



Title	金属選択的配位概念を基盤とする有機銅の不斉共役付加反応
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金属選択的配位概念を基盤とする 有機銅の不斉共役付加反応

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金井 求

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1995年 2月

金 井 求

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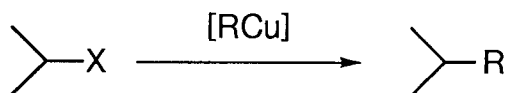
第1章 序 論

不斉合成がなぜ重要で今日の合成化学においてこれほどホットな分野になっているのか。生理活性物質や医薬品を光学活性体として供給することは生体関連科学にたずさわる者の必務である。なぜなら生体はキラルな反応場であり、キラリティーをもつ分子は厳密に識別され別々の分子として働くからである。それならば、数ある光学活性体の供給方法のうちで不斉合成を研究するのはなぜか。それは、反応の理解、言い替えれば反応活性種の構造を決定するという面で立体化学が独特の切り口を持っているからだと考えられる。

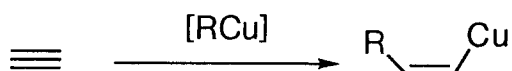
不斉合成の基本的な戦略は、反応が進行するときの substrate と reagent の活性錯体 (active complex) にキラル分子を作用させ、3成分の complex により立体制御を行う。すなわち立体制御がおこることは active complex に「我々の設計した分子」が直接作用していることが大前提になる。active complex は動的な complex であるために静的な手段 (X線結晶構造解析、NMRなど) で構造の知見を得るのは困難であり、「我々の設計した分子」がどのように作用し一方の光学活性体を与えるのかという立体化学の切り口は1つの強力な武器となる。すなわち、「我々の設計した分子」は chiral controller であると同時に reaction probe としての役割を持っている。

本研究ではターゲットとする活性種として有機銅を選んだ。有機銅は有機リチウム、グリニャール試薬のつぎに一般的に用いられる有機金属である。その反応は3種類に分類できる¹。

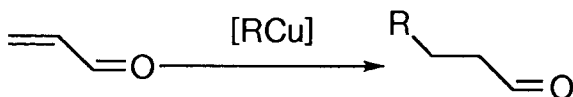
1. Substitution reaction (halides, acetates, acetals, epoxides etc.)



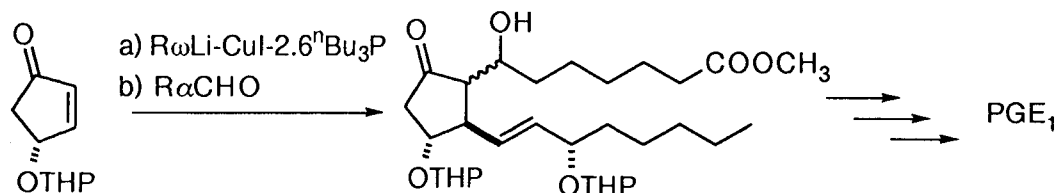
2. Addition reactions to non-activated C-C multiple bonds (Carbocupration to alkynes and allenes)



3. Addition reactions to activated C-C multiple bonds (Conjugate addition to enones, enoates, ynoates etc.)



有機銅の共役付加反応 (3) はさまざまな天然物の全合成で鍵工程として用いられる強力な合成手段である。一例として野依らのプロスタグランジン類の合成法を挙げる²。

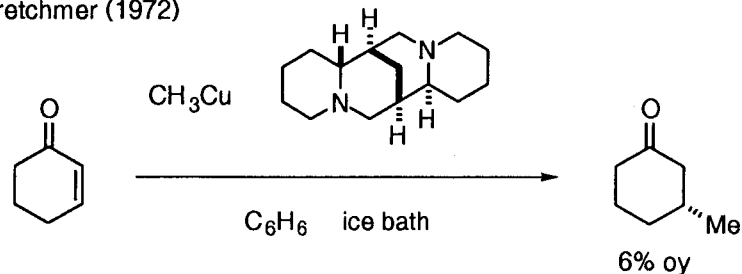


基本的で一般性の高い素反応を不斉反応に応用することは合成化学の重要な課題の一つである。特に本反応では銅を触媒量用いることで合成化学的に最も効率の高い触媒的不斉合成へと発展が期待できる。さらに反応活性種に対して合理的な不斉空間の構築が可能となるならば、活性種の不安定性により構造論的に情報を得るのが困難な銅試薬の反応を立体化学的な切り口で理解するという点においても大きな進歩になることは間違いない。以上の考察から、私は有機銅に対する合理的な不斉配位子の設計を目的として研究を始めた。

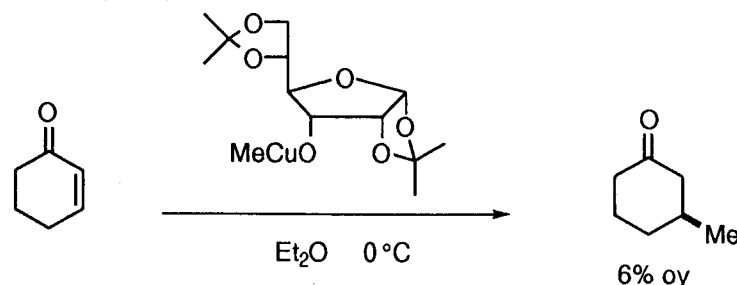
本反応の重要性を反映して、多くの研究がすでに報告されている^{3,4}。以下に代表例を挙げる (Figure 1)。有機銅の不斉共役付加反応はKretchmer のスパルテインを外部配位子としたシクロヘキセノンへのメチル銅の付加体が6% ee で得られた報告が最初である。Crabbé らは銅原子にキラル源を共有結合させたキラルヘテロクプレートを用いて同じ反応を行ったが選択性は6% ee 程度であった。これらの初期の報告は選択性が低くはあったが、クプレートを用いた付加反応の現在に至る2種類のストラテジー、すなわちキラル外部配位子による制御とキラルヘテロクプレートによる制御を提唱している。後者は1980年の向山らの報告、前者は1985年のLeyendeckerらの報告をブレークスルーとして、現在では高い選択性を持つ不斉反応が報告されている。特に後者のストラテジーは1990年のLippardらの報告を皮切りに不斉触媒反応にも応用されている。しかし基質や導入できるアルキル基の一般性が低く、不斉源の合理的な設計という点から見ると十分とはいえない。この点で私はオリジナルな寄与ができるものと考え、キラル配位子の設計概念の確立という点から研究にとりかかった。その結果、銅とリチウムあるいはマグネシウムに選択的な配位部位をもつキラル配位子がFigure 2に挙げる有機銅の反応の立体化学を制御し高い選択性で共役付加体を与えることを見い出した。NMR実験によりキラル配位子のカルボニル酸素とリンの金属選択的配位が実現していることを明らかにした。特にリンは形式的に負電荷を持つクプレートの銅に対しても良好な配位力を持っていることがわかった。さらに触媒量のキラル外部配位子-銅錯体の制御によりグリニャール試薬の不斉共役付加反応が最高92% eeの高い選択性で制御できることを初めて見い出した。

Figure 1. Asymmetric Addition of Organocuprate

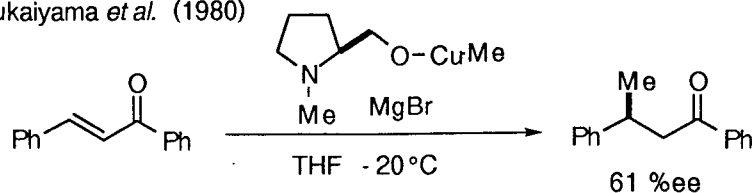
R. A. Kretchmer (1972)



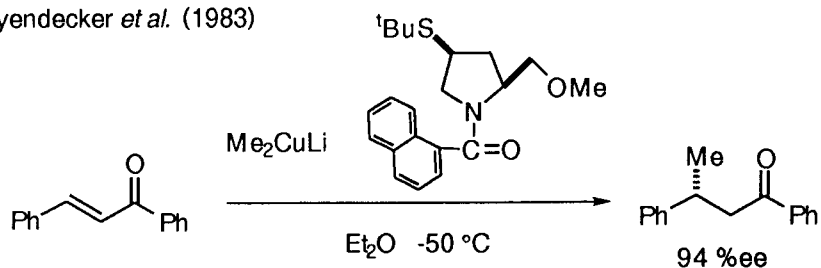
P. Crabbé et al. (1975)



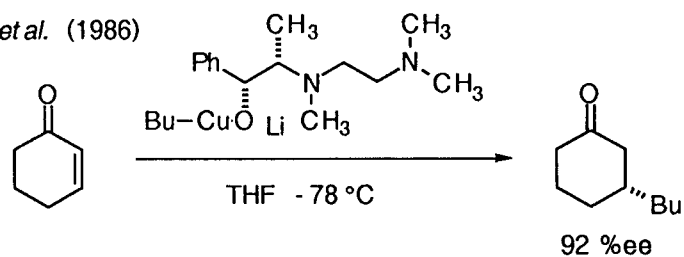
T. Mukaiyama *et al.* (1980)



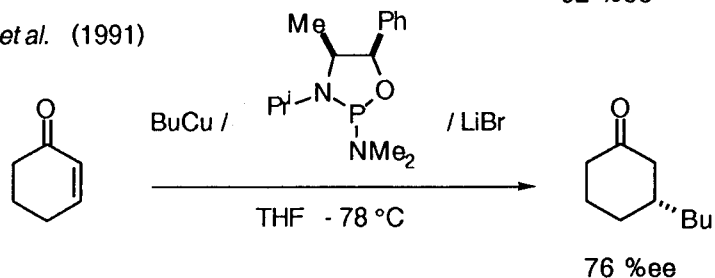
F. Leyendecker *et al.* (1983)



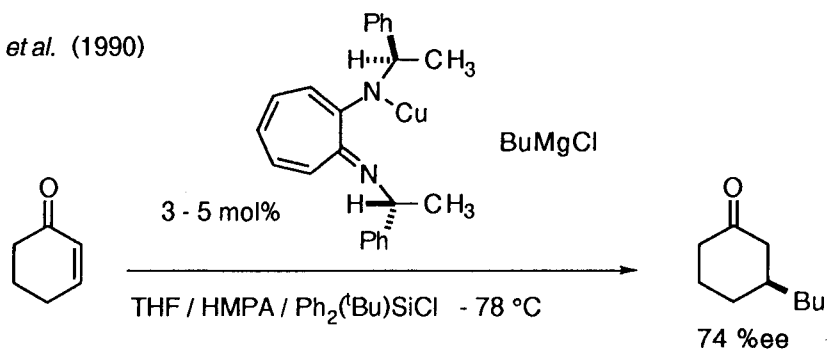
E. J. Corey *et al.* (1986)



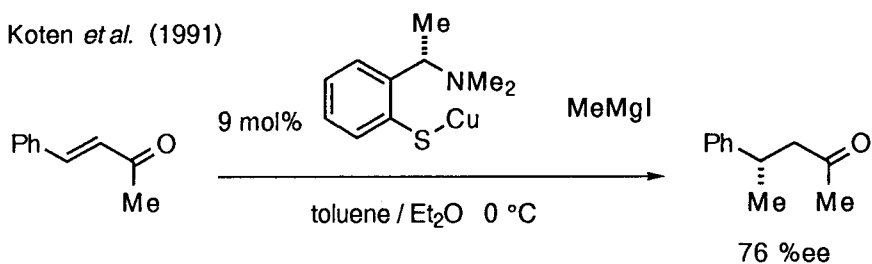
A. Alexakis *et al.* (1991)



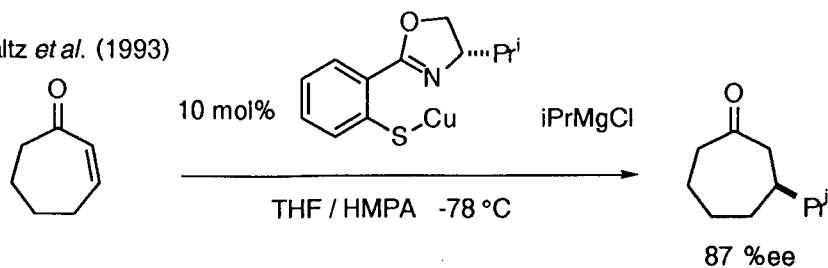
S. J. Lippard *et al.* (1990)



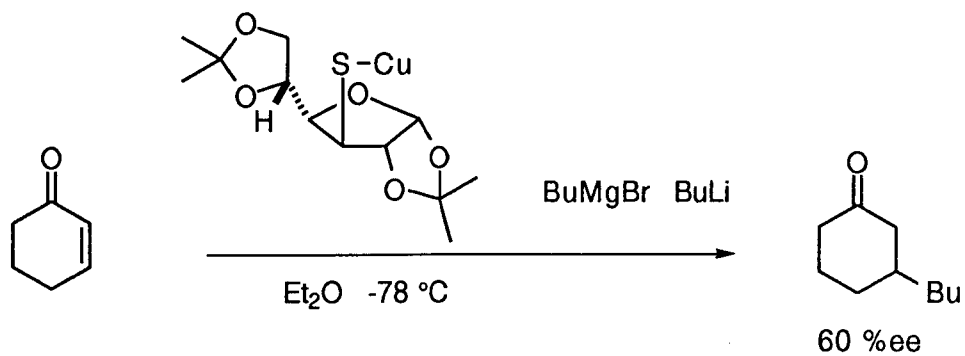
G. van Koten *et al.* (1991)



A. Pfaltz *et al.* (1993)



M. Spescha et al. (1993)



A. Alexakis et al. (1993)

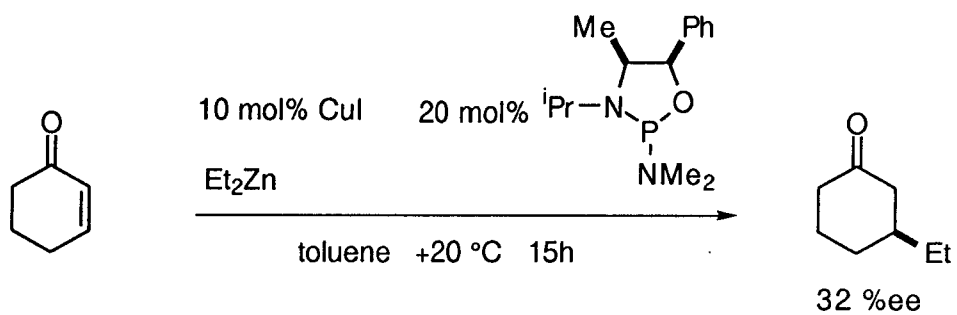
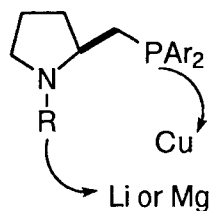
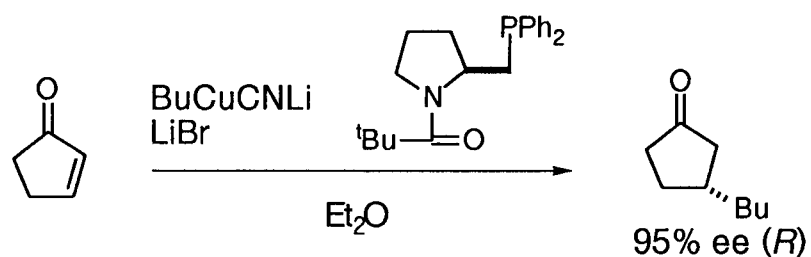
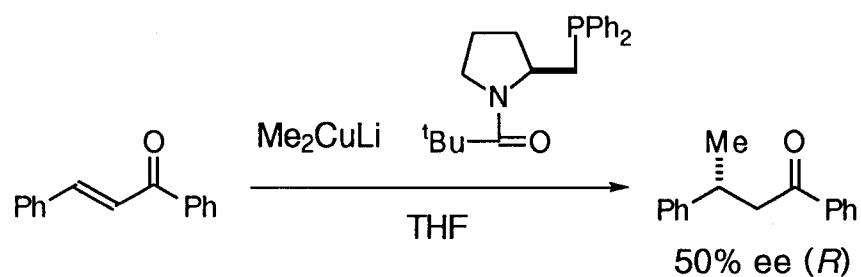
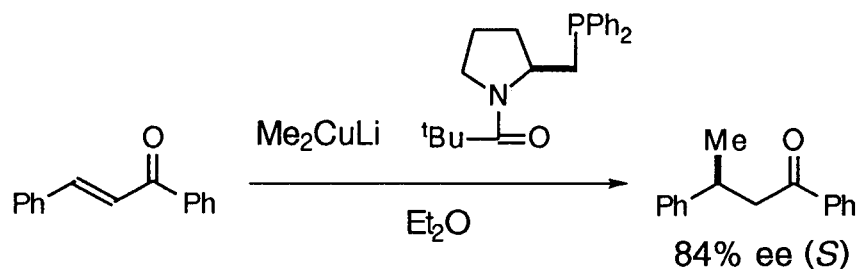


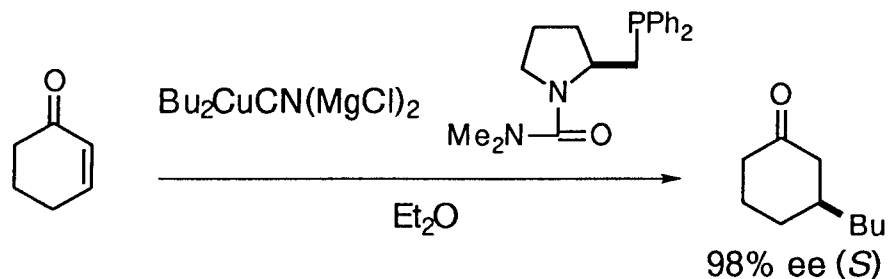
Figure 2.



