H, s, CH_3), 2.34 (1H, d, J = 11.2 Hz, $CH_2{}^tBu$), 2.44 (1H, d, J = 11.2 Hz, $CH_2{}^tBu$), 2.66 (1H, dd, J = 11.9Hz, 9.2 Hz, CH_2CH), 2.86 (1H, dd, J = 11.9Hz, 3.3 Hz, CH_2CH), 4.65 (1H, dd, J = 9.3 Hz, 3.3 Hz, CH), 7.35 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 21.66, 31.54, 57.88, 61.57, 71.12, 125.77, 127.35, 128.28, 142.57.

MS m/z: 208 [$(M+1)^+$], 207 (M^+), 206 [$(M+1)^+$], 189 [$(M-H_2O)^+$].

SR $[\alpha]_D^{25}$ -27.5 (*c* 2.10, EtOH).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.75. Found C, 75.49; H, 10.31; N, 6.66.

(*S*)-2-Amino-1-propanol (45)

To a suspension of lithium aluminum hydride (4.04 g, 0.10 mol) in THF (150 mL), (*S*)-alanine (4.45 g, 50 mmol) was added by small portions. The mixture was heated to reflux for 4 h. After cooling, water (4.1 mL), 15% aqueous sodium hydroxide (4.1 mL), water (12.3 mL) were added successively to the reaction mixture . Potassium carbonate was added and filtered. The precipitate was washed with Et_2O. The filtrate and the washing were combined and concentrated *in vacuo* to leave a colorless oil (3.64 g, 97%).

IR (neat, cm^{-1}) 3500, 3350, 1590, 1455.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.04 (3H, d, J = 6.3 Hz, CH_3), 2.45 (3H, br, NH_2, OH), 3.03 (1H, m, CH), 3.24 (1H, m, CH_2), 3.52 (1H, m, CH_2).

MS m/z: 44 [$(CH_3CHNH_2)^+$].

SR $[\alpha]_D^{25}$ +18 (neat).

(*S*)-2-(2,2-Dimethylpropylamino)-1-propanol (26-OH)

Trimethylacetaldehyde (1.30 mL, 1.03 g, 12 mmol) was added to a suspension of (*S*)-2-aminopropanol (751 mg, 10 mmol) in benzene (20 mL) at 0 °C. The whole was stirred at room temperature for 1 h. Sodium sulfate was added and the reaction mixture was filtered. The precipitate was washed with benzene. The filtrate and the washing were combined and

concentrated *in vacuo* to leave a yellow oil (1.17 g). The oil was dissolved in ethanol (20 mL), and sodium borohydride (757 mg, 20 mL) was added to the solution at 0 °C. The whole was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 10% aqueous potassium hydroxide (10 mL), and the whole was extracted with benzene (4 x 15 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over potasssium carbonate adn concentrated *in vacuo* to afford **26-OH** as a colorless oil (930 mg, 64%).

IR (neat, cm^{-1}) 3300.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.91 (9H, s, ^{t}Bu), 1.05 (3H, d, J = 6.3 Hz, CH_3CH), 1.90 (2H, br, NH, OH), 2.10 (1H, d, J = 11.2 Hz, $CH_2{}^tBu$), 2.52 (1H, d, J = 11.2 Hz, $CH_2{}^tBu$), 2.72 (1H, ddq, J = 6.9 Hz, 6.9 Hz, 4.9 Hz, CH), 3.19 (1H, dd, J = 10.6 Hz, 6.9 Hz, CH_2), 3.57 (1H, dd, J = 10.6 Hz, 4.3 Hz, CH_2).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 17.50, 27.64, 31.43, 54.92, 59.09, 65.12.

SR $[\alpha]_D^{25}$ +36.1 (*c* 1.62, MeOH).

The oil (650 mg, 4.4 mmol) was dissolved in acetone (10 mL), and a solution of oxalic acid (720 mg, 8.8 mmol) in acetone (20 mL) was added. The whole was filtered and the precipitate was washed with acetone and recrystalized from ethanol (10 mL) to afford colorless needles (510 mg, 64%).

mp 180-190 °C (dec).

IR (KBr, cm-1) 3300, 2960, 1595.

SR $[\alpha]_D^{25}$ +13.2 (*c* 1.01, MeOH).

Anal. Calcd for $C_{18}H_{40}N_2O_6$: C, 56.82; H, 10.49; N, 7.36. Found C, 56.78; H, 10.49; N, 7.28.

(*S*)-2-Amino-3-methyl-1-butanol (46)

To a suspension of lithium aluminum hydride (4.04 g, 0.10 mol) in THF (150 mL), (*S*)-valine (5.86 g, 50 mmol) was added by small portions. The mixture was heated to reflux for 2 h. After cooling, water (4.1 mL), 15% aqueous sodium hydroxide (4.1 mL), water (12.3 mL) was added successively to the reaction mixture. Potassium carbonate was added and filtered. The precipitate was washed with Et_2O. The filtrate and the washing were combined and concentrated *in vacuo* to give a yellow oil (6.54 g), which was distilled (83- 85 °C/ 10 mmHg) to give a colorless oil (4.35 g, 85%).

IR (neat, cm^{-1}) 3350, 3280, 1585.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.95 (6H, d, J = 6.0 Hz, CH_3), 1.50 (1H, m, $CHMe_2$), 2.25 (3H, br, NH_2, OH), 2.60 (1H, m, CHN), 3.37 (1H, dd, J = 9.0 Hz, 9.0 Hz, CH_2), 3.62 (1H, dd, J = 9.0 Hz, 4.0 Hz, CH_2).

MS m/z: 104 [(M+1)$^+$].

SR $[\alpha]_D^{25}$ +16.9 (*c* 9.85, EtOH).

(*S*)-2-(2,2-Dimethylpropylamino)-3-methyl-1-butanol (27-OH)

Trimethylacetaldehyde (1.73 g, 22 mmol) was added to the solution of (*S*)-2-amino-3-methylbutanol (2.06 g, 20 mmol) in benzene (20 mL). The whole was stirred for 1 h, and sodium sulfate was added. The whole was filtered off, and the filtrate was concentrated *in vacuo* to leave a yellow oil (3.01 g). The oil was dissolved in ethanol (30 mL), and sodium borohydride (1.51 g) was added at 0 °C. The whole was stirred for 10 h at room temperature. The solvent was evaporated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with hexane (3 x 30 mL). The organic layers were combined, washed successively with water (1 x 10 mL) and brine (1 x 10 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (2.97 g). The oil was purified by column chromatography (SiO_2 50 g, hexane- AcOEt 10: 1) to afford a colorless oil (2.66 g, 76%).

IR (neat, cm^{-1}) 3270, 1465.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.9 Hz, CH_3 (isopropyl)), 0.92 (9H, s, ^{t}Bu), 0.96 (3H, d, *J* = 6.9 Hz, CH_3 (isopropyl)), 1.79 (1H, dq, *J* = 6.9 Hz, 6.9 Hz, C*H*Me$_2$), 2.22 (1H, d, *J* = 11.2 Hz, ^{t}BuC*H*$_2$), 2.31- 2.38 (1H, m, CHN), 2.48 (1H, d, *J* = 11.2 Hz, ^{t}BuC*H*$_2$), 3.27 (1H, dd, *J* = 10.2 Hz, 7.9 Hz, C*H*$_2$OH), 3.40 (1H, br, NH or OH), 3.58 (1H, dd, *J* = 10.2 Hz, 4.6 Hz, C*H*$_2$OH).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) 18.37, 19.61, 27.59, 28.92, 31.52, 59.03, 60.25, 64.69.