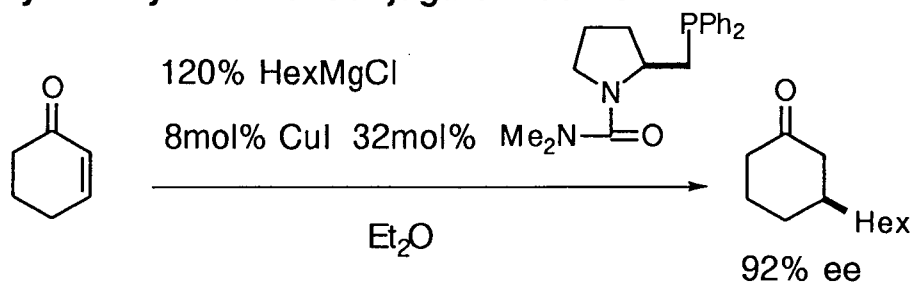
Asymmetric Conjugate Addition of Lithium Cuprate



Asymmetric Conjugate Addition of Magnesium Cuprate



Catalytic Asymmetric Conjugate Addition



第2章 キラル配位子の設計、合成

1. キラル配位子の設計

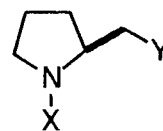
有機銅の構造論的研究から、比較的一般性のある構造として二量体42が知られている⁵。基質のエノンはこの二量体に対しカルボニル酸素をリチウムに配位させて d, π^* -complexを形成して反応が進行すると考えられる⁶。配位子の存在により構造変化が容易に起こる可能性はあるが、この二量体をキラル配位子の制御によりキラルな空間にする設計を行った (Figure 3)。

基本的なストラテジーは、反応点を1つに限定することである。配位子が存在しないとき (42)、反応点は4種類のリチウムと銅の組み合わせの上下の計8つが考えられる。これに配位原子X、Yを持つ二座配位子が錯体を形成すると (43)、配位子間の立体的反発をさけるために二量体の上下から錯体形成すると考えられるので反応点は2つまで減らすことができる。し

かし不斉の要素がないので2つの反応点から同じ確率で生成物が生じラセミ体を与える。従って、2つの反応点のうち一方を立体障害基によってブロックできれば不斉合成が達成できることになる。そのためには2つの配位原子XとYがリチウムと銅にそれぞれ選択的に配位しなければならないと考えた。この金属選択的配位が実現するならば、下側に配位した配位子の立体障害基は下側の反応点をブロックするため、基質は上側でのみ d, π^* -complexを形成して反応し光学活性体が得られる (44)。それに対し、XとYがリチウムと銅に非選択的に配位するならば、あるいは立体障害基が二量体に対しエンドになるという立体的な要請に負けてエキソになってしまうならば、2つの反応点があいてしまうために立体制御は達成できないことになる (45)。すなわち、XとYは立体的には不利な44を電子的に安定化させるほどの金属選択的な親和性をもっていなければならない。

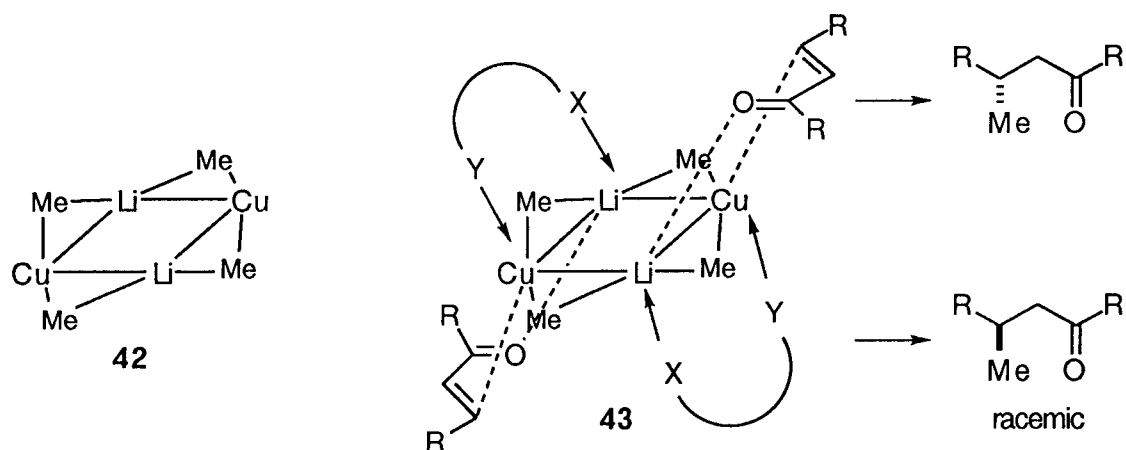
そのようなXとして窒素あるいは酸素、Yとしてリン、イオウ、窒素、酸素を用いキラル配位子 1~13, 16, 17 を設計した。不斉炭素骨格は立体障害として期待した、ピロリジン環に対して配位方向の明確に規定されたL-プロリン骨格を選んだ。

2種類の金属に両方とも配位してクプレートクラスター全体を不斉空間とするこのストラテジーは、グローバルな立体制御法⁷にのっとたもので、活性種に関して得られる情報も多いと考えられる。

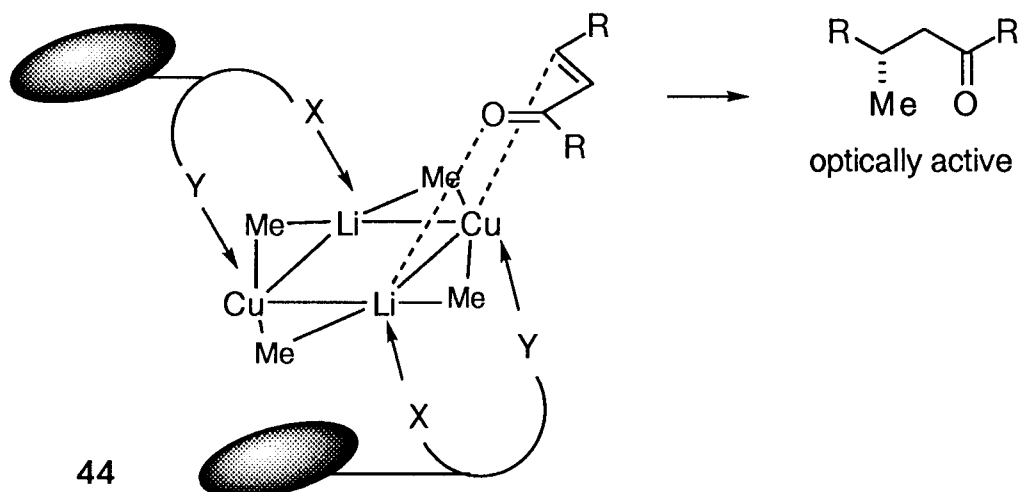


	X	Y
1	Me	PPh ₂
2	tBuCO	PPh ₂
3	(Me ₂ N) ₂ PO	PPh ₂
4	Me ₂ NCO	PPh ₂
5	C ₆ F ₅ CO	PPh ₂
6	C ₆ H ₅ CO	PPh ₂
7	1-NaphCO	PPh ₂
8	CF ₃ CO	PPh ₂
9	Ts	PPh ₂
10	tBuCO	SMe
11	tBuCO	SPh
12	tBuCO	NPh ₂
13	tBuCO	OMe
16	Me ₂ NCO	P(PhOMe) ₂
17	Me ₂ NCO	P(PhNMe ₂) ₂

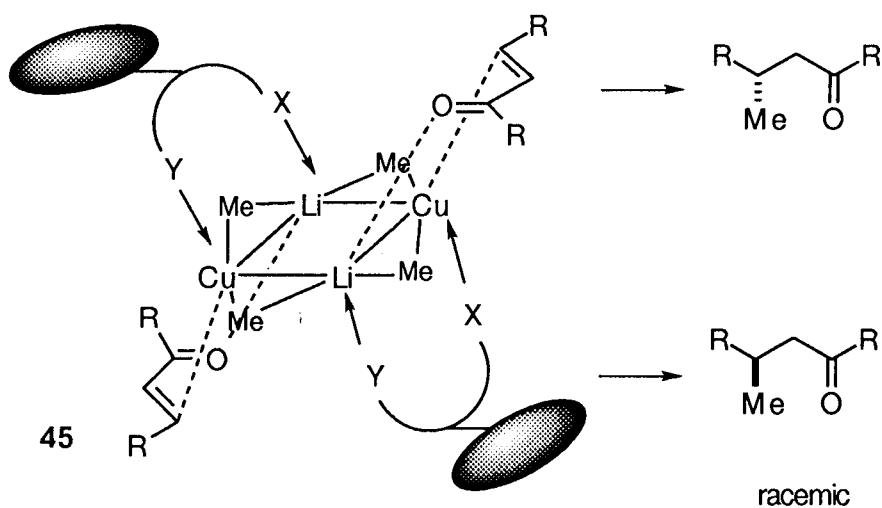
Figure 3. Design of Asymmetric Field



Metal Differentiating Coordination



Non-selective Coordination

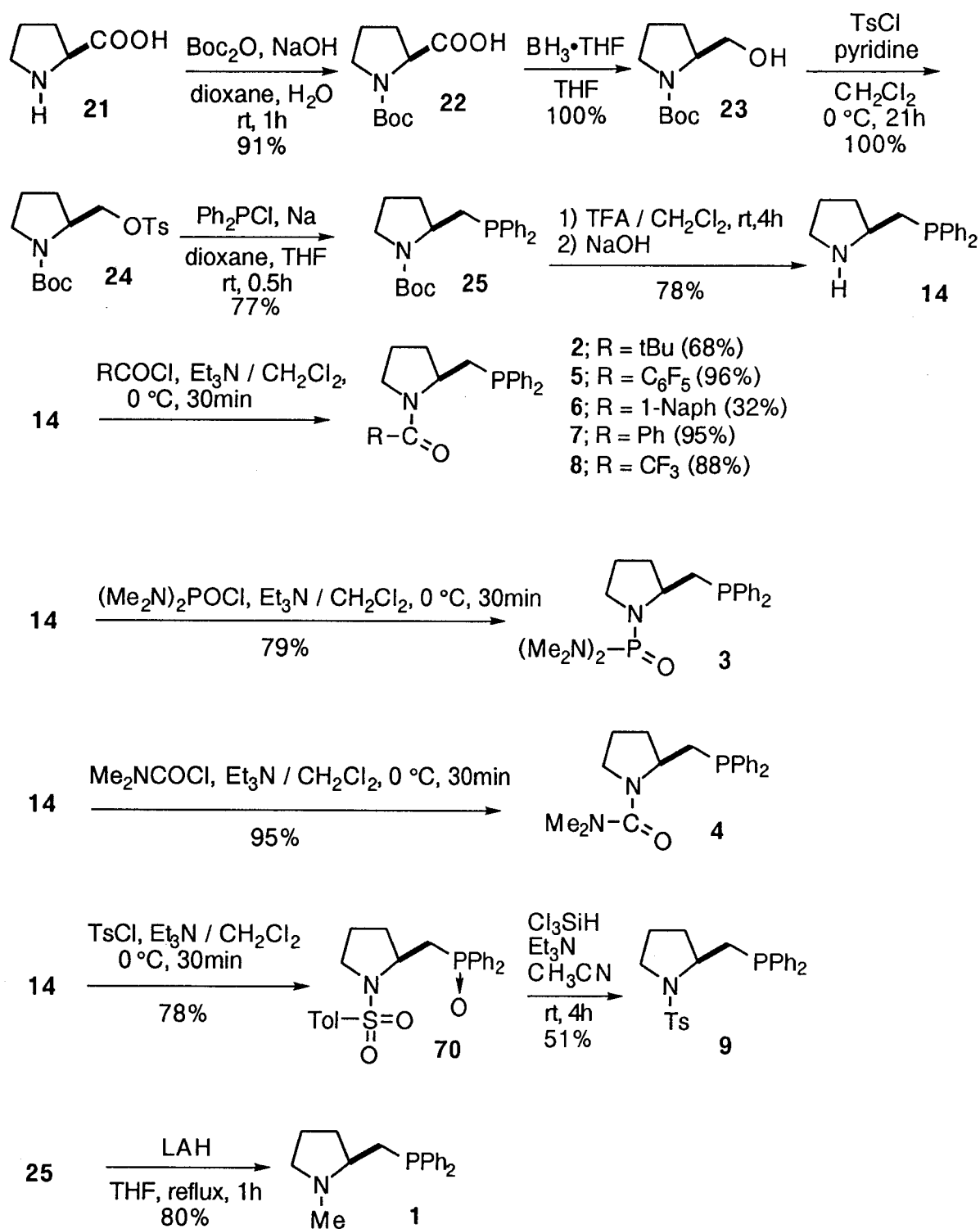


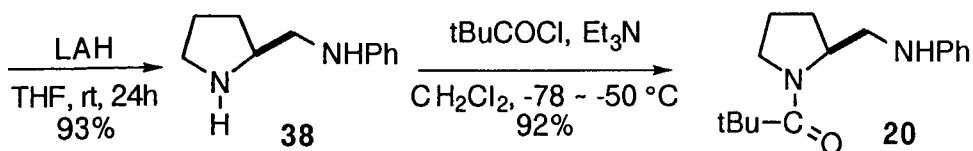
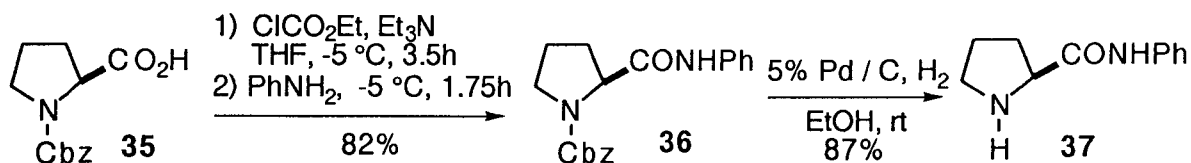
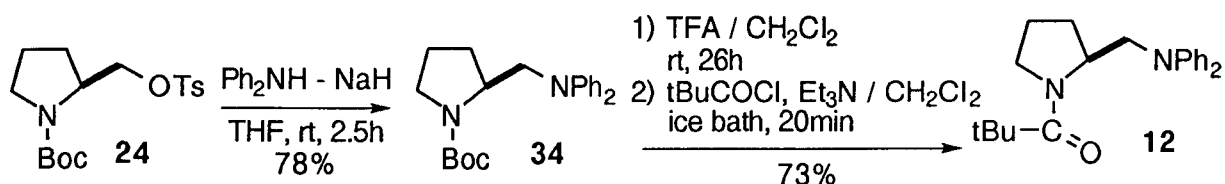
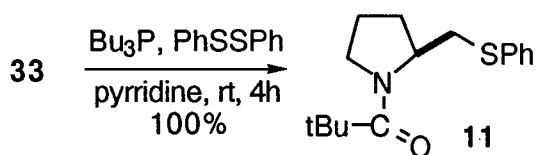
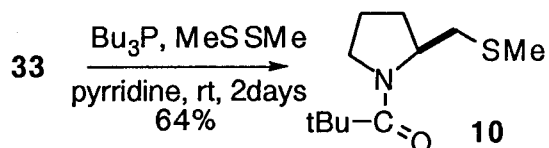
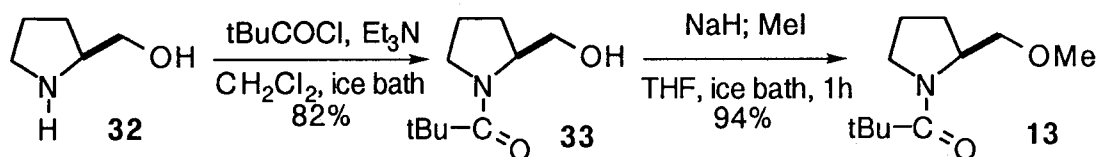
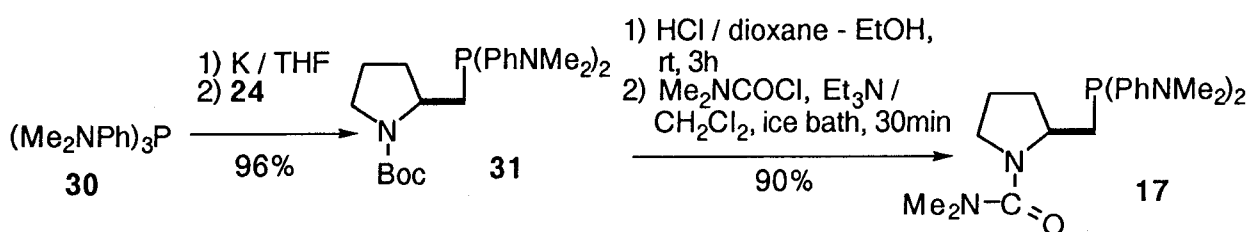
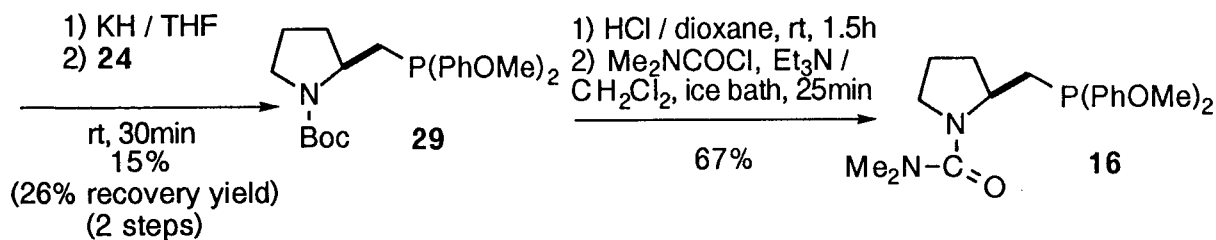
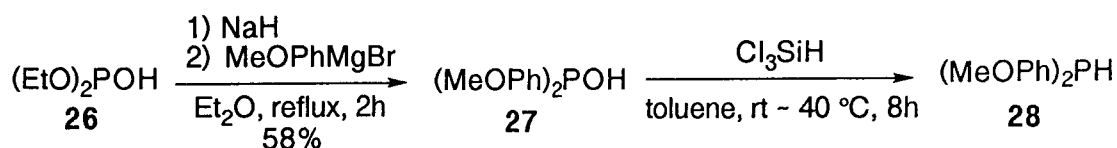
2. キラル配位子の合成 (Figure 4)

キラル配位子 2~9 は共通中間体 14 から合成できた。以下にそのルートを示す。16,

17はホスフィンの電子密度を高めることにより銅への配位力が強まることをを想定した。
10~13は銅への配位原子としてなにが有効なのかを調べるために合成した。

Figure 4. Synthesis of Chiral Ligands





3. 金属選択的配位能の評価

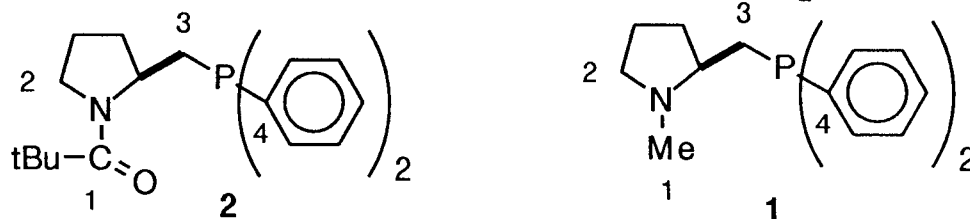
設計したキラル配位子の2つの配位原子が期待通りリチウムと銅にそれぞれ選択的に配位するかをリチウム塩と銅塩を別々に加えたときのNMRのケミカルシフトの変化によって評価した (Table 1, Figure 5)。

トルエン-エーテル溶媒中でアミドホスフィン配位子2に1当量の過塩素酸リチウムを加えたときカルボニル炭素C1は2.6 ppmの低磁場シフトが見られたのに対し、リンの結合したC3, 4では1 ppm程度の変化にとどまった。臭化銅を加えたときにはC1では0.3 ppmの変化であったのに対し、C3で1.7 ppm、C4で6.1, 4.6 ppmと大きな高磁場シフトが見られた。以上の結果はリチウムを加えたときにはカルボニル酸素のまわりの電子的環境が、銅を加えたときにはリンのまわりの電子的環境がそれぞれ選択的に変化することを示している。すなわち2では金属選択的配位が実際におこっていることがわかった。また実際の活性種であるリチウムジメチルクプレートとの錯体ではリチウムと銅それぞれを別々に加えたときを足し併せたような結果が得られ、実際の反応系においても金属選択的配位がおこっていることが示唆された。

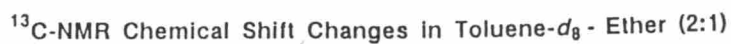
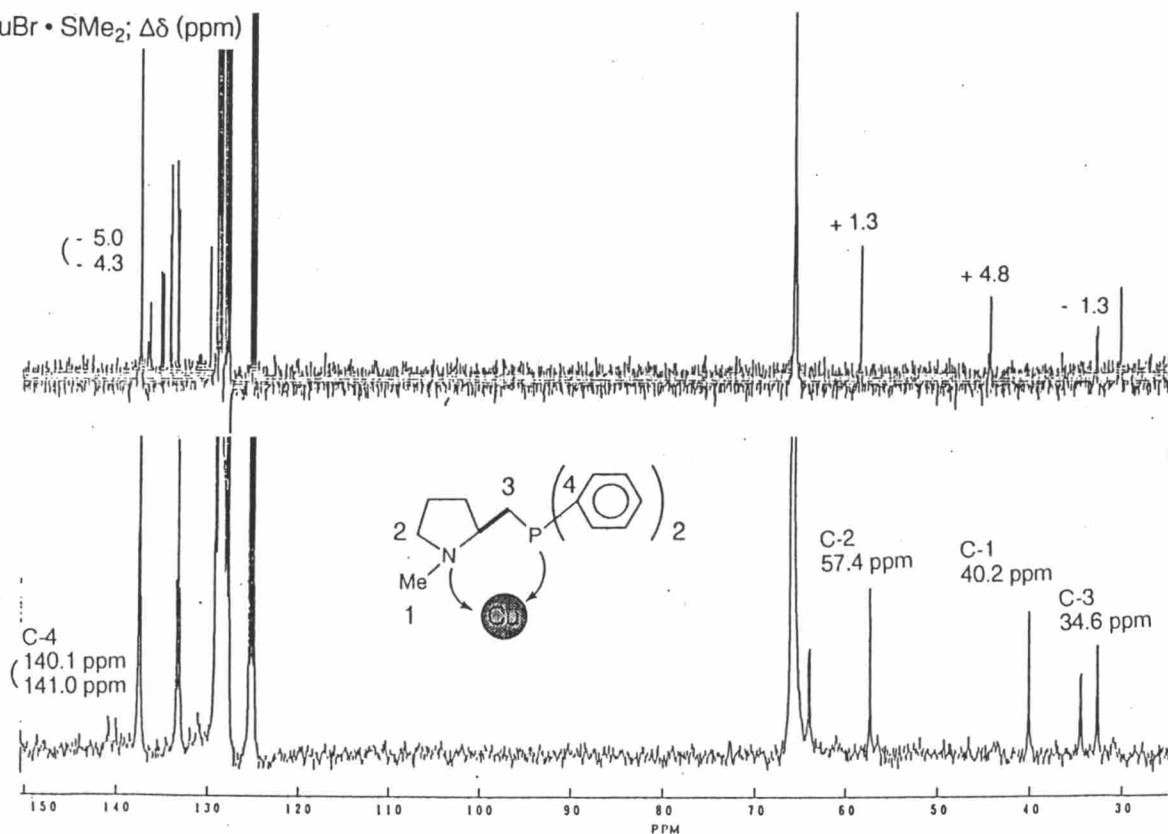
それに対しアミノホスフィン1では臭化銅を加えたときにチッソの結合したC1, 2とリンの結合したC3, 4において顕著なシフトが見られ、1では金属選択的配位がおこらないことがわかった。

すなわち、アミドホスフィン配位子2は金属選択的配位能を持っており、有効な不斉空間を構築できうる可能性が示唆された。それに対し1はキレート型の配位子であるため、不斉誘起能が低いことが予想できた。

Table 1. ^{13}C -NMR Chemical Shift Changes of 2 and 1 in Toluene - Et_2O



		+ LiClO_4	+ $\text{CuBr} \cdot \text{SMe}_2$	+ Me_2CuLi		+ $\text{CuBr} \cdot \text{SMe}_2$
	δ (ppm)	$\Delta\delta$ (ppm)	$\Delta\delta$ (ppm)	$\Delta\delta$ (ppm)	δ (ppm)	$\Delta\delta$ (ppm)
C-1	175.2	+ 2.6	+ 0.3	+ 2.1	C-1	40.2 + 4.8
C-2	48.1	+ 1.0	- 0.2	+ 0.8	C-2	57.4 + 1.3
C-3	33.6	- 0.8	- 1.7	- 0.3	C-3	34.6 - 1.3
C-4	138.6	- 0.7	- 6.1	- 2.2	C-4	140.1 - 5.0
	140.9	- 1.1	- 4.6			141.0 - 4.3

$+ \text{CuBr} \cdot \text{SMe}_2; \Delta\delta \text{ (ppm)}$  $+ \text{CuBr} \cdot \text{SMe}_2; \Delta\delta \text{ (ppm)}$ 

4. X線結晶解析によるリガンドのコンフォメーション解析

金属選択的配位能を持つことがNMR実験から示されたアミドホスフィン配位子に対しX線結晶解析を行い、フリー状態でのコンフォメーションの解析をおこなった (Figure 6)。

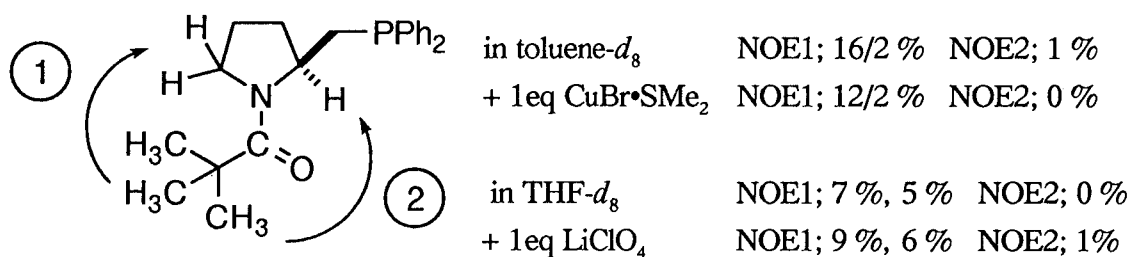
大きな特徴はアミド結合がシスであることと、リンのローンペアアがアミド酸素と逆の方向を向いていることである。

Important Interatomic Distances (Å) and Angles (deg) in 2

C(1)-C(2) 1.546; C(1)-P(13) 1.840; C(2)-C(3) 1.522; C(2)-N(6) 1.490; C(3)-C(4) 1.529; C(4)-C(5) 1.522; C(5)-N(6) 1.488; N(6)-C(7) 1.361; C(7)-O(8) 1.219; C(7)-C(9) 1.550; C(9)-C(10) 1.557; C(9)-C(11) 1.538; C(9)-C(12) 1.538; P(13)-C(20) 1.831; P(13)-C(25) 1.837; P(13)-O(8) 4.443; C(10)-C(9)-C(7)-O(8) -10.223; C(12)-C(9)-C(7)-O(8) -127.531; C(11)-C(9)-C(7)-O(8) +107.815; O(8)-C(7)-N(6)-C(2) -4.815; C(9)-C(7)-N(6)-C(5) +3.054; N(6)-C(2)-C(3)-C(4) +31.801; C(3)-C(4)-C(5)-N(6) +30.741; N(6)-C(2)-C(1)-P(13) +173.203; C(2)-C(1)-P(13)-C(20) -82.251; C(2)-C(1)-P(13)-C(14) +172.507

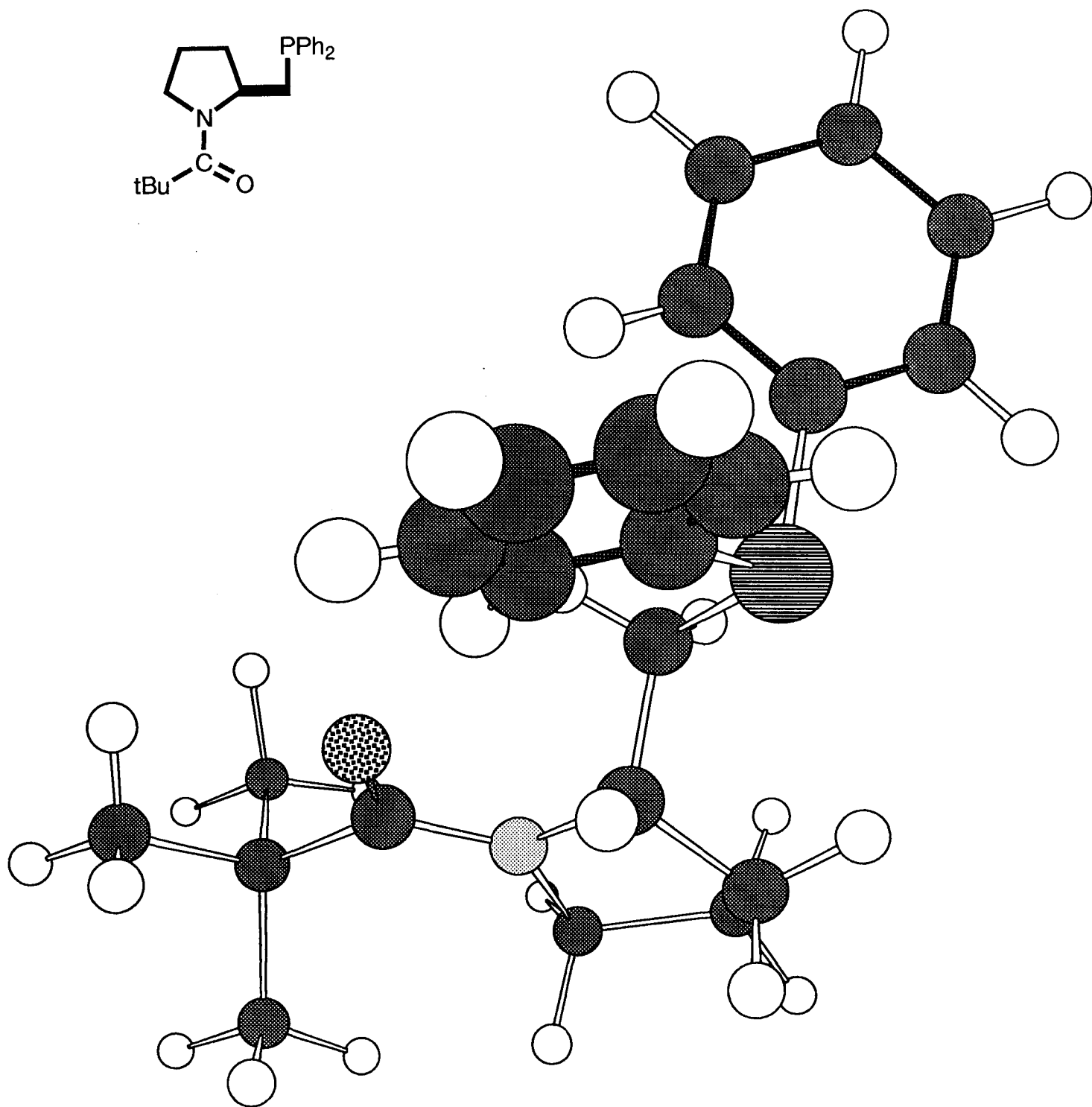
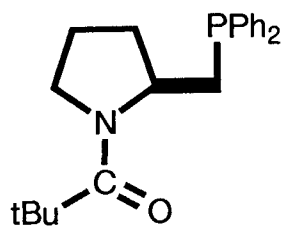
第一の特徴であるシス-コンフィギュレーションのアミド結合は溶液中でも安定系として存在することがNMRのNOE実験から確認された (Figure 7)。

Figure 7.



第二の特徴であるリンのローンペアアがアミド酸素と逆を向いていることは、炭素-炭素結合がアンチにつながった安定コンフォメーションとして予想できる。この特徴ゆえにカルボニル酸素とリンが1つの金属に7員環キレート型の錯体をつくらずに、2種類の金属に対し1座型で配位する形の錯体を作りやすいと考えられる。

Figure 6.



Atom	Bond Atom	Bond Length	Angle Atom	Dist. Angle	Third Atom	Second Angle	Angle Type
C(14)							
P(1)	C(14)	1.837					
C(20)	P(1)	1.831	C(14)	102.334			
C(4)	P(1)	1.840	C(14)	98.767	C(20)	104.431	Pro-R
C(5)	C(4)	1.546	P(1)	112.616	C(14)	-172.505	Dihedral
N(3)	C(5)	1.490	C(4)	109.900	P(1)	-173.207	Dihedral
C(6)	C(5)	1.522	N(3)	103.118	C(4)	112.817	Pro-S
C(7)	C(6)	1.529	C(5)	103.606	N(3)	-31.800	Dihedral
C(8)	N(3)	1.488	C(5)	111.254	C(6)	12.993	Dihedral
C(9)	N(3)	1.361	C(5)	119.138	C(8)	129.358	Pro-R
C(10)	C(9)	1.551	N(3)	120.697	C(5)	178.483	Dihedral
O(2)	C(9)	1.219	N(3)	118.611	C(10)	120.678	Pro-S
C(11)	C(10)	1.557	C(9)	105.391	O(2)	10.225	Dihedral
C(12)	C(10)	1.538	C(9)	109.837	C(11)	109.652	Pro-R
C(13)	C(10)	1.538	C(9)	113.759	C(11)	107.335	Pro-S
C(15)	C(14)	1.359	P(1)	119.166	C(4)	112.941	Dihedral
C(19)	C(14)	1.394	C(15)	118.416	P(1)	122.289	Pro-S
C(16)	C(15)	1.405	C(14)	120.493	C(19)	0.000	Dihedral
C(17)	C(16)	1.374	C(15)	120.965	C(14)	0.949	Dihedral
C(18)	C(19)	1.412	C(14)	119.778	C(15)	-0.448	Dihedral
C(21)	C(20)	1.396	P(1)	116.866	C(4)	178.023	Dihedral
C(25)	C(20)	1.390	C(21)	117.522	P(1)	125.595	Pro-R
C(22)	C(21)	1.414	C(20)	119.419	C(25)	2.918	Dihedral
C(23)	C(22)	1.346	C(21)	122.200	C(20)	-2.282	Dihedral
C(24)	C(25)	1.398	C(20)	121.040	C(21)	-2.348	Dihedral
H(26)	C(4)	1.075	P(1)	109.552	C(5)	108.897	Pro-R
H(27)	C(4)	1.097	P(1)	108.535	C(5)	109.697	Pro-S
H(28)	C(5)	1.098	N(3)	115.658	C(4)	107.255	Pro-R
H(29)	C(6)	1.070	C(5)	113.081	C(7)	110.566	Pro-S
H(30)	C(6)	1.155	C(5)	111.126	C(7)	112.077	Pro-R
H(31)	C(7)	1.121	C(6)	110.689	C(8)	109.655	Pro-R
H(32)	C(7)	1.058	C(6)	113.282	C(8)	113.838	Pro-S
H(33)	C(8)	1.103	N(3)	112.874	C(7)	111.345	Pro-S
H(34)	C(8)	1.106	N(3)	112.079	C(7)	108.846	Pro-R
H(45)	C(11)	1.074	C(10)	109.732	C(9)	-178.904	Dihedral
H(46)	C(11)	1.033	C(10)	111.196	H(45)	110.339	Pro-R
H(47)	C(11)	1.034	C(10)	109.886	H(45)	108.423	Pro-S
H(48)	C(12)	1.063	C(10)	111.964	C(9)	-178.584	Dihedral
H(49)	C(12)	1.062	C(10)	109.902	H(48)	108.253	Pro-R
H(50)	C(12)	1.078	C(10)	112.387	H(48)	105.321	Pro-S
H(51)	C(13)	1.094	C(10)	110.460	C(9)	178.817	Dihedral
H(52)	C(13)	1.086	C(10)	112.376	H(51)	105.954	Pro-R
H(53)	C(13)	1.077	C(10)	110.225	H(51)	109.217	Pro-S
H(35)	C(15)	1.139	C(14)	116.915	C(16)	122.568	Pro-R
H(36)	C(16)	1.113	C(15)	119.500	C(17)	119.517	Pro-R
H(37)	C(17)	1.130	C(16)	120.416	C(18)	120.682	Pro-S
H(38)	C(18)	1.091	C(17)	118.333	C(19)	120.180	Pro-S
H(39)	C(19)	1.088	C(14)	118.783	C(18)	121.383	Pro-S
H(40)	C(21)	1.112	C(20)	118.814	C(22)	121.680	Pro-R
H(41)	C(22)	1.043	C(21)	117.977	C(23)	119.820	Pro-R
H(42)	C(23)	1.114	C(22)	120.491	C(24)	120.725	Pro-R
H(43)	C(24)	1.097	C(23)	117.213	C(25)	121.750	Pro-S
H(44)	C(25)	1.066	C(20)	120.080	C(24)	118.863	Pro-S

第3章 リチウムクプレートの不斉共役付加反応

1. 金属選択的配位能と不斉誘起能の相関

第2章3節で述べた NMR 実験から、キラル配位子 2 はリンが銅、カルボニル酸素がリチウムにそれぞれ選択的に配位する金属選択的配位能をもつのに対し、1 はリンと窒素が金属に非選択的配位することが明らかとなった。対照的な性格を持つ 2 と 1 を用い、リチウムジメチルクプレートのカルコンへの付加反応の系で金属選択的配位能と不斉誘起能の相関を評価した (Table 2)。

Table 2. Asymmetric Addition of Lithium Diorganocuprate to Chalcone in Ether Solvent^a

run	ligand	R ¹	yield/%	ee/%
1	1	Me	89	2
2	2	Me	79	84
3 ^b	2	Me	89	60
4	2	vinyl	67	73
5	2	Bu	97	24
6	3	Me	88	71
7	3	Bu	88	19
8	4	Me	88	67
9	4	Bu	88	16
10	5	Me	72	40
11	5	Bu	87	59
12	6	Me	84	54
13	6	Bu	92	2
14	7	Me	75	20
15	7	Bu	83	9
16	8	Me	89	37
17	8	Bu	95	6
18	9	Me	80	8
19	9	Bu	68	1

R

1: Me
 2: tBuCO
 3: (Me₂N)₂PO
 4: Me₂NCO
 5: C₆F₅CO
 6: PhCO
 7: 1-NaphCO
 8: CF₃CO
 9: Ts

a. Absolute configuration was determined by optical rotation; 47; Leitereg, T. J.; Cram, D. *J. J. Am. Chem. Soc.* **1968**, *90*, 4011. 48; Ahlbrecht, H.; Sommer, H. *Chem. Ber.* **1990**, *123*, 829. 49 was reduced to ethyl derivative; Soai K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571.

b. Methyllithium lithium bromide complex was used.