MS m/z: 172 [(M-1)$^+$], 158 [(M-CH_3)$^+$], 142 [(M-CH_2OH)$^+$], 130 [(M-CH_3CHCH_3)$^+$], 116 [(M-^{t}Bu)$^+$].

SR $[\alpha]_D^{25}$ +17.3 (*c* 1.81, EtOH).

The oil (2.05 g) was dissolved in acetone (20 mL), and a solution of oxalic acid (1.09 g, 12.3 mmol) in acetone (10 mL) was added. The precipitate was washed with acetone, dried *in vacuo* and recrystalized from methanol (30 mL) to afford colorless needles (g, %).

mp 192 °C (dec.).

IR (nujol, cm^{-1}) 3350, 3175, 1610.

SR $[\alpha]_D^{25}$ +9.3 (*c* 1.89, MeOH).

(*S*)-2-Amino-3-phenyl-1-propanol (47)

To a suspension of sodium borohydride (11.3 g, 0.30 mol) in THF (400 mL), (*S*)-phenylalanine (16.5 g, 0.10 mol) and trifluoroborane etherate (49.0 mL, 0.40 mmol) were added

in this order. The mixture was stirred for 2 h at room temperature. Water (50 mL) and hydrochloric acid (36%, 50 ml) were added successively to the reaction mixture at 0 °C. The resultant mixture was refluxed for 1 h. The solvent was concentrated *in vacuo* to small volume. The residure was basified with sodium hydroxide pellete (pH 11) and filtered with Celite pad. The filtlate was extracted with methylene chloride (3 x 100 mL). The organic layers were combined, washed with water (1 x 50 mL) and brine (1 x 50 ml), dried over potassium carbonate and concentrated *in vacuo* to leave colorless solid (11.96 g), which was recrystalized from benzene (15 mL) and hexane (20 mL) to give colorless prisms (11.59 g, 77%).

mp 82- 83 °C.

IR (nujol, cm^{-1}) 3340, 3280, 3000, 1565, 1055.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.78 (3H, br, NH_2, OH), 2.52 (1H, dd, *J* = 13.0 Hz, 8.6 Hz, PhC*H*$_2$), 2.80 (1H, dd, *J* = 13.0 Hz, 5.0 Hz, PhC*H*$_2$), 3.12 (1H, dddd, *J* = 8.6 Hz, 7.3 Hz, 5.0 Hz, 3.6 Hz, CH), 3.38 (1H, dd, *J* = 10.6 Hz, 7.3 Hz, C*H*$_2$OH), 3.63 (1H, dd, *J* = 10.6 Hz, 3.6 Hz, C*H*$_2$OH), 7.33 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 40.99, 54.16, 66.40, 126.40, 126.57, 129.18, 138.69.

MS m/z: 152 [(M+1)$^+$].

SR $[\alpha]_D^{25}$ -22.6 (*c* 1.20, 1 N HCl).

(*S*)-2-(2,2-Dimethylpropylamino)-3-phenyl-1-propanol (28-OH)

Trimethylacetaldehyde (1.19 mL, 11 mmol) was added to a solution of (*S*)-2-amino-3-phenylpropanol (1.51 g, 10 mmol) in benzene (20 mL), and the mixture was stirred for 1 h at room temperature. Anhydrous sodium sulfate (10 g) was added, and the mixture was stirred for 30 min, then filtered. The filtrate was concentrated *in vacuo* to leave a colorless oil. The oil was dissolved in ethanol (30 mL) and sodium borohydride (1.13 g, 30 mmol) was added. The mixture was stirred for 11 h at room temperature. The solvent was evaporated *in vacuo*, and 10% aqueous potassium hydroxide (20 mL) was added to the residue. The whole was extracted with benzene (3 x 50 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil (2.30 g). To the solution of the oil in ethanol (50 mL), 15% hydrochloric acid in ethanol (1.5 mL) was added. The solvent was evaporated *in vacuo*. The residue was recrystalized from ethanol (10 mL) and hexane (15 mL) to give colorless needles (1.39 g, 54%, 2 steps).

mp 187-189 °C.

IR (nujol, cm^{-1}) 3300, 1595, 1580.

SR $[\alpha]_D^{25}$ -4.5 (*c* 2.23, EtOH).

Anal. Calcd for $C_{14}H_{24}ClNO$: C, 65.23; H, 9.38; N, 5.43. Found C, 65.51; H, 9.27; N, 5.26.

The salt (1.45 g) was dissolved in 15% aqueous sodium hydroxide (10 mL), and extracted with hexane (3 x 20 mL). The organic layers were combined, washed with water (1 x 10 mL) and brine (1 x 10 mL), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (1.00 g, 80%), which was distilled (150 °C/ 0.4 mmHg) to give a colorless oil.

IR (nujol, cm^{-1}) 3250, 3050, 3010.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.86 (9H, s, ^{t}Bu), 2.26 (1H, d, J = 11.1 Hz, ^{t}BuCH_2), 2.39 (1H, d, J = 11.1 Hz, ^{t}BuCH_2), 2.67-2.89 (3H, m, PhCH_2CH), 3.27 (1H, dd, J = 10.5 Hz, 5.7 Hz, CH_2OH), 3.59 (1H, dd, J = 10.5 Hz, 4.1 Hz, CH_2OH), 7.33 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 27.57, 31.45, 38.22, 59.16, 60.60, 62.28, 126.36, 128.50, 129.13, 138.53.

MS m/z: 222 [$(M+1)^+$], 220 [$(M-1)^+$], 206 [$(M-CH_3)^+$], .

SR $[\alpha]_D^{25}$ -6.8 (*c* 2.32, EtOH).

(*S*)-1-Hydroxy-2-phenyl-*N*-(2,2-dimetylpropyl)propionamide (48)

2,2-Dimethyl-1-propylamine (4.96 mg, 5.7 mmol), diethyl cyanophosphonate (929 mg, 5.70 mmol) were added to a solution of (*S*)-1-hydroxy-2-phenylpropionic acid (860 mg, 5.20 mmol) in *N*,*N*-dimethlyformamide (10 mL) at 0 °C. Triethylamine (0.79 mL, 576 mg, 5.70 mmol) was added within 5 min. The whole was stirred at room temperature for 15 h. The solvent was evaporated *in vacuo*. Water (20 mL) was added to the residue, and extracted with ethyl acetate (1 x 50 mL, 2 x 20 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL), 10% aqueous hydrochloric acid (1 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate and concentrated *in vacuo* to leave slightly yellow solids (1.16 g), which was recrystalized from hexane to afford colorless leafletts (830 mg, 68%).

mp 76- 78 °C.

IR (nujol, cm^{-1}) 3350, 3260, 1630, 1535.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (9H, s, ^{t}Bu), 2.44- 2.51 (1H, m, OH excahngable with D_2O), 2.90 (1H, dd, J = 14.2 Hz, 8.6 Hz, PhCH_2), 3.03 (1H, dd, J = 13.2 Hz, 6.3 Hz, ^{t}BuCH_2), 3.10 (1H, dd, J = 13.2 Hz, 6.3 Hz, ^{t}BuCH_2), 3.26 (1H, dd, J = 14.2 Hz, 4.3 Hz, PhCH_2), 4.33 (1H, ddd, J = 8.6 Hz, 4.3 Hz, 4.3 Hz, CH), 6.52 (1H, br, NH), 7.24- 7.37 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 21.12, 31.72, 41.06, 50.21, 72.99, 127.06, 128.82, 129.49, 136.87.

MS m/z: 236 [$(M+1)^+$], 220 [$(M-CH_3)^+$], 217 [$(M-H_2O)^+$].

SR $[\alpha]_D^{25}$ -75.6 (*c* 1.53, $CHCl_3$).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found C, 71.60; H, 9.05; N, 5.71.

(*S*)-1-(2,2-Dimethylpropylamino)-3-phenyl-2-propanol (29-OH)

To a suspension of (*S*)-1-hydroxy-2-phenyl-*N*-(2,2-dimethylpropyl)propionamide (766 mg, 3.26 mmol) and sodium borohydride (1.23 g, 32.6 mol) in THF (30 mL), trifluoroborane etherate (4.67 mL, 38.0 mmol) was added at 0 °C. The mixture was heated to reflux for 2 h. Water (10 mL) and 10% aqueous hydrochloric acid (20 mL) were added successively to the reaction mixture at 0 °C. The resultant mixture was refluxed for 1 h. The solvent was concentrated *in vacuo*to a small volume. The residue was basified with sodium hydroxide (pH 11) and extracted with Et_2O (4 x 20 mL). The organic layers were combined, washed with water (1 x 50 mL) and brine (1 x 50 ml), dried over potassium carbonate and concentrated *in vacuo* to leave a colorless oil (0.78 g), which was purified by column chromatography (SiO_2 10 g, $CHCl_3$- MeOH 20: 1- 10:1) to give a colorless oil (727 mg, quant).

IR (neat, cm^{-1}) 3340, 3280, 3000, 1565, 1055.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.89 (9H, s, CH_3), 2.28 (1H, d, J = 11.3 Hz, ^{t}BuCH_2), 2.37 (1H, d, J = 11.3 Hz, ^{t}BuCH_2), 2.49 (1H, dd, J = 11.9 Hz, 9.2 Hz, CH_2), 2.67- 2.75 (2H, m, CH_2), 2.81 (1H, dd, J = 13.5 Hz, 7.3 Hz, CH_2), 3.79 (1H, m, CH), 7.24- 7.37 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 24.67, 31.48, 41.51, 55.22, 61.85, 69.94, 126.25, 128.36, 129.33, 138.47.

HRMS Calcd for $C_{14}H_{23}NO$: m/z: 221.1780. Found: 221.1812.

SR $[\alpha]_D^{25}$ +12.2 (*c* 2.22, EtOH).

(1*R*,2*R*)-2-(2,2-Dimethylpropylamino)-1-phenyl-1-propanol (30-OH)

To a solution of (1*R*,2*R*)-2-amino-1-phenyl-1-propanol (0.92 g, 6.1 mmol) in benzene (20 mL), a solution of trimethylacetaldehyde (0.60 g, 6.9 mmol) in benzene (10 mL) was added. The mixture was stirred for 30 min. Sodium sulfate (10 g) was added to the reaction mixture and filtered. The solvent was evaporated *in vacuo* to give colorless oil (1.48 g). The oil was dissolved in ethanol (20 mL), and sodium borohydride (0.46 g, 12 mmol) was added to the solution. The mixture was stirred for 3 h at room temperature. The solvent was evaporated *in vacuo*, and 10% aqueous potassium hydroxide (20 mL) was added to the residue. The whole was extracted with benzene (3 x 50 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to give colorless solid (1.34 g), which was recrystalized from hexane (2.5 mL) to give colorless needles (1.29 g, 96%).

mp 49- 51 °C.

IR (KBr, cm^{-1}) 3180, 1600, 1450, 700.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.94 (3H, d J = 6.3 Hz, CH_3), 0.94 (9H, s, ^{t}Bu), 2.16 (1H, d, J = 11.2 Hz, ^{t}BuCH_2), 2.58 (1H, m, CH_3CH), 2.60 (1H, d, J = 11.2 Hz, ^{t}BuCH_2), 4.12 (1H, d, J = 8.6 Hz, PhCH), 7.26- 7.37 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.53, 27.66, 31.57, 59.30, 61.15, 77.90, 127.10, 127.58, 128.19, 142.17.

MS m/z: 222 [$(M+1)^+$], 203 [$(M-H_2O)^+$].

SR $[\alpha]_D^{25}$ +2.7 (*c* 2.84, EtOH).

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found C, 75.95; H, 10.18; N, 6.24.

(1*R*,2*S*)-2-(2,2-Dimethylpropylamino)-1,2-diphenylethanol (31-OH)

To a solution of (1*R*,2*S*)-2-amino-1,2-diphenylethanol (3.20 g, 15 mmol) in benzene (20 mL) and methylene chloride (20mL), a solution of trimethylacetaldehyde (1.49 g, 17.5 mmol) in benzene (10 mL) was added. The mixture was stirred for 20 min. Sodium sulfate (10 g) was added to the reaction mixture and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol (40 mL), and sodium borohydride (1.13 g, 30 mmol) was added to the solution. The mixture was stirred for 11 h at room temperature and concentrated *in vacuo*, and 10% aqueous potassium hydroxide (20 mL) was added to the residue. The whole was extracted with benzene (3 x 50 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over potassium carbonate and concentrated *in vacuo* to leave colorless solid (4.39 g), which was recrystalized from hexane (50 mL) to afford colorless needles (4.09 g, 96%).

mp 96-97 °C.

IR (KBr, cm^{-1}) 3180, 1600, 1450, 700.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.90 (9H, s, CH_3), 2.19 (1H, d, *J* = 11.5 Hz, one of CH_2), 2.31 (1H, d, *J* = 11.5 Hz, one of CH_2), 3.86 (1H, d, *J* = 5.3 Hz, CHN), 4.81 (1H, d, *J* = 5.3 Hz, PhCH), 7.06-7.26 (10H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 27.62, 31.52, 59.62, 69.31, 76.12, 126.65, 127.37, 127.78, 127.98, 128.01, 139.64, 140.40.

MS m/z: 284 [$(M+1)^+$], 268 [$(M-H_2O+1)^+$], 266 [$(M-H_2O-1)^+$].

SR $[\alpha]_D^{25}$ +2.7 (*c* 2.84, EtOH).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found C, 80.36; H, 9.18; N, 5.09.

α-Tetralone-β-oxime (49)[36]

Title compoundwas synthesized from α-tetralone (65.8 g, 0.45 mol), butyl nitrite (59.7 g, 0.58 mol), and potassium *tert*-butoxide (50 g, 0.45 mol) following the literature (slightly brown solid (46.0 g, 58%)).

mp 138- 140 °C.

IR (nujol, cm^{-1}) 3170, 1695, 1610.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.98 (4H, m, CH_2CH_2), 7.30 (1H, d, *J* = 7.6 Hz, C[5]-H), 7.38 (1H, m, C[6]-H), 7.55 (1H, m, C[7]-H), 8.13 (1H, d, *J* = 6.6 Hz, C[8]-H).

MS m/z: 177 (M^+), 176 [$(M-1)^+$].

(±)-β-Acetamido-α-tetralone (50)[36]

Title compoundwas synthesized from α-tetralone-β-oxime (77.45 g, 0.44 mol), activated zinc dust (202 g, 3.09 mol), acetic anhydride (1.3 L, 11.5 mol) in acetid acid (750 mL) following the literature (slightly yellow needles (41.85 g, 47%)).

mp 122- 124 °C.