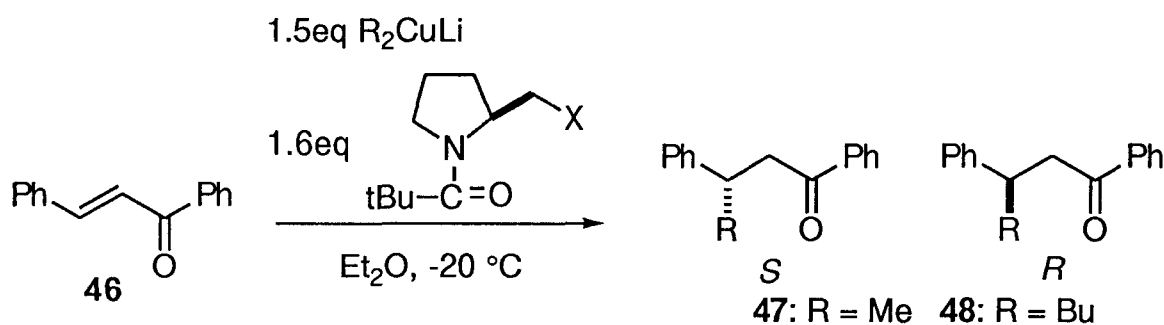
反応はカルコンに対し 1.5 当量のリチウムジメチルクプレートと 1.6 当量のキラル配位子を用い -20 度ですみやかに進行した。金属選択的配位能をもつと考えられる 2 では

84% eeと高い不斉誘起がみられたのに対し、金属選択的配位能のない **1** では2% eeとほとんど不斉誘起がみられなかった。以上の結果から金属選択的配位が不斉誘起を生ずるための必要条件であることがわかった。メチルリチウムはハライドフリーを用いた方が高い選択性が得られた (run 3)。構造的に **2** と類似したキラル配位子 **3**~**8** も不斉誘起能をもつことがわかった。

アルキル基の検討を行ったところ、リチウムジビニルクプレートも同様に反応し73% eeでメチル基と同じ面から付加がおこったのに対し、ブチル基の導入は24% eeと選択性が悪かった。この傾向は **5** 以外のキラル配位子に共通であったが、パーフルオロベンゾイル基を持つ **5** ではブチル基の導入の方が選択性が良かった。

次に銅への配位部位と考えられるリンをイオウ、チッソ、酸素に変えた**10**~**13**で反応をおこなった (Table 3)。その結果ホスフィン以外の配位子では不斉誘起がほとんど見られず、リンが銅に対してすぐれた配位力を持っていることがわかった。

Table 3. Asymmetric Addition of Lithium Cuprate



run	ligand	X	R	yield/%	ee/%	S/R
1	2	PPh ₂	Me	79	84	<i>S</i>
2	2	PPh ₂	Bu	97	24	<i>S</i>
3	10	SMe	Me	99	4	<i>R</i>
4	10	SMe	Bu	95	7	<i>R</i>
5	11	SPh	Me	91	4	<i>S</i>
6	11	SPh	Bu	96	1	<i>S</i>
7	12	NPh ₂	Me	88	2	<i>R</i>
8	12	NPh ₂	Bu	96	0	—
9	13	OMe ^a	Me	89	4	<i>R</i>
10	13	OMe ^a	Bu	79	7	<i>S</i>

a. Solvent was toluene-ether(11 : 1)

2. 基質の検討 (Table 4)

*s-cis*に固定されていると考えられるフェニルケトンで二重結合の先の置換基をフェニル、ブチル、メチルと変化させてクプレートの付加を行った。置換基が立体的に大きなフェニ

ル、ブチルのときは50% ee以上の不斉誘起が得られるのに対し、小さなメチルでは顕著な不斉誘起は見られなかった。基質のこの部位の立体的な大きさが不斉誘起に必須であることをしめしている。注目すべき点は基質50へのメチルクプレート、フェニルクプレートの付加の方向とビニルクプレートの付加の方向が逆になっていることであるが、原因は不明である。またフェニルケトン以外のケトン、*s-trans*のシクロヘキセノン、およびエステルでは顕著な不斉誘起が起こらないことがわかった。

Table 4 . Asymmetric Addition of Lithium Cuprate

$\text{Ph}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{Ph} \xrightarrow[\text{Et}_2\text{O}, -20^\circ\text{C}]{1.5\text{eq R}^1_2\text{CuLi}, 1.6\text{eq } 2} \text{Ph}-\text{CH}(\text{R}^1)-\text{CH}_2-\text{C}(=\text{O})\text{Ph}$ 46 47: R¹=Me 48: R¹=Bu 49: R¹=vinyl		R ¹	yield/%	ee/%	R/S
		Me	79	84	S
		vinyl ^a	67	73	S
		Bu	97	24	S
$\text{Bu}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{Ph} \xrightarrow[\text{Et}_2\text{O}, -20^\circ\text{C}]{1.5\text{eq R}^1_2\text{CuLi}, 1.6\text{eq } 2} \text{Bu}-\text{CH}(\text{R}^1)-\text{CH}_2-\text{C}(=\text{O})\text{Ph}$ 50 52: R¹=Me 53: R¹=vinyl		R ¹	yield/%	ee/%	R/S
		Me ^b	89	55	R
		vinyl ^c	35	50	S
		Ph	93	17	R
$\text{Me}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{Ph} \xrightarrow[\text{Et}_2\text{O}, -20^\circ\text{C}]{1.5\text{eq R}^1_2\text{CuLi}, 1.6\text{eq } 2} \text{Me}-\text{CH}(\text{R}^1)-\text{CH}_2-\text{C}(=\text{O})\text{Ph}$ 51 54: R¹=vinyl		R ¹	yield/%	ee/%	R/S
		vinyl ^d	46	7	R
		Bu ^b	95	16	S
		Ph	78	0	—

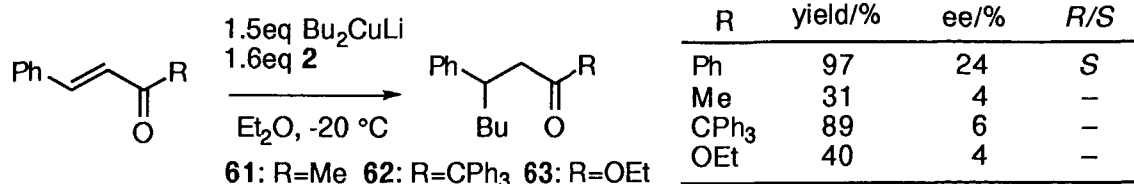
a. Absolute configuration was determined by hydrogenation to ethyl derivatives by palladium on carbon. Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* 1988, 1571. Ee was determined by chiral HPLC. See experimental section.

b. Absolute configuration and optical yield were determined by ruthenium catalyzed oxidation to carboxy acid. Levene, P. A.; Marker, R. E. *Biol. Chem.* 1932, 95, 1.

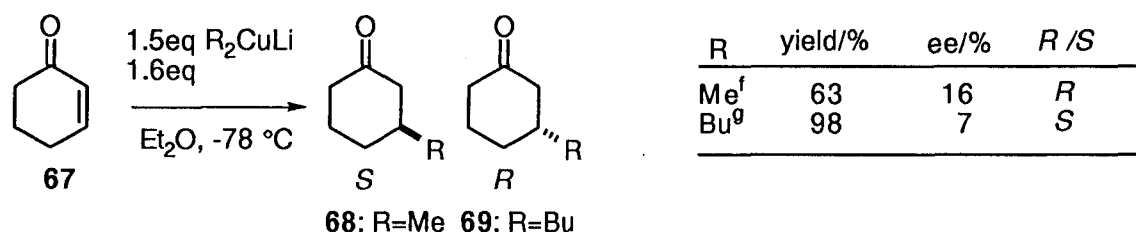
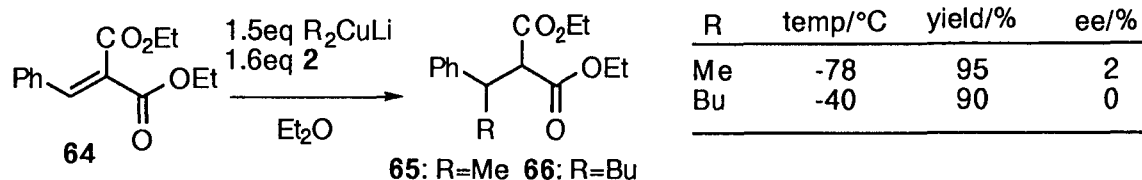
c. Absolute configuration and optical yield were determined by Raney nickel catalyzed hydrogenation and ruthenium catalyzed oxidation to carboxylic acid. Meyers, A. *et al. J. Org. Chem.* 1979, 44, 2250.

d. Absolute configuration and optical yield were determined by Raney nickel reduction. Heppka, G.; Marshall, H.; Nurnberg, P.; Oestreicher, F.; Scherowsky, G. *Chem. Ber.*, 1981, 114, 2501.

$\text{Ph}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{R} \xrightarrow[\text{Et}_2\text{O}, -20^\circ\text{C}]{1.5\text{eq Me}_2\text{CuLi}, 1.6\text{eq } 2} \text{Ph}-\text{CH}(\text{Me})-\text{CH}_2-\text{C}(=\text{O})\text{R}$ 55: R=Me 56: R=CPh₃ 58: R=Me 59: R=CPh₃ 57: R=OEt 60: R=OEt		R	yield/%	ee/%	R/S
		Ph	79	84	S
		Me ^e	10	13	R
		CPh ₃	96	2	—
		OEt	0	—	—



e. Gustafsson, B. *Tetrahedron*, 1978, 34, 3023.



f. Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* 1981, 37, 3601.

g. Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* 1986, 108, 7114.

3. クプレートの検討 (Table 5)

Table 5. Asymmetric Addition of Cuprate

<chem>Ph-CH=CH-C(=O)Ph</chem>		Cuprate		<chem>Ph-CH(R)-CH_2-C(=O)Ph</chem>	
46		Et ₂ O, -20 °C		47: R=Me 48: R=Bu	
Cuprate(eq)	ligand(eq)	yield/%	ee/%		
TMS—≡—CuMeLi (1.5)	(1.6)	9	94		
TMS—≡—CuMeLi (5)	(5.1)	82	54		
TMS—≡—CuBuLi (5)	(5.1)	80	36		
PhSCuBuLi	(5.1)	82	23		
Me ₂ CuCNLi ₂	(1.6)	55	1		

Lower order 型のミックスドクプレート、あるいはヘテロクプレートによる不斉反応を検討したが反応性が悪く、不斉誘起も高くなかった。アセチレニルクプレートを 1.5 当量用いたときの反応で 94% ee が得られているが、これは生成したエノレートが原料にマイケル付加し二量化が主に進行し ee の濃縮が occurring しているためであることが 5 当量用いたときの実験から明らかになった。Higher order 型シアノクプレートでも不斉誘起は見られな

かった。これは銅の電子密度が高くなっているためにキラル配位子のリンが配位できなくなったためと考えられる⁸。

4. 反応の濃度効果、温度効果 (Table 6)

エーテル溶媒中、反応系は懸濁液であるが (0.07M)、5 倍に薄めることで溶液になる (0.012M)。しかし希釈することにより立体選択性は低下することがわかった。また反応温度を-20度から-40度にさげることによる立体選択性の上昇はみられなかった。

Table 6. Asymmetric Addition of Lithium Cuprate; Effect of Concentration and Temperature

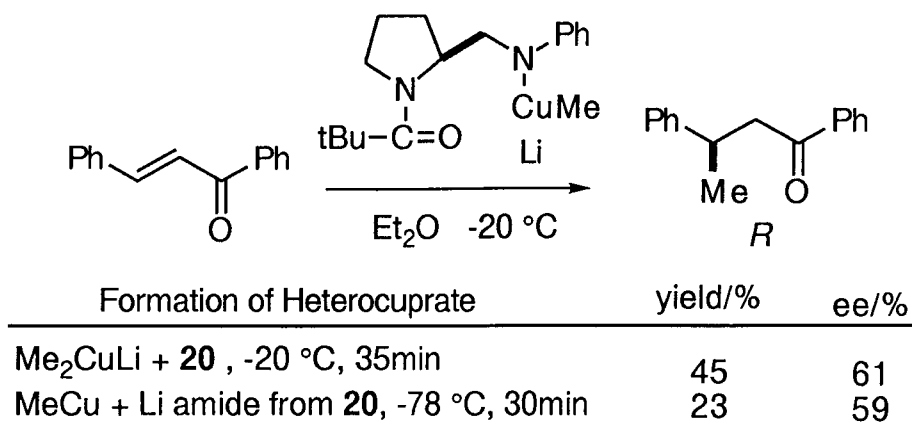
conc/M	temp/°C	yield/%	ee/%
0.07	-20	79	84
0.012	-20	82	61
0.07	-40	69	82
0.07	0	90	76

5. ヘテロkupレートによる検討 (Table 7)

Table 7. Addition of Heterocuprate to Chalcone

run	solvent	temp/°C	time/h	conc/M	yield/%	ee/%
1	Et ₂ O	-78	4	0.07	32	87
2	Et ₂ O	-60	17	0.07	39	76
3	Et ₂ O	-20	1	0.07	30	73
4	Et ₂ O	-78	4.5	0.2	26	54
5 ^a	Et ₂ O	-78	4	0.07	38	80
6 ^b	Et ₂ O	-78	2	0.07	26	75
7	THF	rt	0.8	0.07	3	0

a. 12eq of cuprate was used. b. Methyl lithium lithium bromide complex was used.



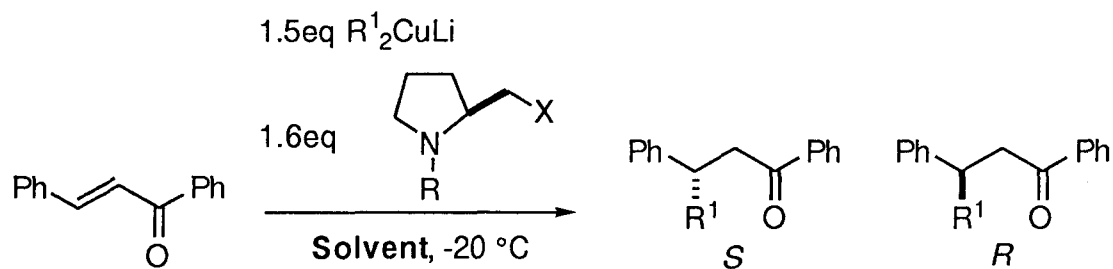
カルコンへのメチル基の導入をキラルアミドクプレートで行った。その結果、最高 87% eeという高い ee がえられるものの、おそらくクプレートの不安定性により収率が 40% 程度にとどまった。クプレートの安定性を上げる目的でより pKa の小さなプロトン酸の共役塩基であるアニリンをキラル配位子として用いたが収率の上昇は見られなかった。

6. 面選択の溶媒依存性 (Table 8)

反応溶媒の検討を行ったところ、エーテル、トルエン、ジメチルスルフィド中ではほとんど同じ反応性（反応時間 1 h）、立体選択性であったのに対し、THF、DME といったリチウムへの配位力の強い溶媒中では反応が遅くなり（反応時間 4 h）、立体選択性が逆転した。この興味深い現象は、2`4 のキラル配位子について一般的であることがわかった。特に、3 や 4 では溶媒によるほぼ完全な選択性の逆転がみられた。この原因を NMR を用いて調べた (Table 9)。

THF-*d*₈ 溶媒中において過塩素酸リチウムを加えてもキラル配位子 2 のカルボニル炭素を含むすべての炭素及びリンにおいて化学シフトの顕著な変化は認められなかった。これはリチウムへの配位力の強い THF 中では、溶媒和によりキラル配位子カルボニル酸素のリチウムへの配位が阻害されているためと考えられる。これに対し、臭化銅を加えたときはカルボニル炭素は変化しなかったものの、リンの結合した C2, 3 で顕著な化学シフト変化がみられ、THF 中においてもリンは銅に配位していることがわかった。³¹P-NMR の化学シフトも 4 ppm の変化が観測されたと同時にその半値幅が 28 Hz から 94 Hz と大きく増大している。これは大きな核四極子モーメントをもつ銅がリン近傍に存在することで緩和が促進されたためと考えられる。実際の活性種であるリチウムジメチルクプレートとの錯体では、カルボニル炭素のシフト変化がほとんどないのでカルボニル酸素はリチウムに配位できないでいると考えられるのに対し、銅のアニオン性を反映してシフト変化は小さくなっているものの C3 で 0.8 ppm の変化がみられ、³¹P-NMR の半値幅が 4.3 Hz から 49 Hz へと増大していることから、リンは銅に配位していると考えられる。すなわち THF 中ではキラル配位子はリンのみが銅に配位する単座型で機能していることが NMR 実験により示された。溶媒による面選択性逆転の原因はキラル配位子の機能がエーテル中の二座型から THF 中の単座型へ転換するためであることが示唆された (Figure 8)。このような反応溶媒依存的な面選択性の逆転はこれまでも報告されているが、本系におけるほど高いレベルでの逆転は知られてなく、その構造論的研究は全くなされていない⁹。

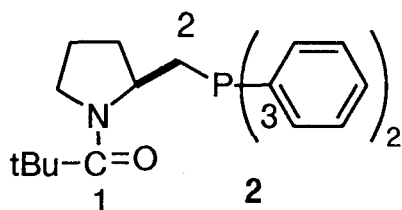
Table 8. Asymmetric Addition of Lithium Cuprate; Solvent Effect



run	ligand	R	X	R ¹	solvent	yield/%	ee/%	S/R
1	2	tBuCO	PPh ₂	Me	Et ₂ O	79	84	S
2	2	tBuCO	PPh ₂	Me	toluene	87	78	S
3	2	tBuCO	PPh ₂	Me	DMS	63	79	S
4	2	tBuCO	PPh ₂	Me	THF	72	50	R
5	2	tBuCO	PPh ₂	Me	DME	34	30	R
6	2	tBuCO	PPh ₂	Me	Et ₂ O-HMPA	3	78	S
7	2	tBuCO	PPh ₂	Bu	Et ₂ O	97	24	S
8	2	tBuCO	PPh ₂	Bu	toluene	35	2	S
9	2	tBuCO	PPh ₂	Bu	THF	39	30	R
10	3	(Me ₂ N) ₂ PO	PPh ₂	Me	Et ₂ O	88	71	S
11	3	(Me ₂ N) ₂ PO	PPh ₂	Me	THF	72	66	R
12	3	(Me ₂ N) ₂ PO	PPh ₂	Bu	Et ₂ O	88	19	S
13	3	(Me ₂ N) ₂ PO	PPh ₂	Bu	THF	59	19	R
14	4	Me ₂ NCO	PPh ₂	Me	Et ₂ O	88	67	S
15	4	Me ₂ NCO	PPh ₂	Me	THF	70	68	R
16	4	Me ₂ NCO	PPh ₂	Bu	Et ₂ O	88	16	S
17	4	Me ₂ NCO	PPh ₂	Bu	THF	78	2	R
18	5	C ₆ F ₅ CO	PPh ₂	Me	Et ₂ O	72	40	S
19	5	C ₆ F ₅ CO	PPh ₂	Me	THF	29	14	R
20	5	C ₆ F ₅ CO	PPh ₂	Bu	Et ₂ O	87	59	S
21	5	C ₆ F ₅ CO	PPh ₂	Bu	THF	40	3	S
22	6	C ₆ H ₅ CO	PPh ₂	Me	Et ₂ O	84	54	S
23	6	C ₆ H ₅ CO	PPh ₂	Me	THF	39	63	R
24	6	C ₆ H ₅ CO	PPh ₂	Bu	Et ₂ O	92	2	S
25	6	C ₆ H ₅ CO	PPh ₂	Bu	THF	71	0	—
26	7	1-NapCO	PPh ₂	Me	Et ₂ O	75	20	S
27	7	1-NapCO	PPh ₂	Me	THF	83	9	S
28	8	CF ₃ CO	PPh ₂	Me	Et ₂ O	89	37	S
29	8	CF ₃ CO	PPh ₂	Me	THF	86	0	—
30	8	CF ₃ CO	PPh ₂	Bu	Et ₂ O	95	6	S
31	8	CF ₃ CO	PPh ₂	Bu	THF	87	0	—
32	9	Ts	PPh ₂	Me	Et ₂ O	80	8	R
33	9	Ts	PPh ₂	Me	THF	68	1	R