IR (nujol, cm^{-1}) 3270, 1690, 1640.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.89 (1H, dddd, *J* = 13.2 Hz, 13.2 Hz, 13.2 Hz, 4.6 Hz, C[3]-H), 2.10 (1H, m, C[3]-H), 2.81 (1H, m, C[4]-H), 3.00 (1H, ddd, *J* = 17.5 Hz, 13.2 Hz, 4.6 Hz, C[4]-H), 3.28 (1H, ddd, *J* = 13.2 Hz, 13.2 Hz, 4.6 Hz, C[2]-H), 6.65 (1H, br, NH), 7.27 (1H, d, *J* = 7.6 Hz, C[6]-H), 8.01 (1H, d, *J* = 7.6 Hz, C[8]-H).

MS m/z: 204 [$(M+1)^+$], 203 (M^+).

(1*R*,2*R*)-2-Acetamido-1,2,3,4-tetrahydronaphthalenol (51)[36]

Title compound was synthesized from (±)–β-acetamido-α-tetralone (40 g, 0.20 mol) and sodium borohydride (12 g, 317 mmol) in ethanol (500 mL) following the literature (colorless needles (24.00 g, 58%)).

mp 176- 179 °C (dec).

IR (nujol, cm^{-1}) 3280, 1640.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.79 (1H, dddd, *J* = 12.9 Hz, 10.3 Hz, 10.3 Hz, 5.3 Hz, C[3]-H), 2.04 (3H, s, CH_3), 2.12- 2.20 (1H, m, C[3]-H), 2.83 (1H, ddd, *J* = 16.8 Hz, 5.3 Hz, 5.3 Hz, C[4]-H), 4.08 (1H, dddd, *J* = 10.3 Hz, 7.6 Hz, 7.6 Hz, 3.6 Hz, C[2]-H), 4.59 (1H, d, J = 7.6 Hz, C[1]-H), 7.21- 7.56 (4H, m, Ph).

(1S,2S)-1-[(-)-Mentyloxycarbonyloxy]-1,2,3,4-tetrahydro-naphthalene-2-acetamide (52)

(-)-Mentyl chloroformate (32.17 mL, 150 mmol) was added to a solution of (±)-(1*R*,2*R*)-2-acetamido-1,2,3,4-tetrahydronaphthalenol (20.53 g, 100 mmol) in pyridine (300 mL) under ice-water bath. The whole was stirred at room temperature for 1 h, then quenched with methanol (50 mL). Saturated aqueous sodium bicarbonate (100 mL) was added, and the whole was extracted with chloroform (1 x 300 mL, 2 x 100 mL). The organic layers were combined, washed with 10% aqueous hydrochloric acid (4 x 300 mL) and brine (1 x 100 mL), dried over sodium sulfate and

concentrated *in vacuo* to leave slightly brown solid (62.76g), which was recrystalized from ethyl acetate (600 mL) to afford cololress needles (16.61 g, 43%).

mp 172- 175 °C.

IR (KBr, cm^{-1}) 3240, 1728, 1550, 1250.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 7.3 Hz), 0.91 (3H, d, *J* = 6.9 Hz), 0.94 (3H, d, *J* = 6.9 Hz), 0.9-1.2 (2H, m), 1.04-2.10 (11H, m), 2.20 (1H, m), 2.83 (1H, ddd, *J* = 17.5 Hz, 5.6 Hz, 5.6Hz), 3.10 (1H, ddd, *J* = 17.5 Hz, 8.9 Hz, 5.6 Hz), 4.38 (1H, dddd, *J* = 9.6 Hz, 7.9 Hz, 7.9 Hz, 5.3 Hz), 4.58 (1H, ddd, *J* = 9.6 Hz, 10.9 Hz, 10.9 Hz, 4.3 Hz), 5.77(1H, d, *J* = 7.6 Hz), 5.80 (1H, br), 7.13- 7.28 (4H, m).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.35, 20.65, 21.98, 23.40, 23.47, 26.20, 26.27, 26.62, 31.42, 34.02, 40.63, 40.87, 50.21, 75.87, 79.08, 126.43, 128.41, 128.80, 132.49, 136.50, 155.88, 169.68.

SR $[\alpha]_D^{25}$ -46.9 (*c* 0.59, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found C, 71.35; H, 8.73; N, 3.45.

(1*S*,2*S*)-2-Acetamido-1,2,3,4-tetrahydro-1-naphtalenol (53)

Potassium *tert*-butoxide (0.40g, 4.0 mmol) was added to a suspension of (1S,2S)-1-[(-)-mentyloxycarbonyloxy]-1,2,3,4-tetrahydronaphthalene-2-acetamide (790 mg, 2.0 mmol). The whole was stirred at room temperature for 24 h. Water (10 mL) was added, and the whole was extracted with chloroform (1 x 50 mL, 2 x 20 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave colorless solid (0.73 g), which was suspended in Et_2O (20 mL), then filtered. The precipitate was dried *in vacuo* to afford colorless solid (330 mg, 79%).

mp 181- 185 °C.

IR (nujol, cm-1) 3280, 1640.

^{1}H-NMR is identical with that of (±)- form except: d 3.63 (1H, d, *J* = 5.4 Hz), 4.61 (1H, dd, *J* = 7.6 Hz, 5.4 Hz).

SR $[\alpha]_D^{25}$ +147.6 (*c* 0.50, $CHCl_3$).

HPLC (Opti-pak XC, hexane- isopropanol 20: 1, 10 mL/ min, 254 nm) Only single peak at 22.26 min was observed (another peak should be obsereved at 17 min.).

(1*R*,2*S*)-2-Amino-1,2,3,4-tetrahydro-1-naphthalenol (54)[37]

A solution of (1*S*,2*S*)-2-acetamido-1,2,3,4-tetrahydro-1-naphtalenol (2.00 g, 14.9 mmol) in 0.3 N hydrochloric acid (80 mL) was heated to reflux for 5 h. After cooling, the whole was washed with ethyl acetate (1 x 50 mL), basified with potassium hydroxide (pH 11), and further

extracted with benzene (1 x 100 mL, 2 x 50 mL). The organic layers were combined, dried over potassium carbonate and concentrated *in vacuo* to leave colorless needles (0.86 g), which was recrystalized from etyl acetate (10 mL) and petloeum ether (3 mL) to afford slightly purple needles (495 mg, 20%).

mp 121- 123 °C.

IR (KBr, cm^{-1}) 335, 3280, 3120, 1585.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.77- 2.04 (5H, m, C[3]-H, OH, NH_2), 2.81 (1H, ddd, *J* = 17.2Hz, 9.9 Hz, 6.2 Hz, C[4]-H), 2.90 (1H, ddd, *J* = 17.2Hz, 10.6 Hz, 5.9 Hz, C[4]-H), 3.18 (1H, ddd, *J* = 10.2Hz, 3.6 Hz, 3.6 Hz, C[2]-H), 4.55 (1H, d, *J* = 3.6 Hz, C[1]-H), 7.12- 7.45 (4H, m).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 26.53, 27.51, 50.62, 69.78, 126.22, 127.84, 128.63, 130.19, 135.92, 137.13.

SR $[\alpha]_D^{25}$ -99.6 (*c* 2.28, EtOH).

MS m/z: 163 (M^+), 145 [$(M-H_2O)^+$].

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.07; N, 8.58. Found C, 73.41; H, 8.07; N, 8.58.