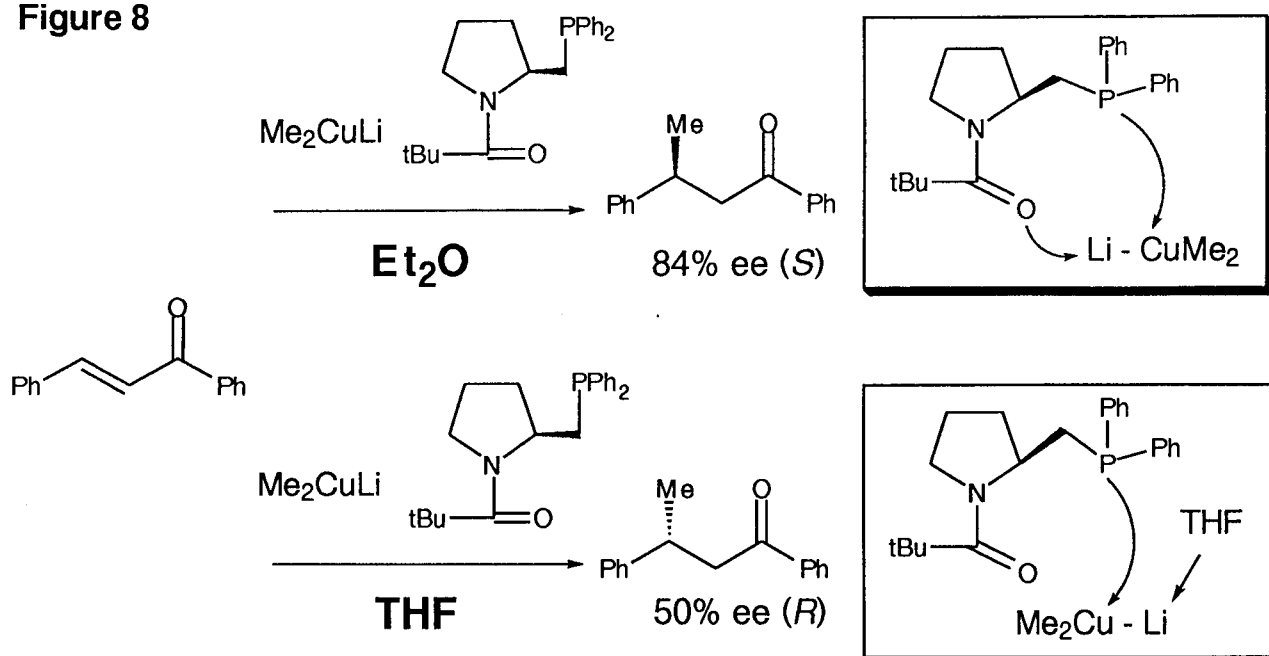
run	ligand	R	X	R ¹	solvent	yield/%	ee/%	S/R
34	10	tBuCO	SMe	Me	Et ₂ O	99	4	R
35	10	tBuCO	SMe	Me	THF	83	1	R
36	10	tBuCO	SMe	Bu	Et ₂ O	95	7	R
37	10	tBuCO	SMe	Bu	THF	67	2	S
38	11	tBuCO	SPh	Me	Et ₂ O	91	4	S
39	11	tBuCO	SPh	Me	THF	79	0	—
40	11	tBuCO	SPh	Bu	Et ₂ O	96	1	S
41	11	tBuCO	SPh	Bu	THF	76	1	R
42	12	tBuCO	NPh ₂	Me	Et ₂ O	88	2	R
43	12	tBuCO	NPh ₂	Me	THF	92	1	S
44	12	tBuCO	NPh ₂	Bu	Et ₂ O	96	0	—
45	12	tBuCO	NPh ₂	Bu	THF	96	0	—
46	13	tBuCO	OMe	Me	toluene	89	4	R
47	13	tBuCO	OMe	Me	THF	78	0	—
48	13	tBuCO	OMe	Bu	toluene	79	7	S
49	13	tBuCO	OMe	Bu	THF	58	1	R

Table 9. ¹³C- and ³¹P-NMR Chemical Changes in THF-*d*₈



	δ(ppm)	+LiClO ₄ δ(ppm)	+CuBr•SMe ₂ δ(ppm)	+Me ₂ CuLi* δ(ppm)
C-1	175.7	+0.3	+0.3	+0.3
C-2	33.7	+0.1	-1.7	-0.4
C-3	(138.8 141.3)	(0 0)	(-6.0 -4.9)	(-0.8 0)
P	-20.0	-0.2	+4.0	-0.2
	(Δ _{1/2} =28Hz)	(Δ _{1/2} =38Hz)	(Δ _{1/2} =94Hz)	
	*(Δ _{1/2} =4.3Hz)		*(Δ _{1/2} =49Hz)	

Figure 8



7. 考察

キラルアミドホスフィン配位子 2 の制御によりリチウムジメチルクプレートはカルコンに付加し、エーテル溶媒中高い選択性で *S*-付加体が得られた。2 による有効な不斉空間は、カルボニル酸素がリチウムにリンが銅にそれぞれ選択的に配位するために構築されることが NMR 実験により明らかになった。この知見をもとに立体選択性発現のモデルを 71 のように仮定した (Figure 9)。リチウムジメチルクプレート二量体の上下から 2 が金属選択的に配位することにより、二量体の下側は下側に配位した配位子によりブロックされ、基質は立体的に最もすいたリチウムと銅の組み合わせの上側でのみ d, π^* 錯体を形成し反応する。このときフェニル基を上側の配位子から遠ざけるようにエキソに出して反応し *S* 体得られる。この部位の立体的な大きさが不斉発現に必須であったことも、このモデルにより説明できる。これに対し、アミノホスフィン配位子 1 は金属選択的配位能を持たないために有効な不斉空間を構築できないと考えられる。

ヘテロクプレートの立体選択性も同様な考え方から説明できる。14 から調製されるキラルアミドクプレートでは (72)、銅の下側の配位部位がホスフィンの配位によりふさがれるために上側のみで d, π^* 錯体形成がおこる。このとき反応部位は 2 つあるが、どちらから反応が進行しても *S*-付加体が生成する。20 から調製されるクプレートでは (73)、二量体の下側は下側のリガンドによりブロックされるために上側のみで d, π^* 錯体形成がおこる。このときフェニル基の立体障害により反応部位は 1 つに決まり *R*-付加体が得られる。

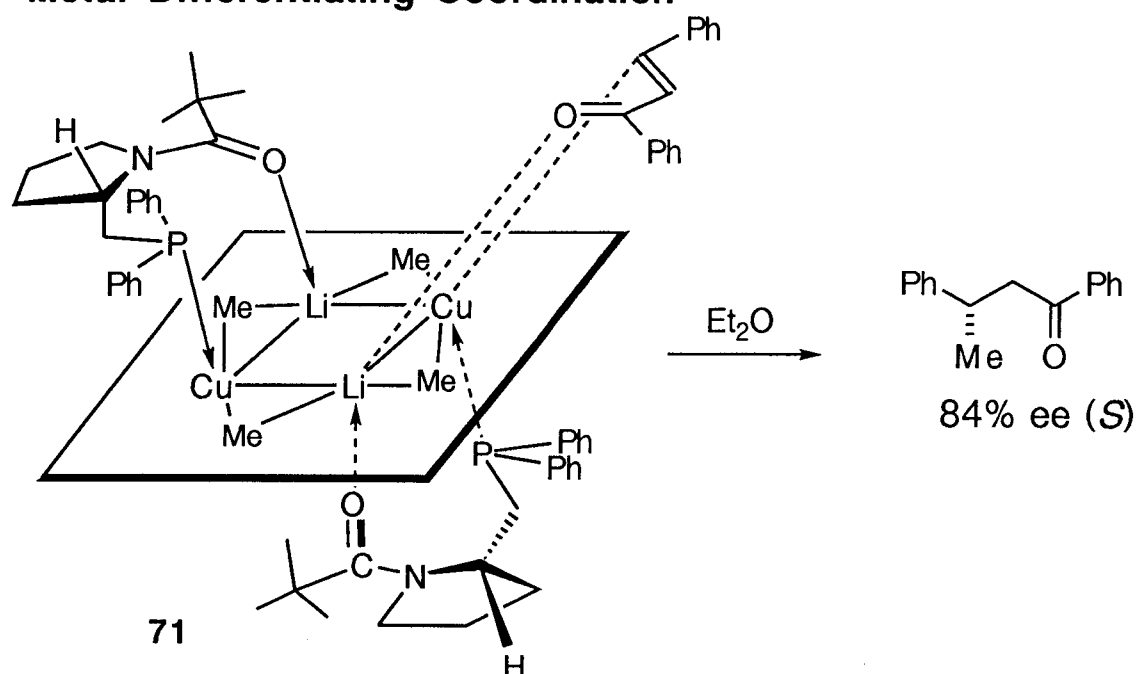
面選択性の溶媒依存の原因について、NMR 実験を行った。リチウムへの配位力の弱いエーテルなどの溶媒中ではキラル配位子のカルボニル酸素とリンが配位原子として働くが、THF などのリチウムへの配位力の強い溶媒中では、キラル配位子カルボニル酸素のリチウムへの配位が溶媒和により阻害され、リンのみが配位原子として働く。すなわち、溶媒のリチウムへの配位力によってキラル配位子が二座型で機能するか、単座型で機能するかの

転換がおこり、面選択の逆転がおこったものと考えられる (Figure 8)。以上の知見をもとに THF 中での生成物の立体化学は 74 のように説明できる。THF 中においてもクプレートの二量体構造が保持されているとすれば、安定コンフォメーションで (第2章、4) キラル配位子のリンが銅に配位すると、立体的にすいた反応部位は2つだけにしぼられ、どちらから反応が進行しても *R* 体が生じる。

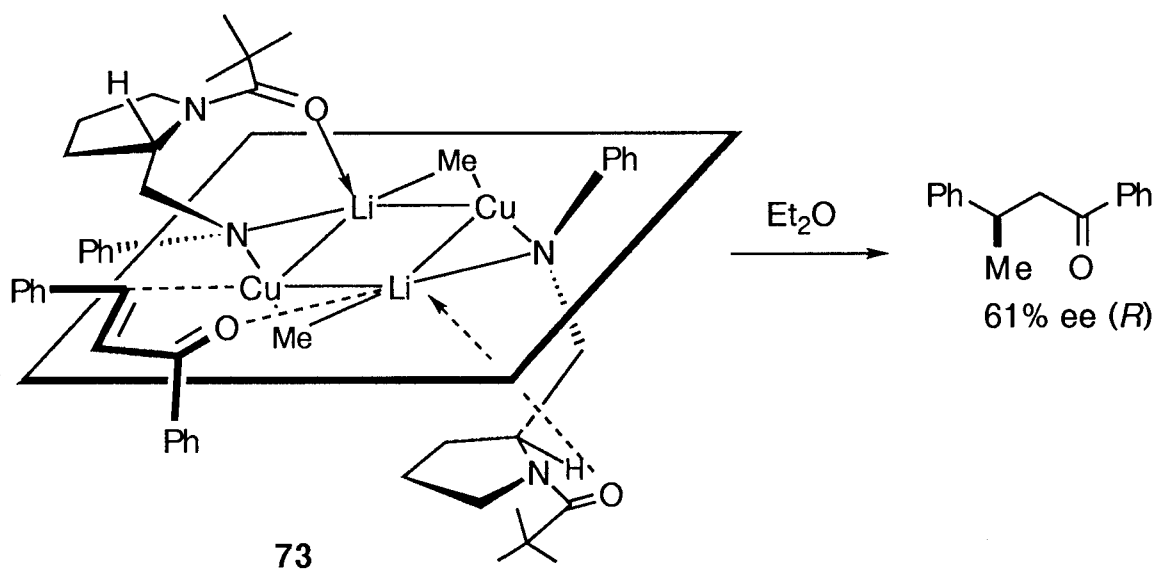
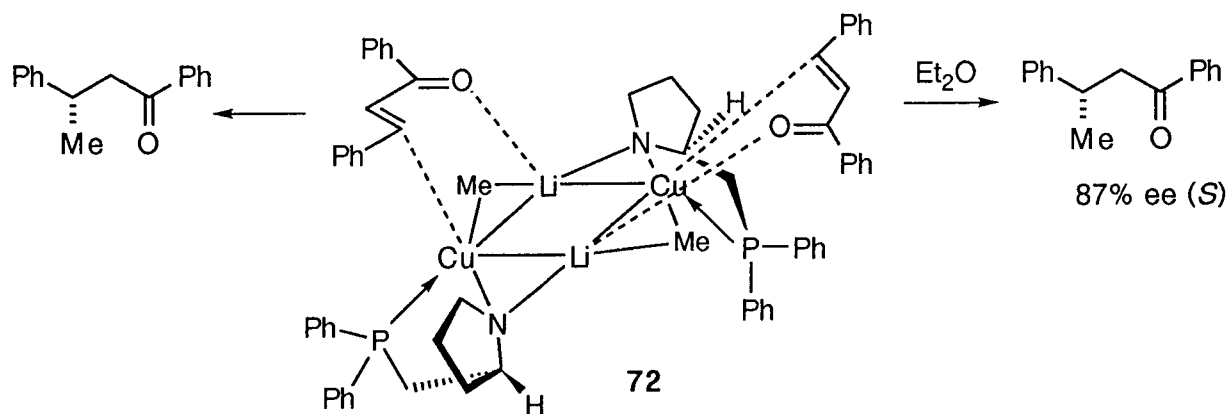
以上の考察から2つの基本概念を提唱することができる。第一は、有機銅-キラル配位子錯体が有効な不斉空間を構築するためには、キラル配位子の2種類の配位原子が電子的にはっきりと性格分けされ、リチウムと銅を見分けて選択的に配位することが必要となる。この金属選択的配位概念は、2種類の配位原子としてカルボニル酸素とリンを用いることで実現されることが明らかとなった。特に形式的に負電荷を持つクプレートの銅への配位原子はリンが際立って優れていることがわかった。また、キラル配位子の安定コンフォメーションがカルボニル酸素のローンペアとリンのローンペアを全く別の方向に向かせていることも、1つの金属へのキレートをおこさず、金属選択的な配位をおこす要因になっていると考えられる。ヘテロクプレートによる反応は2つの配位原子の性格分けの問題を1つのヘテロ原子と銅の結合をつくることで解決していると解釈できる。第二は、反応溶媒によりキラル配位子の機能が二座型から単座型へと転換され、その結果、二種類の不斉空間が一つのキラル配位子から構築できる点である。この溶媒依存的機能転換は、キラル配位子の2種類の配位原子の性格がはっきりと区別されているために可能となる。特に、リンの銅への配位が普通のドナー性溶媒により阻害されないことは他の遷移金属にも応用できると考えられるので、全く新しい反応系への拡張が期待できる。また、遷移金属へ親和性を持ちリチウムへは配位力の弱いアセトニトリルなどの溶媒を使って見るとどういう結果になるか、今後検討していきたい課題である。

Figure 9. Explanation of Enantioselectivity

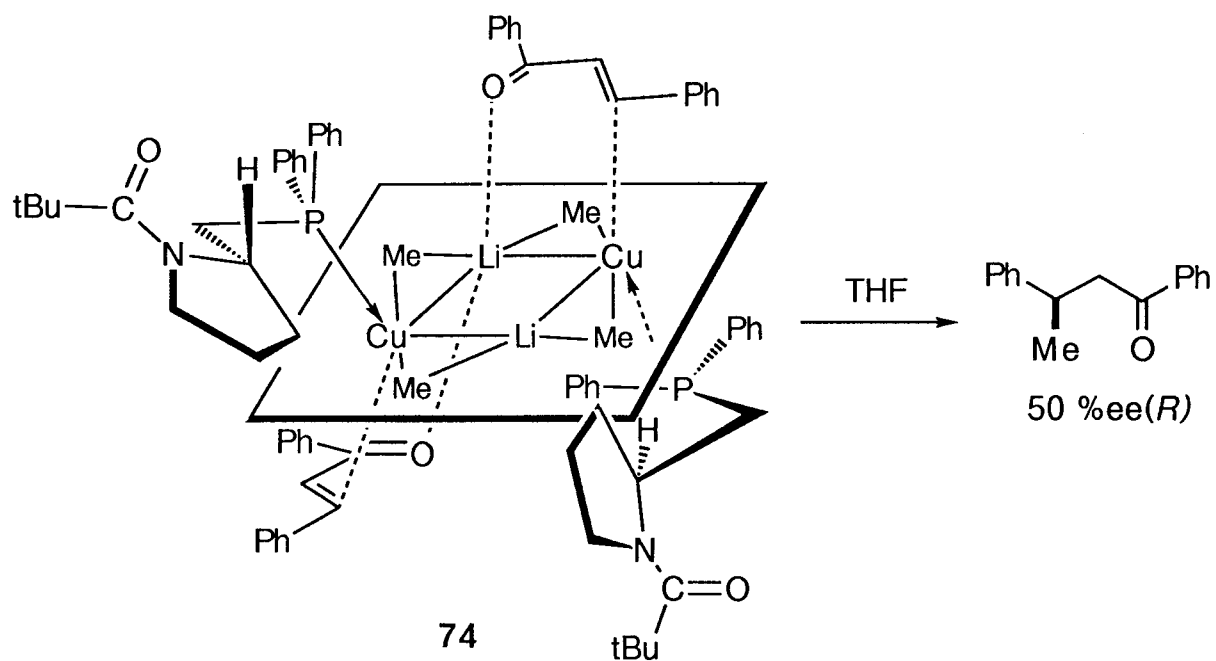
Metal Differentiating Coordination



Asymmetric Addition of Heterocuprates



Explanation of Enantioselectivity in THF Solvent



第4章 リチウムシアノクプレートの不斉共役付加反応

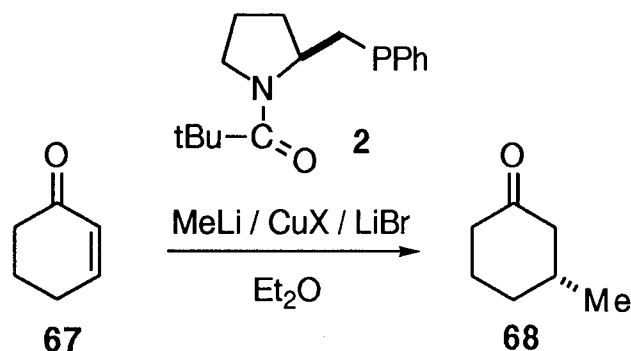
1. 臭化リチウムの添加効果 (Table 10)

金属選択的配位概念がホモクプレートに対する不斉配位子を設計する上で有効であることがわかった。しかし、この不斉空間は *s-trans* の基質には有効でなかった。金属選択的配位概念から設計した配位子の一般性を拡張するために、反応条件の検討を行った。

リチウムジメチルクプレートは、キラル配位子 **2** の制御により -78 度でシクロヘキセノンと反応し 16% ee で付加体を与えた (run 1)。一方、メチル銅では反応性が低下して -20 度で反応が進行したにもかかわらず、26 %ee と選択性の上昇がみられた (run 2)。

リチウムハライドは有機金属試薬の構造、反応性を修飾する 1 つの因子として知られている^{10,11}。また、Alexakis らは、臭化リチウムの添加によりブチル銅のシクロヘキセノンへの付加反応の立体選択性が向上することを報告している⁴。そこで、本反応系における臭化リチウムの添加効果を調べた。臭化リチウムを 3、6、12、24 当量加えるとその当量に応じて選択性は上昇し、12 当量加えたときに、最高 55 %ee が得られた (run 3~7)。臭化リチウムの添加効果は、シアニ化銅を銅源として用いたときにさらに顕著であった。臭化リチウムが存在しないときには、4 %ee で逆配置の付加体を得られたのに対し、12 当量の臭化リチウムを添加したときには 70 %ee まで選択性が上昇した。

Table 10. Asymmetric Addition of Lithium Cuprate to Cyclohexenone: Effect of LiBr



run	CuX(eq)	MeLi/eq	LiBr/eq	2/eq	temp/°C	ee/%	yield/%
1	CuI(1.5)	3	0	1.6	-78	16	63
2	CuI(1.5)	1.5	0	3	-20	26	44
3	CuI(1.5)	1.5	3	3	-20	37	69
4	CuI(1.5)	1.5	6	3	-20	47	83
5	CuI(1.5)	1.5	12	3	-20	55	61
6	CuI(1.5)	1.5	24	3	-20	52	26
7	CuCN(1.5)	1.5	0	3	-20	4 ^a	47
8	CuCN(1.5)	1.5	12	3	-20	70	88

a. The opposite configuration.