(1*S*,2*R*)-2-Methoxy-1-methyl-2-phenylethylamine hydrochloride (54)

To a suspension of sodium hydride (60%, 3.03 g 75.7 mmol, washed with hexane) in THF (80 mL), (1*R*, 2*S*)-2-amino-1-phenyl-1-propanol (9.54 g, 63.1 mmol) in THF (25 mL) was added at 0 °C within 5 min. The mixture was stirred for 1 h at room temperature. Iodomethane (4.1 mL, 66.3 mmol) was added, and the mixture was refluxed for 3 h, and quenched with saturated aqueous ammonium chloride (100 mL). The organic layer was separated, and the aqoueous layer was extracted with Et_2O (3 x 50 mL). The organic layers were combined, dried over potassium carbonate and concentrated *in vacuo* to leave a yellow oil (10.74 g), which was purified with column chromatography (SiO_2 200 g, $CHCl_3$- MeOH 10: 1) to give a colorless oil (6.91 g).

To the solution of amine in methanol (20 mL), hydrochloric acid (20% MeOH solution, 20 mL) was added, and the solvent was evaporated *in vacuo*. The residure was recrystalized from ethanol (20 mL) and Et_2O (20 mL) to give colorless needles (3.81 g, 30%).

mp >200 °C.

IR (KBr, cm^{-1}) 3400, 1590, 1500, 1090.

^{1}H-NMR (270 MHz, D_2O as 4.80 ppm) δ 1.19 (3H, d, *J* = 6.9 Hz, CH_3), 3.37 (3H, s, OMe), 3.68 (1H, qd, *J* = 6.9 Hz, 3.6 Hz, CH_3CH), 7.39-7.53 (5H, m, Ar).

13C-NMR (67.8 MHz, D_2O, CH_3CN as -1.96 ppm) δ 9.56, 48.66, 54.14, 79.66, 124.31, 126.07, 126.12, 132.68.

SR $[\alpha]_D^{25}$ -97.1 (*c* 1.61, MeOH).

Anal. Calcd for $C_{10}H_{16}NO$: C, 59.55; H, 8.00; N, 6.94. Found C, 59.29; H, 7.82; N, 6.87.

(1*S*,2*R*)-*N*-(2-Methoxy-1-methyl-2-phenylethyl)-2,2-dimethylpropyl-amine hydrochloride (34-NH)

To a suspension of (1S,2R)-2-methoxy-1-methyl-2-phenylethylamine hydro-chloride (2.02 g, 10 mmol) and triethylamine (1.60 mL, 11 mmol) in methylene chloride (30 mL), trimethylacetaldehyde (1.21 mL, 0.95 g, 11 mmol) was added at 0 °C. The whole was stirred for 40 min, and magnesium sulfate was added. The mixture was filtered, and the precipitate was washed with methylene chloride. The filtrate and the washings were combined and concentrated *in vacuo*, and the residue was suspended in Et_2O (20 mL) and filtered off. The filtrate was concentrated *in vacuo* to leave imine as a colorless oil (1.82 g). To the soluion of imine in ethanol (10 mL), sodium borohydride (0.83 g, 11 mmol) was addeed at 0 °C, and the whole was stirred for 12 h at room temperature. The solvent was evaporated *in vacuo*, and the residue was dissolved in water (20mL). The whole was extracted with Et_2O (5 x 20 mL). The organic layers were combined, dried over potassium carbonate, and concentrated *in vacuo* to leave a colorless oil (1.76 g), which was purified by column chromatography (SiO_2 60 g, hexane- isopropylamine 20: 1) to give a colorless oil (1.59 g, 68%).

IR (neat, cm^{-1}) 3300, 1470, 695.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.80 (9H, s, CH_3), 1.03 (3H, d, J = 6.6 Hz, C*H*$_3$CH), 2.20 (1H, d, J = 11.2 Hz, CH_2), 2.37 (1H, d, J = 11.2 Hz, CH_2), 2.71 (1H, qd, J = 6.6 Hz, 5.3 Hz, CH_3C*H*), 3.25 (3H, s, OMe), 4.11 (1H, d, J = 5.3 Hz, C*H*Ph), 7,24-7.37 (5H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.84, 27.61, 31.40, 57.23, 59.48, 59.78, 86.55, 127.28, 127.40, 128.15, 140.20.

SR $[\alpha]_D^{25}$ -40.5 (*c* 2.45, EtOH).

MS m/z: 236 [(M+1)$^+$], 220 [(M-CH_3)$^+$], 204 [(M-OMe)$^+$], 178 [(M-^{t}Bu)$^+$].

Synthesis of ketone

Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate[38]

Title compoundwas synthesized from glyoxal (40% solution in water, 11.8 g, 81 mmol) and dimethyl 1, 3-acetonedicalboxylate (25 g, 0.14 mol) following the literature (a brown oil (25.1 g, 84%)).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.64 (2H, t, J = 2.6 Hz, CH), 3.78 (6H, s, CH_3), 3.88 (2H, t, J = 2.6 Hz, CH).

***cis*-Bicyclo[3.3.0]octane-3,7-dione**[38]

Title compound was synthesized from tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (25.1 g, 68 mmol) following the literature (colorless needles (2.66 g, 28%, 2nd crop 1.32 g, total 42%).

mp 72-73 °C

IR (KBr, cm^{-1}) 1730, 1395, 1175, 1140.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.15 (4H, dd, J = 19.1 Hz, 5.0 Hz, concave H), 2.58 (4H, dd, J = 19.1 Hz, 8.6 Hz, convex H), 3.04 (2H, m, CH).

7,7-Ethylenedioxy-*cis*-bicyclo[3.3.0]octane-3-one

To a solution of *cis*-bicyclo[3.3.0]octane-3,7-dione (3.87 g, 28 mmol) in benzene (20 mL), ethylene glycol (4.9 g, 78.5 mmol) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) was added. The whole was heated for reflux for 4 h with Dean-Stark apparatus. The resultant mixture was diluted with benzene (20 mL), and washed successively with saturated aqueous sodium bicarbonate (2 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave diacetal as colorless needles (6.25 g). This compound was dissolved in acetone- H_2O (3:1, 60 mL) and *p*-toluenesulfonic acid monohydrate (99 mg, 0.55 mmol) added to the solution. The whole was stirred for 1.5 h at room temperature. The resultant mixture was diluted with benzene (50 mL), and washed successively with saturated aqueous sodium bicarbonate (2 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a colorless oil (7.61 g). The oil was purified by column chromatography (SiO_2, 250g, hexane- AcOEt 3: 1- 1: 1) to give a colorless oil (1.49 g, 30%).

IR (neat, cm^{-1}) 1730, 1105, 1020.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.73 (2H, dd, J = 13.8 Hz, 5.6 Hz, acetal α-position (concave)), 2.18 (2H, dd, J = 13.8 Hz, 5.6 Hz, α-position (convex)), 2.21 (2H, dd, J = 18.5 Hz, 4.9 Hz, ketone α-position (concave)), 2.18 (2H, dd, J = 18.5 Hz, 4.9 Hz, ketone α-position (convex)), 2.85 (2H, br, CH), 3.90 (4H, s, CH_2CH_2).

Syntheses of phosphonates

Cyanomethylphosphonic acid diethly ester (2b)

A mixture of triethyl phoshite (6.17 g, 51.4 mmol) and bromoacetonitrile (8.55 g, 51.4 mmol) was heated to reflux for 23 h. The resultant oil was distilled (bp_8 136-138 °C) to give a colorless oil (8.19 g, 90%).