2. Additive Salt の効果 (Table 11)

ハロゲン化リチウムの添加が反応性、立体選択性をともに向上させることがわかったので、シクロヘキセノンへのエチルシアノクプレートの付加反応において添加する塩の種類を検討した。エチルシアノクプレートは -78 度で反応が進行し、塩を加えないときは 54 %ee であったのに対し、臭化リチウムを加えると 91 %ee、シアニ化リチウムを加えると 86 %ee で付加体を与えた。反応の様子は塩を加えないときは bright yellow suspension であったのに対し、臭化リチウムを加えたときには colorless clear solution となり活性種の構造が変化したことを示唆している。

Table 11. Asymmetric Addition of Lithium Cyanocuprate to Cyclohexenone: Effect of Added salt

run	Added Salt	ee/%	yield/%
1	none	54	62
2	LiBr	91	89
3	LiCN	86	38
4	LiCl	41	77
5	LiI	14	80
6	Bu ₄ NBr	60	46

3. キラル配位子の当量と立体選択性の相関 (Table 12)

Table 12. Asymmetric Addition of Cyanocuprate: Effect of Ligand Equivalence

1.5 eq MeLi / 1.5eq CuCN /
12eq LiBr / 2

Et₂O -20 °C 1h

run	2/eq to Cu	conc/M	ee/%	yield/%
1	0	0.03	—	87
2	0.2	0.03	4	86
3	1	0.03	24	99
4	2	0.06	69	89
5	2	0.03	70	88
6	3	0.09	76	99
7	6	0.15	80	99

臭化リチウム存在下のリチウムメチルシアノクプレートのシクロヘキセノンへの付加反応において、興味深いキラル配位子の当量と選択性の相関が見られた。銅に対し 1 当量のキラル配位子を用いたときには 24 %ee であったのに対し、2 当量以上用いると明らかに選

択性が向上し、6当量で最高 80 %ee が得られた。濃度を半分にしても同じ選択性が得られることから、この効果は銅-キラル配位子錯体の濃度が上昇するためでないことが明らかになった (run 4, 5)。すなわち、高い立体選択性を持つ活性種の形成には銅に対して2当量以上の配位子が必要であることがわかった¹²。また、キラルホスフィンが存在しなくても同一条件下で収率の大幅な低下が見られないことから、キラル配位子による反応性の顕著な上昇はおこらないことがわかった。以上の結果から予想できるように、キラル配位子を触媒量まで落とすと、選択性は激減した (run 2)。

4. TMSCl の添加効果 (Table 13)

Table 13. Asymmetric Addition of Cyanocuprate: Effect of TMSCl/HMPA

run	R	additives ^a	method ^b	temp/°C	ee/%	yield/%
1	Me	none		-20	76	99
2	Me	TMSCl	A	-78	86	99
3	Me	TMSCl	B	-78	76	62
4	Me	TMSCl/HMPA	A	-78	92	78
5	Me	TMSCl/HMPA	A	-20	80	99
6	Me	HMPA		-20	74	99
7	Me	TMSBr/HMPA	A	-78	40	77
8	Me	TMSI/HMPA ^c	A	-78→-40	64	18
9	Me	TMSOTf/HMPA ^c	A	-78	30	73
10	Me	tBuPh ₂ SiCl/HMPA ^c	A	-78→-20	71	27
11	Et	none		-78	91	89
12	Et	TMSCl/HMPA	A	-78	67	48
13	Bu	none		-78	90	97
14	Bu	TMSCl/HMPA	A	-78	77	96
15	Ph	none		-78	73	63
16	Ph	TMSCl/HMPA	A	-78	29	67

a. TMSCl and HMPA was 3eq to cyclohexenone.

b. Method A; A solution of TMSCl and cyclohexenone was added. Method B; Cyclohexenone was added to the solution of cuprate and TMSCl.

c. Incomplete trapping by silyl reagents.

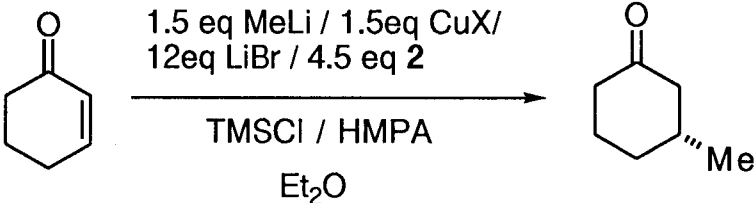
シリル化剤が有機銅の反応を活性化することが知られている¹³。リチウムメチルシアノプレート反応を低温で進行させ選択性を向上させる目的で、シリル化剤の添加を行っ

た。TMSCl と基質を一緒に加えるA法によって -78 度で反応が進行するようになり、86 %ee と選択性の向上が見られた (run 2)。クプレートと TMSCl の溶液に基質を加えるB法よりもA法が優れていることがわかった (run 3)。シリル化剤のトラップ力を高める目的で HMPA の添加を行ったところ、選択性はさらに向上し 92 %ee で付加体を得られた (run 4)。反応温度を下げることで TMSCl/HMPA の主な効果であることがわかった (run 5)。TMSCl 以外のシリル化剤では選択性の向上は見られなかった (run 7~10)。また、もともと反応性の高いエチル、ブチル、フェニルシアノクプレートでは TMSCl/HMPA の添加は逆効果であった。

5. 銅源の効果 (Table 14)

銅源の検討をメチルクプレートの付加反応において検討したところ、シアニ化銅が最も優れていることがわかった。シアネート同様、銅に親和性のあると考えられるチオシアネートでは反応性、選択性ともに低かった。

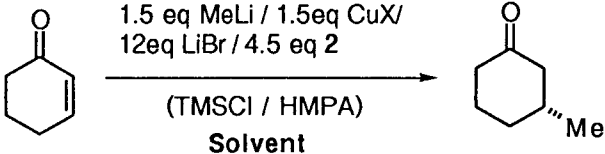
Table 14. Asymmetric Addition of Cyanocuprate: Effect of Cu Source

				
run	CuX	temp/°C	ee/%	yield/%
1	CuCN	-78	92	66
2	CuSCN	-10~0	41	45
3	CuMe(cuprate) ^a	-78	14	81
4	CuBr	-78→-45	45	81

a. Cuprate from CuBr.

6. 溶媒効果 (Table 15)

Table 15. Asymmetric Addition of Cyanocuprate: Solvent Effect

						
run	Solvent	additive	temp/°C	time/min	ee/%	yield/%
1	Et ₂ O	none	-20	30	76	76
2	THF	none	-20	30	27	42
3	Et ₂ O	HMPA	-20	30	74	99
4	THF	HMPA	-20	30	35	79
5	Et ₂ O	TMSCl	-78	15	86	99
6	THF	TMSCl	-78	15	2	99
7	Et ₂ O	TMSCl/HMPA	-78	10	92	66
8	THF	TMSCl/HMPA	-78	10	0	99

反応溶媒はエーテルが THF よりも選択性の面で優れていた。反応性に関しては、ホモクプレートのような低下は見られず、絶対配置も同じであった。また、THF 中では TMSCl の添加により、選択性がなくなった。

7. 基質、付加するアルキル基の検討 (Table 16)

Table 16. Asymmetric Addition of Cyanocuprate: Substrates and Alkylolithiums

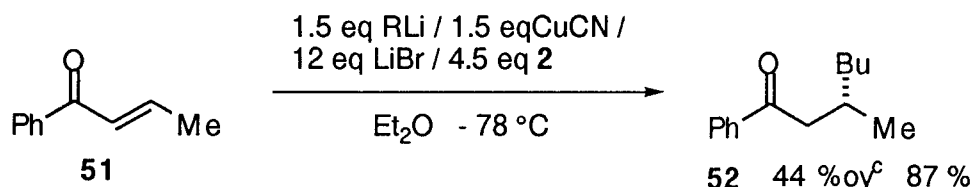
67: n=1
83: n=2
84: n=3

78: n=1, R=Et
79: n=1, R=Bu
68: n=2, R=Me
75: n=2, R=Et
76: n=2, R=Bu
77: n=2, R=Ph
80: n=2, R=vinyl
81: n=3, R=Me
82: n=3, R=Bu

run	n	R	additives	ee/ % ^a	yield/ %
1	1	Et	-	94	90
2	1	Bu	-	95	99
3	2	Me	TMSCl / HMPA	92	66
4	2	Et	-	91	89
5	2	Bu	-	90	97
6	2	Ph	-	60	63
7	2	vinyl	-	44	60
8	3	Me	TMSCl / HMPA	68	46
9	3	Bu	-	74 ^b	92

a. Ee was determined by ¹³C NMR analysis of the corresponding diastereomeric ketals prepared with (*R, R*)-2,3-butanediol. Absolute configuration was determined by optical rotation. Cyclopentanones (3-ethyl: Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401; 3-butyl: Tamura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 4349), Cyclohexanones (3-methyl: Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, *22*, 3601; 3-ethyl, 3-phenyl, 3-vinyl: Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88; 3-butyl: Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114, 3-Methylcycloheptanone: Djerassi, C.; Burrows, B. F.; Overberger, C. G.; Takekoshi, T.; Gutsche, C. D.; Chang, C. T. *J. Am. Chem. Soc.* **1963**, *85*, 949.

b. Absolute configuration was not determined.



c. Optical yield was determined by optical rotation of the corresponding acid obtained by ruthenium catalyzed oxidation. Levene, P. A.; Marker, R. E. *Biol. Chem.* **1932**, *95*, 1.

以上のように最適化した反応条件で基質と付加するアルキル基の検討を行った。*s-trans*の系に対しメチル、エチル、ブチル基が高い選択性で導入でき、一般性も高いことがわかった。基質の環の大きさが小さい方が選択性が高い傾向があった。また、*s-cis*の系 (51) に対してもある程度有効であることがわかった。

8. 考察

反応の条件検討から明らかになった不斉空間構築のための必須条件は、リチウムシアノクプレートに対し過剰の臭化リチウムと2当量以上のキラル配位子である。第3章で仮定したホモクプレートとキラル配位子の構築する不斉空間をこれらの因子が修飾して、有効な不斉空間に変換したものと考えられる。第2章、3章で述べたようにホスフィンがクプレートの銅に配位するので、これが2当量以上必要であるということは、モノメリックな活性種が不斉誘起能が高いことを示唆しているものと考えられる。2当量以上のモノホスフィンによりモノメリックな有機銅が生成することについては、山本らの構造研究の例がある¹⁴。リチウムハライドの効果として、過剰に存在することで溶媒の性質（極性、伝導度など）を変化させて立体選択に有効な活性種を発生しやすくするのか、ミックスドアグリゲート形成により活性種になんらかの形で作用するのかの2つの可能性が考えられる。第一の可能性は加えた塩の検討（Table 11）において立体選択性と塩のモル伝導率¹⁵（in sulfolane 2.41 (LiCl), 9.50 (LiBr), 10.88 (LiI), in propyl carbonate 12.28 (LiCl), 23.41 (LiBr), 26.35 (Bu₄NBr), 単位 $\Lambda/\text{S cm}^2 \text{ mol}^{-1}$, 41%ee (LiCl), 91%ee (LiBr), 14%ee (LiI), 60%ee (Bu₄NBr)）に相関がないことから否定できるであろう。よって、臭化リチウムがクプレートとミックスドアグリゲートを形成し二量体をモノマーへと変換させ易くすると考えられる。

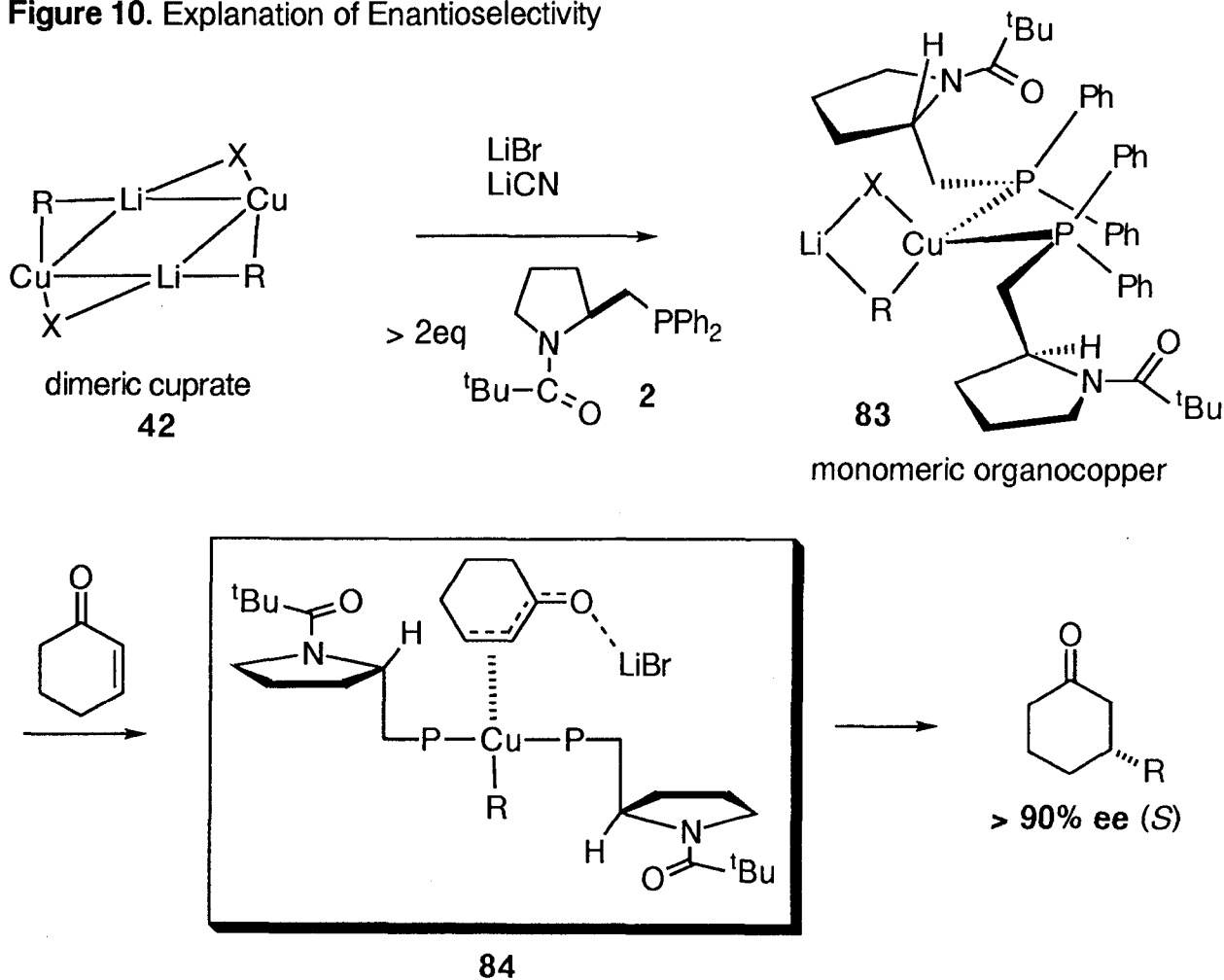
以上のようにモノメリックな活性種が生成したときに、キラル配位子が錯体を形成することによって構築される不斉空間は次のように考えられる（Figure 10）。金属選択的配位によりキラル配位子はリンのみで銅に配位し、カルボニル酸素は過剰に存在する臭化リチウムに配位して安定配座をとっているとすれば、83のような不斉空間が構築される。これはキラル配位子のピロリジン環が銅の上下左右に位置を定めて固定された、C2型の不斉空間である。基質はカルボニル酸素が臭化リチウムに配位して立体的に大きくなっていると考えられるので、こちらを立体障害からはなすように d, π^* 錯体を経由して反応し S-付加体を得られると考えられる。この考え方から基質の環の大きさが小さい方がピロリジン環とのぶつかりが小さくなるので選択性がよくなることが説明できる。

本反応から得られた知見をまとめると、キラル配位子は不斉空間の構築とともに新しい反応活性種の生成という二つの働きを行っていると考えられる。しかし、キラル配位子による反応性の向上は見られず、触媒反応への展開はできなかった。触媒反応と当量反応の結果を比較し、触媒反応の収率 86% のうちリガンド非関与の反応が x%、リガンドが関与した 24%ee の反応が $kx/4\%$ 進行するとして簡単な数式を解くと、リガンド関与の反応速度はリガンド非関与の反応速度の 0.8 倍となる。キラル配位子が有機リチウムの反応の立体制御と反応加速を両立して行い新規な触媒反応系を形成する例としては、富岡らの研究がある¹⁶。

モノメリックなクプレートを安定化させる以上の二つの条件のうちどちらが主たる寄与をしているのかについても、本反応の検討結果から明らかになった。臭化リチウム非存在下、2当量のキラルホスフィンが存在する反応は（Table 10, run 7）、収率 47%、4%ee と反応性、選択性ともに悪く、有効な活性種が形成されていない。それに対し、キラル配位子が存在せず、臭化リチウムが存在する反応では（Table 12, run 1）、収率 87% と反応性は明らかに向上しており、新しい活性種が生成されていることを示している。従って、臭化リチウムの効果が有効な活性種生成に主たる寄与をしていると考えられる。

本反応系は種々のシクロアルケノンに対しある程度一般性のあるアルキル基を極めて高い選択性で導入できる点で非常に優れた反応である。さらに、キラルホスフィンの当量、リチウムハライドの効果、TMSClの効果について興味深い仮説や疑問点を投げかけている。以上の点についての構造論的アプローチは今後の課題である。