IR (neat, cm^{-1}) 2245, 1550, 1260, 1020, 970.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.40 (6H, t, J = 6.9 Hz, CH_3), 2.89 (2H, d, J = 20.5 Hz, CH_2CN), 4.25 (4H, dq, J = 6.3 Hz, 6.3 Hz, CH_2O).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.22 (d, J = 6.1 Hz, CH_3), 16.42 (d, J = 143 Hz, CH_2CN), 63.84 (d, J = 6.1 Hz, CH_2O), 112.57 (d, J = 11 Hz, CN).

MS m/z: 178 [$(M+1)^+$], 150 [$(M-HCN)^+$].

Cyanomethylphosphonic acid dimethyl ester (2c)

A mixture of trimethyl phoshite (6.20 g, 50 mmol) and bromoacetonitrile (7.20 g, 60mmol) was stirred for 3 h at 100 °C. The resultant mixture was distilled (bp_{10} 140-142 °C) to give a colorless oil (4.32 g, 58%). (By-product: methylphosphonic acid dimethyl ester, bp_{10} 65 °C, 4.60 g)

IR (neat, cm^{-1}) 2245, 1640, 1260, 1190, 1040.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.89 (2H, d, J = 11.1 Hz, CH_2), 3.89 (6H, d, J = 11.1 Hz,CH_3).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 15.35 (d, J = 134 Hz, CH_2), 54.00 (d, J = 7.3 Hz, CH_3), 112.28 (d, J = 11.0 Hz, CN).

MS m/z: 150 [$(M+1)^+$], 149 (M^+), 124 [$(M-CN+1)^+$].

Cyanomethylphosphonic acid bis(1-methylethyl) ester (2d)

A mixture of tris(1-methylethyl) phoshite (9.21 g, 44 mmol) and bromoacetonitrile (5.31 g, 45mmol) was stirred for 11 h at 120 °C. The resultant mixture was distilled (bp_4 129-130 °C) to give a colorless oil (6.00 g, 60%).

IR (neat, cm^{-1}) 2250, 1260, 995.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.40 (12H, dd, J = 6.3Hz, 2.7Hz, CH_3), 2.82 (2H, d, J = 10.8 Hz, CH_2), 4.83 (2H, ddq, J = 6.3 Hz, 6.3 Hz, 6.3 Hz, CH).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 17.50 (d, J = 144 Hz, CH_2), 23.81 (d, J = 4.9Hz, CH_2), 23.88 (d, J = 4.9 Hz, CH_3), 73.02 (d, J = 8.1Hz, CH).

MS m/z: 206 [$(M+1)^+$], 205 (M^+), 204 [$(M-1)^+$].

Anal. Calcd for $C_8H_{16}NO_3P$: C, 46.83; H, 7.86; N, 6.83. Found: C, 46.64; H, 7.61; N, 6.60.

Cyanomethylphosphonic acid diphenyl ester (2e)

A mixture of triphenyl phosphite (15.5 g, 50 mmol), bromoacetonitrile (3.83 mL, 55 mmol), ethanol (4.10 mL, 70 mmol), and *p*-toluenesulfonic acid monohydrate (0.10 g, 0.50 mmol) was stirred for 16 h at 150 °C. The resultant oil was purified by column chromatography (SiO_2 200 g, $CHCl_3$ only ~ $CHCl_3$- MeOH 30: 1) to give a brown oil (12.0 g). The oil was triturated with benzene (20 mL) to give brown solid, which was recrystalized from benzene (50 mL) and hexane (50 mL) to give colorless needles (3.84 g, 28%).

mp 67- 68 °C.

IR (nujol, cm^{-1}) 2250, 1280.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.18 (2H, d, J = 21.1 Hz, CH_2), 7.24- 7.41 (10H, m, Ph).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.36 (d, J = 148 Hz), 111.56 (s, CN), 120.39 (d, J = 5.0 Hz), 126.16 (s), 130.12 (s), 149.41 (d, J = 8.5 Hz).

MS m/z: 273 (M^+), 272 [$(M-1)^+$], 247 [$(M-CN)^+$].

Anal. Calcd for $C_{14}H_{12}NO_3P$: C, 61.54; H, 4.43; N, 5.13. Found: C, 61.52; H, 4.39; N, 4.84.

Chlorophosphonic acid bis(2,2,2-trifluoloethyl) ester

To a solution of phosphorus oxychloride (12.8 mL, 21.1 g, 0.137 mol) in benzene (100 mL), a solution of 2,2,2-trifluoloethanol (12.5 g, 0.125 mol) and pyridine (10.1 mL, 0.125 mol) in benzene (20 mL) was added within 1 min at 0 °C. The suspension was stirred for 1 h. The resultant mixture was filtered off, and the precipitate was washed with benzene. The filtrate and the washing were combined and concentrated under ambient atmosphere. The residure was distilled (52 mmHg).

~ 79 °C colorless oil benzene.

79- 83 °C colorless oil monoester.

92- 95 °C colorless oil diester (30% from 2,2,2-trifluoloethanol).

^{1}H-NMR (270 MHz, $CDCl_3$) 4.39- 4.65 (4H, m, CH_2).

Cyanomethylphosphonic acid bis(2,2,2-trifluoloethyl) ester (2f)

Under nitrogen atmosphere, to a solution of acetonitrile (2.00 mL, 1.57 g, 38.3 mmol) in THF (30 mL), BuLi (1.62 N in hexane, 21.6 mL, 35 mmol) was added within 15 min at -78 °C. The slurry was stirred for 1 h, and the solution of chlorophosphonic acid bis(2,2,2-trifluoloethyl) ester (4.20 g, 15.0 mmol) in THF (10 mL) was added within 5 min. The whole was stirred for 1

h, and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed successively with water (2 x 30 mL) and brine (1 x 30 mL), dried over sodium sulfate and concentrated *in vacuo* to leave a brown oil (5.21 g). The crude oil was purified by column chromatography (SiO_2 200 g, hexane- AcOEt 10: 1) to give a colorless oil (1.77 g), which was distilled (bulb-to-bulb, 200 °C/ 0.7 mmHg) to give a colorless oil (1.52 g, 36%).

IR (neat, cm^{-1}) 2250.

^{1}H-NMR (270 MHz, $CDCl_3$) 3.19 (2H, d, J = 22.1 Hz, CH_2), 4.53 (4H, dq, J = 10.3 Hz, 7.8 Hz, CH_2).

^{13}C-NMR (67.8 MHz, $CDCl_3$ as 77.0 ppm) δ 16.68 (d, J = 151 Hz, CH_2CN), 63.37 (qd, J = 39 Hz, 6.1 Hz, CF_3CH_2), 110.63 (d, J = 12 Hz, CN), 126.99 (qd, J = 277 Hz, 7.3 Hz, CF_3).

HRMS Calcd. for $C_6H_6F_6NO_3P$: m/z: 284.9990. Found: 285.0026.