Figure 10. Explanation of Enantioselectivity

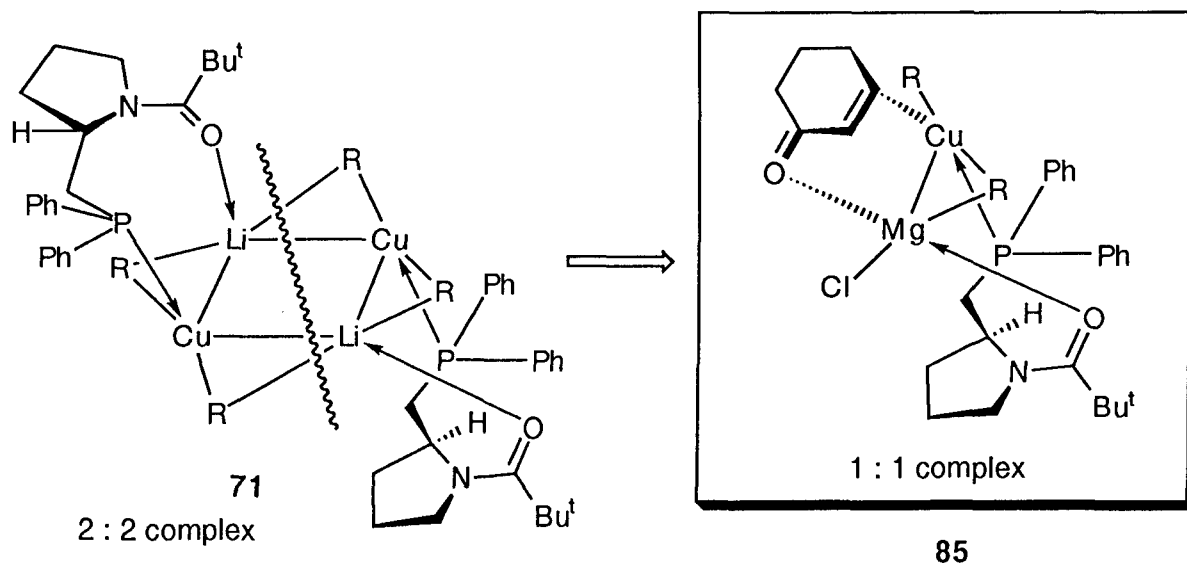


第5章 マグネシウム Kuprate の不斉共役付加反応

1. 反応系の設計

第3章で述べたホモ Kuprate-キラル配位子錯体の反応とキラルヘテロ Kuprate の反応の立体選択性が同一の考え方から説明できることは、この考え方が新しい反応系の設計に応用できる可能性を示唆している。リチウム Kuprate では sp^3 混成にあるリチウムの4つの空軌道のうち2つはキラル配位子のカルボニル酸素、基質のカルボニル酸素でしめられるが、残りの2つの空のままなので二量体を形成し 71 のような形で反応すると想定できた。リチウムのかわりに2価の金属を用いると、4つの空軌道のうち3つがキラル配位子のカルボニル酸素、基質のカルボニル酸素、対アニオンによりしめられるので、残り1つのアルキル基としか結合できず会合状態を形成せずにモノマーで反応すると考えられる。すなわち、マグネシウム Kuprate を用いることで当量以上のキラル配位子や臭化リチウムの助けなしにモノメリックな活性種を発生させることができ、これによって新しい不斉空間の構築が可能になると期待し検討を始めた。

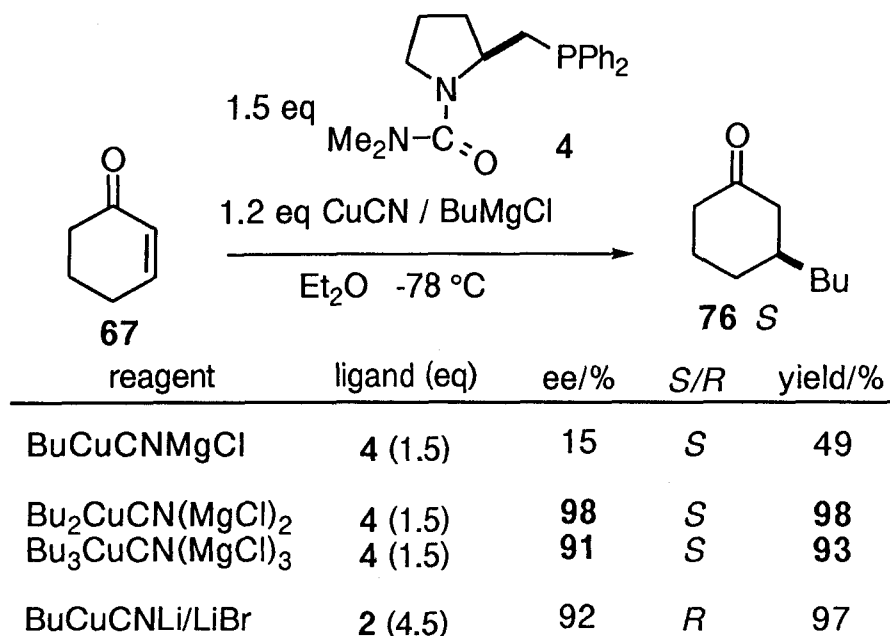
Figure 11. Design of Asymmetric Field Utilizing Magnesium Cuprate



2. マグネシウム Kuprate の反応 (Table 17)

反応はシクロヘキセノンに対して1.2当量のジブチルシアノマグネシウム Kuprate、1.5当量のキラル配位子 4 を用いてエーテル溶媒中 -78 度で瞬時に進行した。立体選択性と反応性は、銅とグリニャール試薬の比率に依存しており、1:1 のときは 15 %ee, 49% 収率であったのに対し、1:2 のとき 98 %ee, 1:3 のとき 91 %ee ときわめて高い選択性で S 体が得られることがわかった。選択される面はリチウムシアノ Kuprate のときと逆であり、単一のキラル源を用いて両エナンチオマーの作りわけが高いレベルで可能となった。

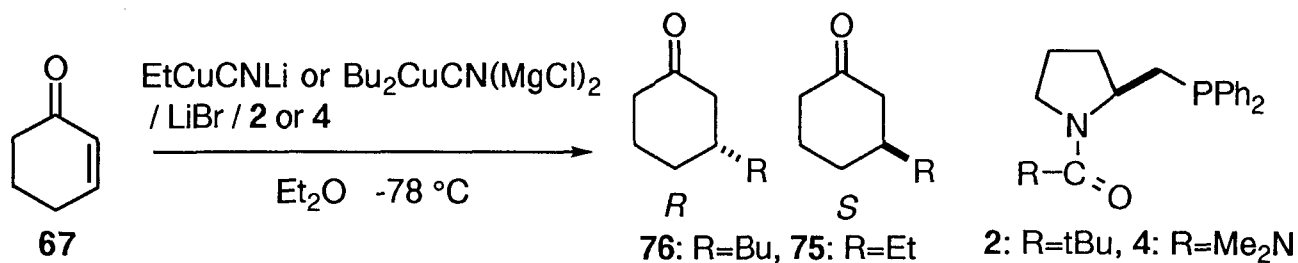
Table 17. Asymmetric Addition of Magnesiumcuprate



3. 臭化リチウムの効果 (Table 18)

リチウムシアノクプレートの反応において立体選択性発現に必須であった臭化リチウムはモノメリックな活性種の発生に寄与していると考えられたので、マグネシウムクプレートではあまり重要でないと予想できる。実際マグネシウムクプレートで 98 %ee と高い選択性が得られる系に 9.6 当量の臭化リチウムを添加すると 79 %ee まで選択性が低下した。これはマグネシウムに配位すべきキラル配位子のカルボニル酸素が、過剰のリチウムに配位してしまい有効な不斉空間が構築できなくなったためと考えられる。

Table 18. Asymmetric Addition of Magnesium Cuprate: Effect of Lithium Bromide



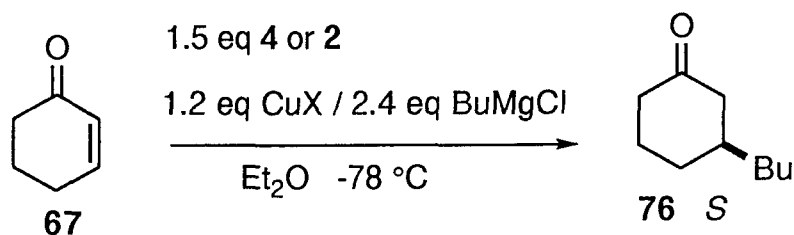
reagent (eq)	ligand (eq)	LiBr/eq	ee/%	R/S	yield/%
Bu ₂ CuCN(MgCl) ₂ (1.2)	4 (1.5)	0	98	S	98
Bu ₂ CuCN(MgCl) ₂ (1.2)	4 (1.5)	9.6	79	S	79
EtCuCNLi (1.5)	2 (4.5)	0	54	R	62
EtCuCNLi (1.5)	2 (4.5)	12	91	R	89

4. 銅源の検討 (Table 19)

銅源の検討を行ったところシアニ化銅が最も高い選択性を与えた。しかし、リチウムシアノクプレートで見られたほど顕著な効果はなく、ヨウ化銅、臭化銅でも高い選択性が見

られた。

Table 19. Asymmetric Addition of Magnesiumcuprate: Effect of Copper Source



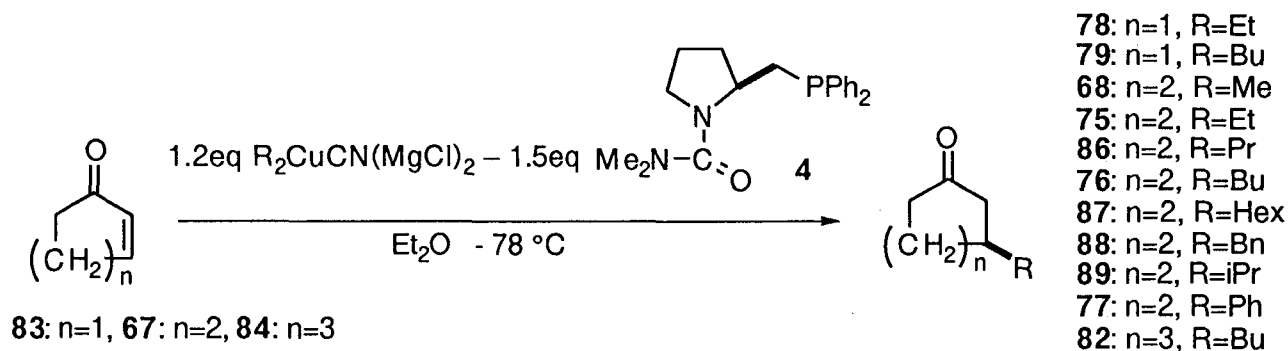
run	ligand	CuX	ee/%	yield/%
1	4	CuCN	98	98
2	4	CuI	90	99
3	4	CuBr	76	80
4	2	CuCN	89	94
5	2	CuI	86	91

5. 基質と付加するアルキル基の検討 (Table 20)

以上のような最適化された反応条件で基質と付加するアルキル基の検討を行った。シクロペンテノンの反応は収率、選択性ともに悪かったが、シクロヘキセノン、ヘプテノンに対しては直鎖のアルキル基を良い選択性、収率で導入することができた。生成物の絶対配置は既知のものに関してすべてリチウムシアノクプレートの反応と逆であった。分枝アルキル基、およびフェニル基の導入は選択性、収率ともに悪かった。*s-cis* の系 (2-pentenophenone 51) には適用できなかった。

以上まとめると、マグネシウムクプレートの反応はリチウムクプレートの反応ほど適用範囲は広くないが逆の面選択性を有し、中でもブチル基の導入は 98 %ee ときわめて高い選択性で達成できた。

Table 20. Asymmetric Addition of Magnesiumcuprate



run	Substrate	R	ee/% ^a	R/S	cy/%	RLi conditions		
						ee/%	R/S	cy/%
1	83	Et	21	S	10	94	R	90

2	83	Bu	22	<i>S</i>	36	97	<i>R</i>	99
3	67	Me	7	<i>S</i>	22	96	<i>R</i>	66
4	67	Et	75	<i>S</i>	63	91	<i>R</i>	89
5	67	Pr	83	— ^b	63			
6	67	Bu	98	<i>S</i>	98	92	<i>R</i>	97
7	67	Hex	94	— ^b	73			
8	67	PhCH ₂	53	— ^b	61			
9	67	iPr	15	— ^b	40			
10	67	Ph	19	<i>R</i>	20	60	<i>R</i>	63
11	84	Bu	82	— ^c	61	74	— ^d	92
12	51	Bu	1	<i>R</i>	67	44	<i>S</i>	87

a. *Ee* was determined by ¹³C NMR analysis of the corresponding diastereomeric ketals prepared with (*R, R*)-2, 3-butanediol. Absolute configuration was determined by optical rotation. See Table 16.

b. Absolute configuration was not determined.

c. The sign of optical rotation was minus.

d. The sign of optical rotation was plus.

6. 考察

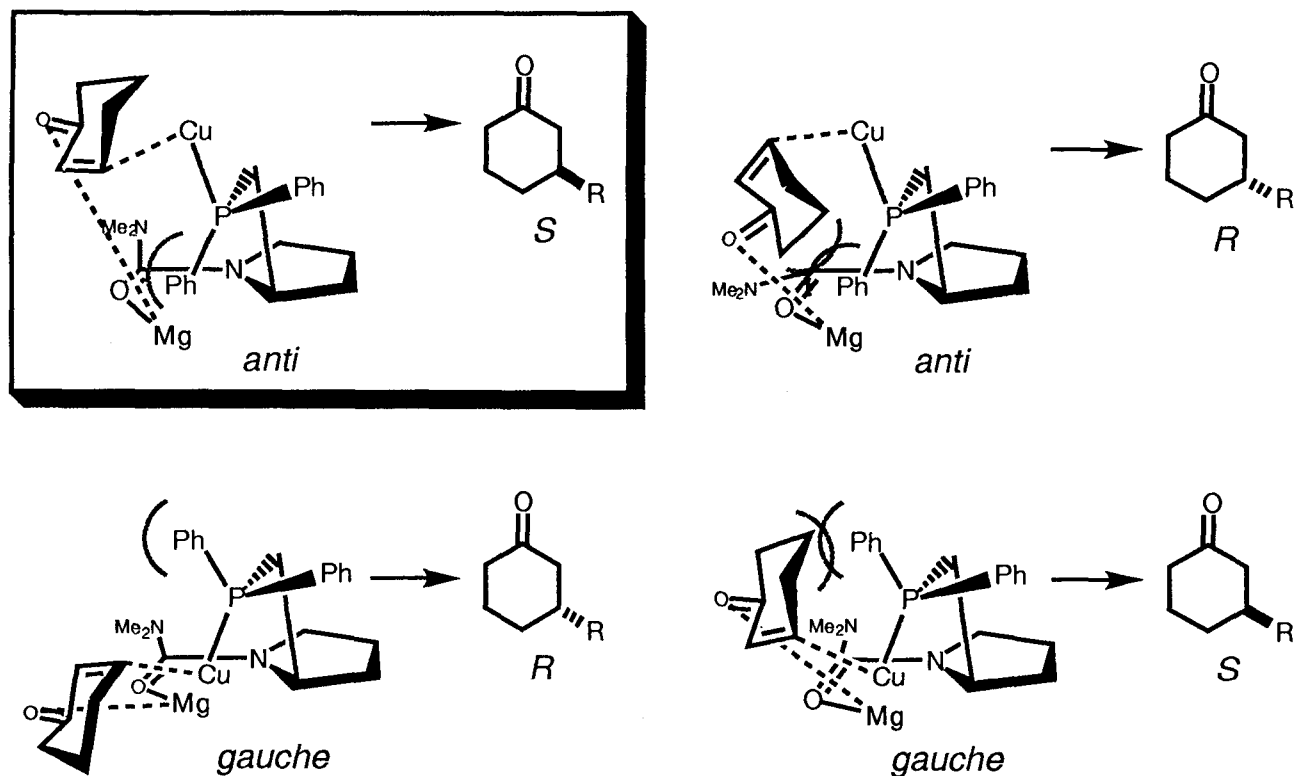
臭化リチウムの添加が選択性に良い影響を及ぼさないことと銅源あるいはトランスメタル化によって生成する MgX₂ が選択性に大きな影響を与えないことは、活性種がモノメリックであると考えることと矛盾しない。なぜなら、第4章でのべたようにこれらの効果がモノメリックな活性種を安定化させることだと仮定すると、マグネシウムクプレートの場合は第1節で示した立体電子的要請によりもともとモノマーとして反応するので、これらの効果が顕著に現われてこないものと説明できるからである。

反応がモノマーから進行すると仮定して面選択性がどう発現するかを考える。キラル配位子は金属選択的配位能によりウレア酸素がマグネシウムに、リンが銅にそれぞれ選択的に配位する。マグネシウムと銅はアルキル基を介して2電子3中心型の結合を形成しているため3 Å以内の距離に存在する。従って、これと錯体を形成するキラル配位子の配座としてリン—銅結合と炭素—炭素結合がアンチのものとゴーシュのものの2種類のみが考えられる (Figure 12)。アンチ型ではリン上の pro-*R* のフェニル基が立体障害基となり下側に張り出すために基質は環上の炭素鎖を上側にむけて d,π* 錯体を形成して反応し *S* 体が生成する。ゴーシュ型ではリン上の pro-*S* のフェニル基が立体障害基となり上側に張り出すために基質は環上の炭素鎖を下側にむけて d,π* 錯体を形成して反応し *R* 体が生成する。アンチ型とゴーシュ型を比較すると、ゴーシュ型では立体的に大きい銅がこみいったところに来るために不安定化しアンチ型から反応が進行して *S* 体が生成するものと説明できる。シクロペンテノンで選択性が低下する実験事実はキラル配位子のフェニル基と基質環上の炭素鎖との立体反発がシクロヘキセノンに比べて小さくなるためと理解できる。また、シクロヘプテノンで選択性が低下するのは、エノンの平面性が落ちるため d,π* 錯体において基質と銅の距離が遠くなり立体障害がききにくくなるためと考えられる。

本反応で確立された点は、マグネシウムクプレートとリチウムクプレートの立体選択性

が同一のキラル源により制御され、それぞれ相補的な面が高いレベルで選択されることである。また本反応を設計したときに用いた、金属の酸化数を高めることにより配位座を減らしモノメリックな活性種を生成させて反応系を設計するという手法は、複雑な会合状態を形成する有機金属の反応設計に威力を発揮すると考えられる。