X線結晶構造解析のデータ

アルドール中間体(±)-*cis*-**38** について，大正製薬株式会社，創薬研究所の森本繁夫氏，松本慶太氏に，X線結晶構造解析を依頼し，測定を行っていただいた．

ここに示すデータは，以下の通りである．

2)-1

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
C 1	0.1279 (2)	-0.1788 (3)	-0.0893 (2)	6.5 (1)
C 2	0.1981 (2)	-0.2318 (3)	-0.0204 (3)	7.4 (1)
C 3	0.2002 (2)	-0.3324 (3)	0.0639 (2)	7.0 (1)
C 4	0.1322 (2)	-0.3815 (3)	0.0794 (2)	7.0 (1)
C 5	0.0617 (2)	-0.3284 (3)	0.0125 (2)	6.1 (1)
C 6	0.0576 (1)	-0.2248 (2)	-0.0740 (2)	5.2 (1)
C 7	-0.0184 (1)	-0.1628 (2)	-0.1476 (2)	5.2 (1)
C 8	-0.0534 (1)	-0.2581 (3)	-0.2537 (2)	5.6 (1)
C 9	-0.1275 (1)	-0.1881 (3)	-0.3312 (2)	5.8 (1)
C 10	-0.1884 (1)	-0.1564 (2)	-0.2699 (2)	5.0 (1)
C 11	-0.1527 (1)	-0.0666 (3)	-0.1610 (2)	5.6 (1)
C 12	-0.0800 (1)	-0.1417 (3)	-0.0855 (2)	5.4 (1)
O 13	-0.21572 (9)	-0.2983 (2)	-0.2439 (1)	5.76 (9)
C 14	-0.2578 (1)	-0.0654 (2)	-0.3485 (2)	5.6 (1)
C 15	-0.3095 (1)	-0.0052 (3)	-0.2863 (2)	6.4 (1)
N 16	-0.3500 (1)	0.0434 (3)	-0.2386 (2)	8.8 (1)
P 17	-0.31632 (4)	-0.15477 (7)	-0.47875 (5)	6.10 (9)
O 18	-0.2711 (1)	-0.2028 (2)	-0.5537 (1)	7.3 (1)
O 19	-0.3756 (1)	-0.0242 (2)	-0.5229 (1)	7.8 (1)
C 20	-0.4423 (2)	-0.0344 (4)	-0.6229 (3)	8.8 (1)
C 21	-0.4674 (2)	0.1214 (5)	-0.6607 (3)	10.0 (2)
O 22	-0.36684 (9)	-0.2806 (2)	-0.4473 (1)	7.1 (1)
C 23	-0.3471 (3)	-0.4384 (4)	-0.4555 (4)	10.3 (2)
C 24	-0.3838 (6)	-0.532 (1)	-0.401 (1)	20.0 (6)
H 1	0.126 (2)	-0.105 (3)	-0.153 (2)	6.19
H 2	0.242 (2)	-0.202 (3)	-0.033 (2)	7.06
H 3	0.249 (2)	-0.368 (3)	0.111 (2)	6.89
H 4	0.134 (2)	-0.451 (4)	0.135 (2)	6.80
H 5	0.014 (2)	-0.363 (3)	0.019 (2)	5.88
H 7	-0.008 (1)	-0.061 (3)	-0.174 (2)	5.01
H 8 A	-0.066 (2)	-0.361 (3)	-0.230 (2)	5.38
H 8 B	-0.012 (2)	-0.268 (3)	-0.294 (2)	5.38
H 9 A	-0.116 (2)	-0.087 (3)	-0.359 (2)	5.60
H 9 B	-0.151 (2)	-0.250 (3)	-0.394 (2)	5.60
H 11A	-0.192 (2)	-0.054 (3)	-0.118 (2)	5.40
H 11B	-0.142 (2)	0.032 (3)	-0.187 (2)	5.40
H 12A	-0.060 (1)	-0.083 (3)	-0.015 (2)	5.25
H 12B	-0.092 (1)	-0.239 (3)	-0.062 (2)	5.25
H 13	-0.232 (2)	-0.288 (3)	-0.184 (2)	5.55
H 14	-0.237 (1)	0.022 (3)	-0.378 (2)	5.36
H 20A	-0.422 (2)	-0.082 (4)	-0.679 (3)	8.83
H 20B	-0.482 (2)	-0.096 (4)	-0.608 (3)	8.83
H 21A	-0.466 (2)	0.177 (4)	-0.594 (3)	9.93
H 21B	-0.418 (2)	0.180 (4)	-0.674 (3)	9.93
H 21C	-0.511 (2)	0.113 (4)	-0.730 (3)	9.93
H 23A	-0.299 (2)	-0.453 (4)	-0.470 (3)	9.66
H 23B	-0.408 (2)	-0.499 (5)	-0.521 (3)	9.66
H 24A	-0.448 (4)	-0.510 (8)	-0.402 (5)	18.29
H 24B	-0.379 (4)	-0.665 (8)	-0.428 (6)	18.29
H 24C	-0.358 (6)	-0.53 (1)	-0.35 (1)	18.29

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1)

-----< Summary of structure determination >-----

Specimen name	TOUDAI-sample
Chemical Formula	C18 H26 N1 O4 P1
Formula Weight	351.00
Crystal Size	0.55 * 0.55 * 0.10 mm**3
Unit-cell Dimensions :	a = 17.948 (2) Å b = 8.896 (1) Å c = 12.287 (3) Å beta = 106.78 (1) degrees } 格子定数
Volume of unit cell	1878.2 (5) Å**3
Crystal System	Monoclinic 晶系：単斜晶系
Space Group	P21/c (# 14) 空間群：P2₁/c
Z value	4
Densities: Dobs ;Dcalc	1.24; 1.24 g/cm**3
F(000)	752
Linear Absorption Coefficient	13.71 /cm (Cu K-alpha)
Diffractometer used	Mac Science MXC18
Radiation	Cu K-alpha (lambda= 1.54178)
Maximum sine(theta)/lambda	0.584
Total Reflections Measured	3606
Unique Reflections	3149
Internal Consistency : Rint	0.01
Function Minimized was sum[w(|Fo|**2-|Fc|**2)**2] where w = 1.0/sqrt[(sigma|Fo|)**2+(0.004*|Fo|)**2]	
Reflections used (F>3.00(sig(F)))	2911
No. of Variables	305
Residuals: R; Rw	0.045; 0.051
Goodness of Fit : S	5.22
Maximum Shift/e.s.d. in final cycle	0.97
Maximum Negative Peak in Final Diff. Map	-0.26 e/Å**3 (0.391 0.998 0.933)
Maximum Positive Peak in Final Diff. Map	0.39 e/Å**3 (-0.369-0.531-0.373)

{ R = 4.5% (信頼度因子)
{ wR = 5.1% (重みつきの信頼度因子)

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3) atom u11, 22, 33, 12, 13, 23

U values with e.s.d. in parentheses

atom	u11	u22	u33	u12	u13	u23
C 1	0.072 (1)	0.054 (1)	0.117 (3)	0.001 (1)	0.039 (1)	0.003 (1)
C 2	0.065 (2)	0.061 (2)	0.146 (4)	0.001 (1)	0.035 (2)	-0.008 (2)
C 3	0.076 (2)	0.063 (2)	0.114 (3)	0.012 (1)	0.014 (1)	-0.016 (1)
C 4	0.095 (2)	0.066 (2)	0.095 (3)	0.017 (2)	0.023 (1)	0.005 (1)
C 5	0.075 (1)	0.056 (1)	0.096 (3)	0.005 (1)	0.031 (1)	0.004 (1)
C 6	0.065 (1)	0.041 (1)	0.087 (3)	0.001 (1)	0.028 (1)	-0.0059 (9)
C 7	0.064 (1)	0.043 (1)	0.086 (3)	-0.001 (1)	0.027 (1)	0.001 (1)
C 8	0.070 (1)	0.062 (1)	0.079 (3)	0.008 (1)	0.031 (1)	-0.002 (1)
C 9	0.070 (1)	0.069 (2)	0.078 (3)	0.009 (1)	0.028 (1)	0.002 (1)
C 10	0.065 (1)	0.045 (1)	0.076 (3)	0.002 (1)	0.024 (1)	-0.0007 (9)
C 11	0.067 (1)	0.054 (1)	0.086 (3)	0.005 (1)	0.026 (1)	-0.008 (1)
C 12	0.064 (1)	0.058 (1)	0.079 (3)	0.003 (1)	0.022 (1)	-0.010 (1)
O 13	0.076 (1)	0.0514 (9)	0.085 (3)	-0.0015 (7)	0.0265 (8)	0.0012 (7)
C 14	0.069 (1)	0.054 (1)	0.083 (3)	0.006 (1)	0.025 (1)	0.002 (1)
C 15	0.071 (1)	0.069 (2)	0.092 (3)	0.016 (1)	0.017 (1)	-0.003 (1)
N 16	0.090 (2)	0.123 (2)	0.112 (3)	0.038 (2)	0.027 (1)	-0.017 (1)
P 17	0.0715 (4)	0.0692 (4)	0.084 (3)	0.0012 (3)	0.0242 (3)	-0.0031 (3)
O 18	0.088 (1)	0.097 (1)	0.089 (3)	-0.009 (1)	0.0362 (9)	-0.0143 (9)
O 19	0.094 (1)	0.086 (1)	0.099 (3)	0.018 (1)	0.000 (1)	0.0008 (9)
C 20	0.093 (2)	0.113 (3)	0.112 (3)	-0.003 (2)	0.001 (2)	0.015 (2)
C 21	0.102 (2)	0.125 (3)	0.132 (4)	0.017 (2)	0.006 (2)	0.028 (2)
O 22	0.074 (1)	0.075 (1)	0.117 (3)	-0.0047 (9)	0.0386 (9)	-0.0072 (9)
C 23	0.134 (3)	0.067 (2)	0.186 (4)	-0.024 (2)	0.079 (3)	-0.018 (2)
C 24	0.25 (1)	0.121 (4)	0.40 (2)	0.008 (5)	0.21 (1)	0.064 (6)

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Intramolecular Distances (Å) with e.s.d. in parentheses

atom	atom	distance	atom	atom	distance
C 1	--C 2	1.382 (3)	C 10	--C 14	1.563 (3)
C 1	--C 6	1.390 (4)	C 11	--C 12	1.521 (3)
C 2	--C 3	1.361 (4)	C 14	--C 15	1.464 (4)
C 3	--C 4	1.361 (5)	C 14	--P 17	1.824 (2)
C 4	--C 5	1.378 (4)	C 15	--N 16	1.142 (4)
C 5	--C 6	1.392 (3)	P 17	--O 18	1.456 (2)
C 6	--C 7	1.507 (3)	P 17	--O 22	1.557 (2)
C 7	--C 12	1.525 (4)	P 17	--O 19	1.562 (2)
C 7	--C 8	1.530 (3)	O 19	--C 20	1.450 (3)
C 8	--C 9	1.527 (3)	C 20	--C 21	1.490 (6)
C 9	--C 10	1.523 (4)	O 22	--C 23	1.458 (4)
C 10	--O 13	1.423 (2)	C 23	--C 24	1.35 (1)
C 10	--C 11	1.531 (3)			

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle	atom	atom	atom	angle
C 2	--C 1	--C 6	121.3 (2)	C 11	--C 10	--C 14	109.1 (2)
C 3	--C 2	--C 1	120.7 (3)	C 12	--C 11	--C 10	111.9 (2)
C 2	--C 3	--C 4	119.2 (2)	C 11	--C 12	--C 7	111.5 (2)
C 3	--C 4	--C 5	120.9 (2)	C 15	--C 14	--C 10	112.3 (2)
C 4	--C 5	--C 6	121.3 (2)	C 15	--C 14	--P 17	109.0 (2)
C 1	--C 6	--C 5	116.6 (2)	C 10	--C 14	--P 17	118.0 (2)
C 1	--C 6	--C 7	120.7 (2)	N 16	--C 15	--C 14	179.1 (3)
C 5	--C 6	--C 7	122.7 (2)	O 18	--P 17	--O 22	114.6 (1)
C 6	--C 7	--C 12	113.9 (2)	O 18	--P 17	--O 19	116.5 (1)
C 6	--C 7	--C 8	112.7 (2)	O 18	--P 17	--C 14	113.4 (1)
C 12	--C 7	--C 8	108.4 (2)	O 22	--P 17	--O 19	103.5 (1)
C 9	--C 8	--C 7	112.0 (2)	O 22	--P 17	--C 14	109.0 (1)
C 10	--C 9	--C 8	112.8 (2)	O 19	--P 17	--C 14	98.2 (1)
O 13	--C 10	--C 9	106.9 (2)	C 20	--O 19	--P 17	124.1 (2)
O 13	--C 10	--C 11	110.5 (2)	O 19	--C 20	--C 21	107.9 (3)
O 13	--C 10	--C 14	109.5 (2)	C 23	--O 22	--P 17	120.3 (2)
C 9	--C 10	--C 11	110.5 (2)	C 24	--C 23	--O 22	113.2 (6)
C 9	--C 10	--C 14	110.3 (2)				

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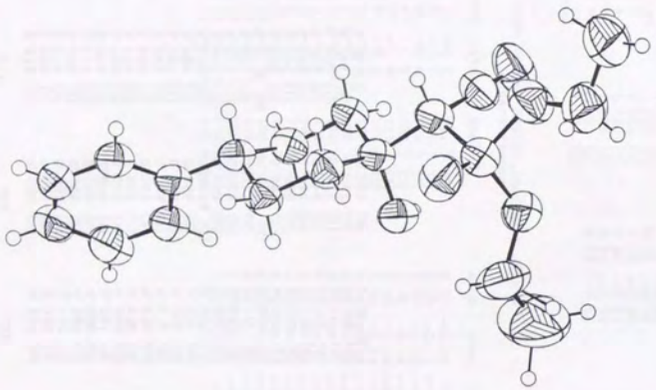
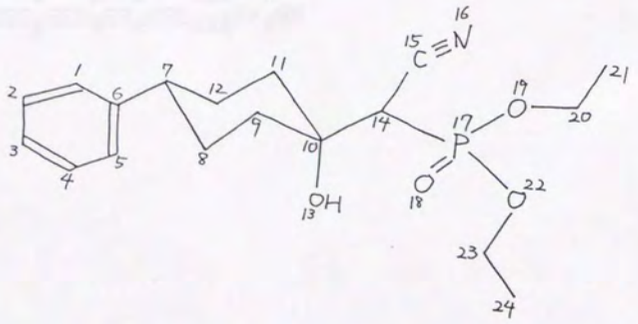
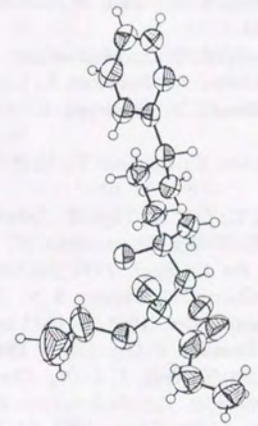
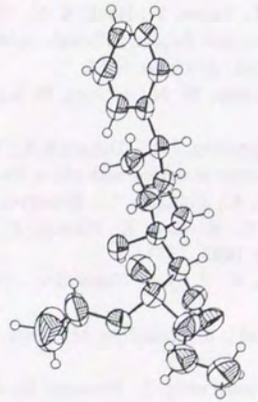




※上記の番号は、原子座標、結合距離及び角度の表中の番号に対応しています。





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