Figure 12

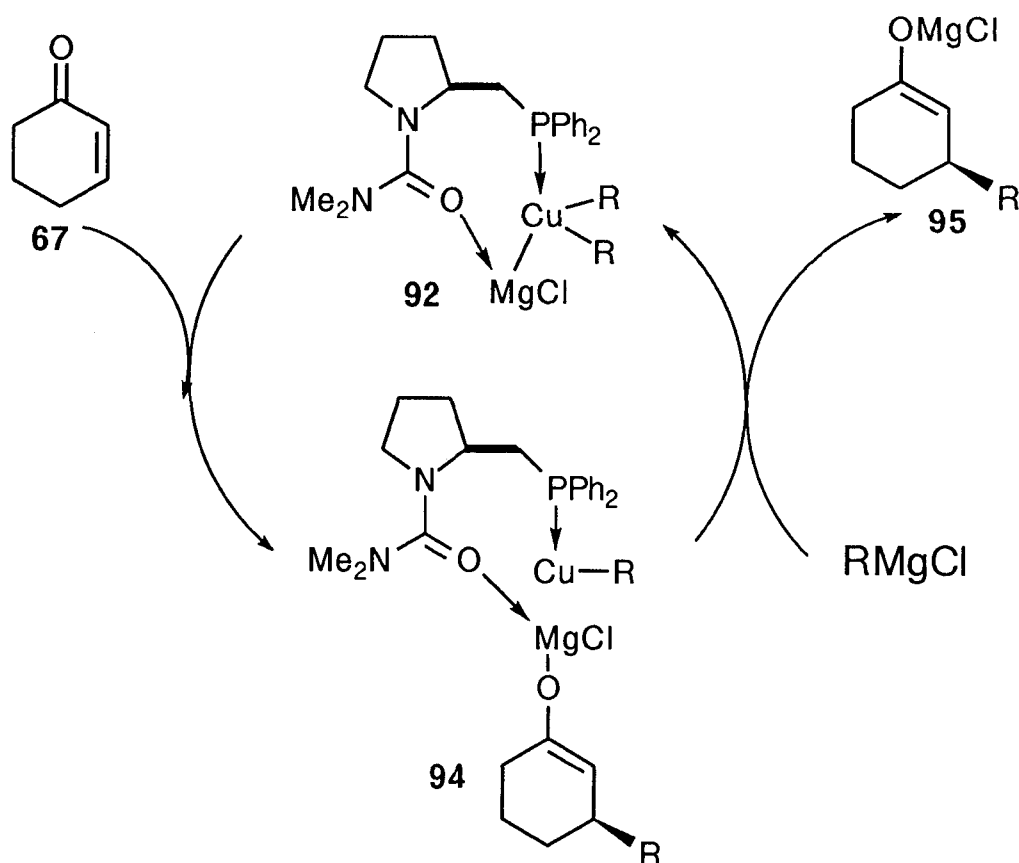


第6章 不斉触媒反応への展開

1. 反応系の設計

グリニャール試薬の不斉共役付加反応の立体制御に成功したことは、触媒的不斉反応への展開が可能であることを示している。想定できる触媒サイクルを Figure 13 に示す。マグネシウムクプレートとキラル配位子との錯体 **92** が高い不斉誘起能をもっていることはすでにわかっている。触媒反応が可能となるためには、付加反応がおこったあとの **94** にグリニャール試薬がトランスメタル化をし、不斉誘起能をもつ反応活性種 **92** が再生することが必要である。このステップで銅に配位したキラル配位子が過剰のグリニャール試薬によりキックアウトされ、アキラルな活性種が生ずると不斉誘起はおこらない。この問題を解決することが不斉触媒反応への展開する上での鍵となる。現在までに報告されている銅触媒による不斉反応は、銅とキラル配位子とに結合を作って触媒を構成させる方法をとっている (Figure 1)。従って、この問題はキラル配位子制御による系に特有の問題である。

Figure 13. Probable Catalytic Cycle



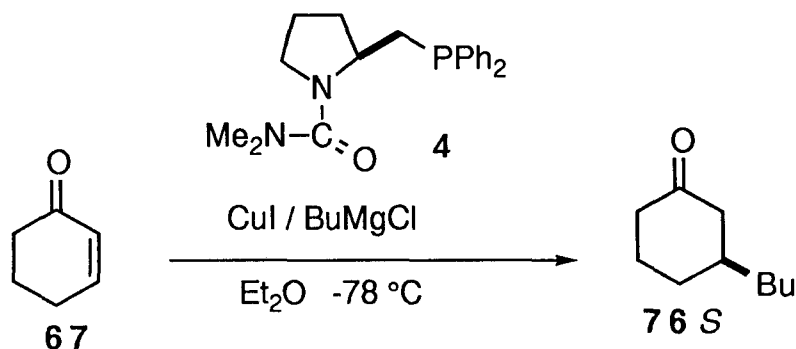
2. キラル配位子-銅錯体による触媒的不斉反応 (Table 21)

2 モル%のヨウ化銅、3 モル%のキラル配位子の制御によりブチルマグネシウムクロリドはシクロヘキセノンに共役付加し、収率 78%、67% ee で付加体を得られた。この結果は過剰のグリニャール試薬の存在下でもキラル配位子は銅と錯体を形成し立体制御を行っていることを示している。本反応はキラル配位子-銅錯体の制御により触媒的不斉共役付

加反応を達成したはじめての例である。

キラル配位子の当量を増やしていくと選択性は上昇し、8 mol% のヨウ化銅と 32 mol% のキラル配位子の錯体の制御により 90 %ee が得られた。ee の上昇の仕方はキラル配位子とグリニャール試薬のモル比とよい相関がある。これは銅の上でキラル配位子とグリニャール試薬が競合していることを示していると考えられる。従って、銅に対してより配位力の強い配位子を用いることで触媒の当量を減らせるものと考え、リンの電子密度を高める目的でキラル配位子 16 と 17 を設計した。

Table 21. Catalytic Asymmetric Addition of Grignard Reagent



run	CuI/mol%	4/mol%	BuMgCl/mol%	4/BuMgCl	ee/%	yield/%	1,4-/1,2-
1	2	3	120	0.025	67	78	16
2	2	10	120	0.083	74	69	9
3	8	10	120	0.083	67	89	65
4	8	20	120	0.17	80	83	12
5	8	32	120	0.27	90	92	32

3. キラル配位子の検討 (Table 22)

配位子／グリニャール試薬の比の増加にともなって ee が増加する現象はキラル配位子 2 でも同様に見られた。しかし配位力の強い 16 や 17 ではほぼ一定の ee が得られた。特にジメチルアミノフェニル基をもつ 17 では 3 mol% の制御でも 75% ee という高い選択性が得られた。しかし 16 や 17 を 32 mol% 用いるとリンがシクロヘキセノンに求核反応した付加体を得られ収率が低下した。

4. 当量反応による活性種の検討 (Table 23)

ee とキラル配位子／グリニャール試薬の比率に相関があることの原因としてキラル配位子－銅錯体の濃度が増すことの他に活性種に変化がおこっている可能性がある。この点について当量反応で検討を行った。銅に対してグリニャール試薬の当量を 3 に固定してキラル配位子の当量を 1~4 まであげたとき ee は 89% から 99% まで上昇した (run 1~3)。次に銅に対してキラル配位子の当量を 4 に固定してグリニャール試薬の当量を 3~15 まであげると、ee は 56% まで下がった (run 4~6)。この結果は活性種は変わらないにもかかわらず、配位子／グリニャール試薬の比率が減少したためにキラル配位子－銅錯体の濃度が減少したためと説明できる。それを裏づける結果として配位子／グリニャール試薬の比率

を一定に保つと ee がほぼ一定になった (run 7-9)。

Table 22. Catalytic Asymmetric Addition of Grignard Reagent

67

$\xrightarrow[\text{Et}_2\text{O} \ -78\text{ }^\circ\text{C}]{\text{CuI} / \text{BuMgCl}}$

76 S

4: R=Me₂NCO, Ar=Ph
 2: R=tBuCO, Ar=Ph
 3: R=(Me₂N)₂PO, Ar=Ph
 16: R=Me₂NCO, Ar=PhOMe
 17: R=Me₂NCO, Ar=PhNMe₂

run	CuI/mol%	ligand(mol%)	BuMgCl/mol%	ligand/BuMgCl	ee/%	yield/%	1,4-/1,2-
1	2	4(3)	120	0.025	67	78	16
2	8	4(10)	120	0.083	67	89	65
3	8	4(32)	120	0.27	90	92	32
4	8	2(10)	120	0.083	70	85	31
5	8	2(32)	120	0.27	80	87	18
6	10	3(30)	150	0.20	25	54	5
7	8	16(10)	120	0.083	81	47	1.5
8	8	16(32)	120	0.27	70	5	0.13
9	2	17(3)	120	0.025	75	70	5
10	8	17(10)	120	0.083	80	74	8
11	8	17(32)	120	0.27	87	18	1

Table 23. Asymmetric Addition of Grignard Reagent in Stoichiometric Conditions

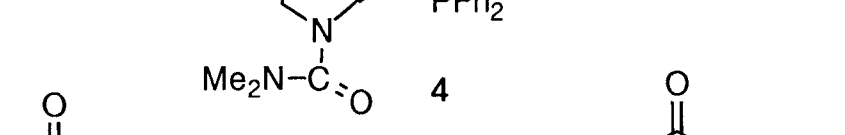
67

run	CuI/mol%	4/mol%	BuMgCl/mol%	4/BuMgCl	ee/%	yield/%
1	120	150	360	0.41	89	100
2	120	300	360	0.83	99	94
3	120	480	360	1.3	95	97
4	120	480	360	1.3	95	97
5	120	480	960	0.5	84	100
6	120	480	1800	0.27	56	98
7	120	150	560	0.27	77	100
8	120	300	1100	0.27	71	100
9	120	480	1800	0.27	70	95

5. 反応方法の検討 (Table 24)

キラル配位子／グリニャール試薬の比率を高く保つために基質と触媒の溶液にグリニャール試薬を滴下していく方法 (Method B) と触媒の溶液にグリニャール試薬と基質を同時に加えていく方法 (Method C) で反応を行ったが、触媒とグリニャール試薬の溶液に基質を滴下していく方法 (Method A) が最も優れていた。

Table 24. Asymmetric Addition of Grignard Reagent



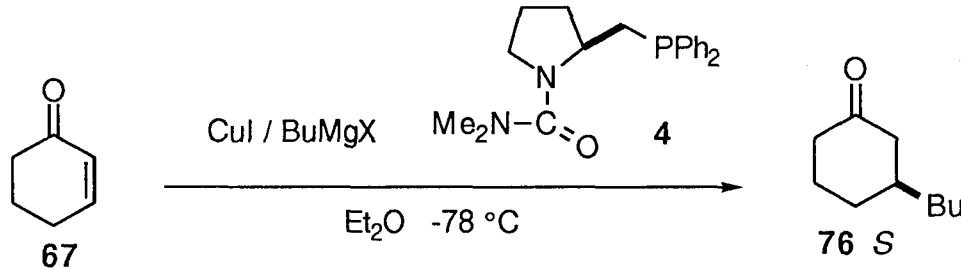
Reaction scheme showing the asymmetric addition of a butyl group to cyclohex-2-en-1-one (67) using a chiral catalyst (4) and BuMgCl in Et₂O at -78 °C to form 2-butyrocyclohexanone (76 S).

run	CuI/mol%	4/mol%	BuMgCl/mol%	Method ^a	ee/%	yield/%	1,4-/1,2-
1	8	32	120	A	90	92	32
2	8	32	120	B	64	43	2
3	8	32	120	C	85	57	2

- a. Method A: Substrate was added to the solution of catalyst and Grignard reagent.
 Method B: Grignard reagent was added to the solution of catalyst and substrate.
 Method C: Grignard reagent and substrate was added simultaneously to the solution of catalyst.

6. グリニャール試薬の検討 (Table 25)

Table 25. Asymmetric Addition of Grignard Reagent

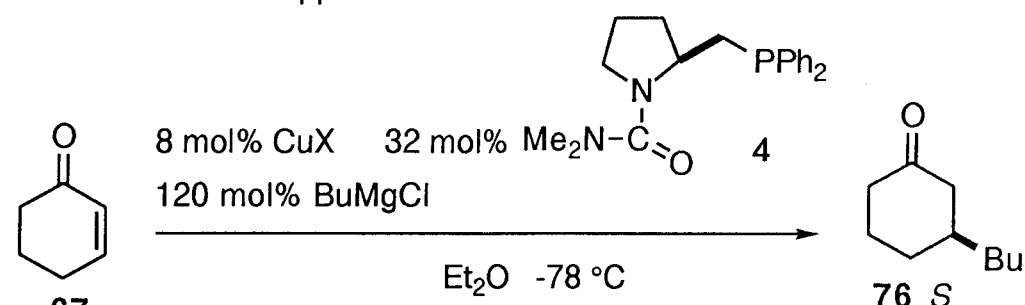
						
run	CuI/mol%	4/mol%	BuMgX (mol%)	ee/%	yield/%	1,4-/1,2-
1	8	32	BuMgCl (120)	90	92	32
2	8	32	Bu ₂ Mg (120)	94	71	4
3	8	32	BuMgNPr ^t ₂ (120)	84	70	5
4	8	32	BuMgBr (120)	68	10	0.8
5	8	32	BuMgI (120)	46	27	2

グリニャール試薬の検討を行ったところブチルマグネシウムクロリド、ジブチルマグネシウム、ブチルマグネシウムジイソプロピルアミドでは極めて高い選択性で付加体を得られたのに対して、ブチルマグネシウムブロミド、ブチルマグネシウムイオダイドでは反応性、選択性ともに悪いことがわかった。

7. カッパー源の効果 (Table 26)

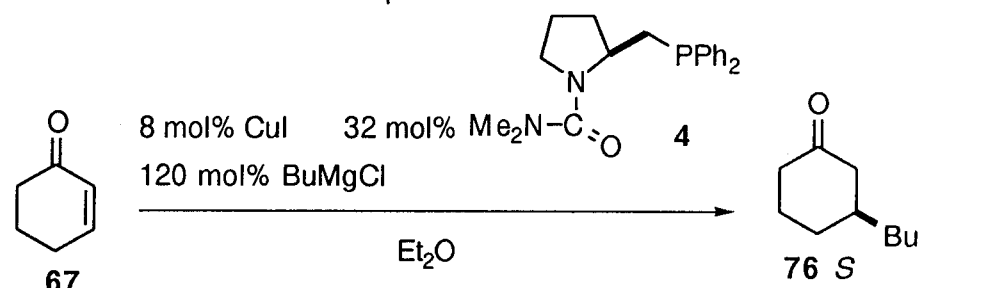
カッパー源としてよう化銅がエナンチオ選択性、収率ともに最も優れていた。よう化銅—ジメチルスルフィド錯体では、溶解度が良くなるためだと考えられるがレジオ選択性が上昇するものの、キラル配位子に競合する配位子が存在するためエナンチオ選択性は低下した。塩化銅、臭化銅、シアン化銅でも高いエナンチオ選択が得られるものの、レジオ選択性は低下した。

Table 26. Effect of Copper Source

				
run	CuX	ee/%	yield/%	1,4-/1,2-
1	CuI	90	92	32
2	CuI·SMe ₂	76	73	64
3	CuCl	81	52	5
4	CuBr	77	56	3
5	CuCN	82	40	3

8. 温度効果 (Table 27)

Table 27. Effect of Reaction Temperature

					
run	temp/°C	ee/%	yield/%	1,4-/1,2-	ΔΔG [‡] /kcal/mol
1	-100	95	30	2	1.26
2	-78	90	92	32	1.14
3	-45	84	84	32	1.11
4	-20	76	94	43	1.00

-100 度では 95%ee まで選択性の向上が見られたが、レジオ選択比が低下し触媒回転が悪くなったと考えられる。温度が上昇するにつれてレジオ選択性は上昇した。ee から計算される活性化エネルギーの差 ($\Delta\Delta G^\ddagger$) は温度上昇とともに小さくなっている。

9. 溶媒効果 (Table 28)

エーテル、トルエン、ジメチルスルフィド中では選択性が良かったものの、ジイソプロピルエーテル、THF中では選択性は悪かった。

Table 28. Solvent Effect

run	solvent	ee/%	yield/%	1,4-/1,2-
1	Et ₂ O	90	92	32
2	iPr ₂ O	18	29	1
3	toluene	73	90	11
4	DMS	77	82	130
5	THF	0	55	11

10. 濃度効果 (Table 29)

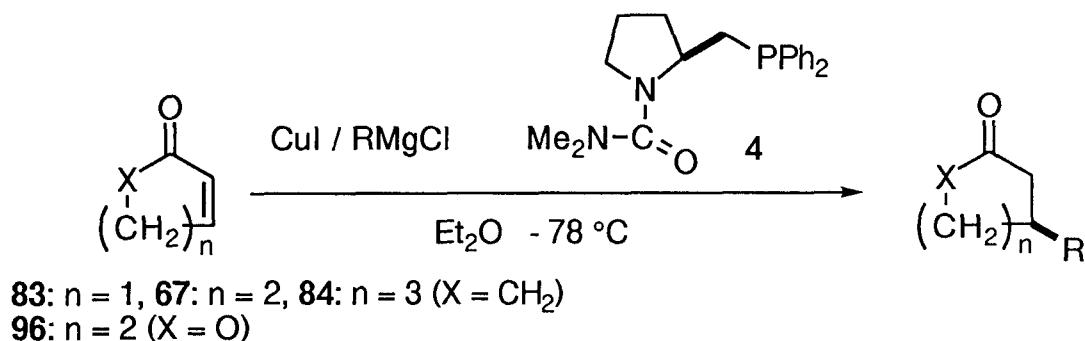
Table 29. Concentration Effect

run	conc of 4/M	ee/%	yield/%	1,4-/1,2-
1	0.01	90	85	32
2	0.038	90	92	32
3	0.2	89	41	2

グリニャール試薬との濃度比を保ったままキラル配位子の濃度を0.01Mから0.2Mまで動かしたが、エナンチオ選択性の変化はなかった。これは、銅からのキラル配位子の解離が自発的にはおこらず、グリニャール試薬との競合によっておこることを示している。

1 1. 基質とアルキル基の検討 (Table 30)

Table 30. Catalytic Asymmetric Addition of Grignard Reagent



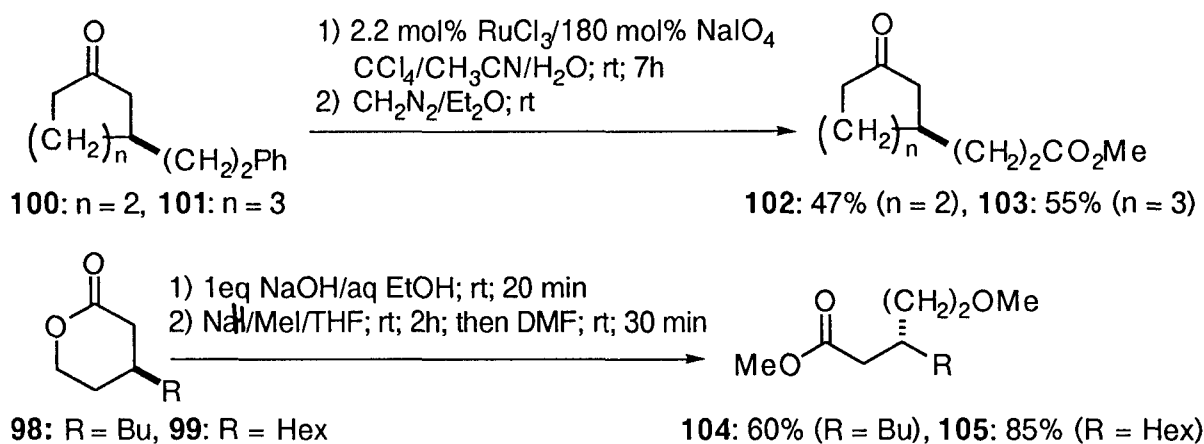
entry	n	X	CuI (mol%)	4 (mol%)	RMgCl (120 mol%)	Product	ee/% ^a	yield/% ^b
1	2	CH ₂	8	32	Et	75	73	83
2	2	CH ₂	8 ^c	32	Pr	86	72 ^d	77
3	2	CH ₂	8	32	Bu	76	90	92
4	2	CH ₂	8 ^c	32	Hex	87	92 ^d	90
5	2	CH ₂	8	32	Ph(CH ₂) ₂	100	84 ^g	74
6	2	CH ₂	8	32	Me ^h	68	5	23
7	2	CH ₂	8	32	Ph ^h	77	4	10
8	2	CH ₂	8	32	PhCH ₂	88	12 ^d	40
9	2	CH ₂	8	32	iPr	89	4 ^d	24
6	1	CH ₂	8	32	Bu	79	42	88
7	3	CH ₂	8	32	Bu	82	81 ^d	91
8	3	CH ₂	8	32	Ph(CH ₂) ₂	101	83 ^{dg}	70
9	2	O	8 ^c	32	Pr	97	76 ^f	66
10	2	O	8	32	Bu	98	91 ^e	70
11	2	O	8 ^c	32	Hex	99	90 ^{de}	70

^a Ee was determined by ¹³C NMR analysis of the corresponding diastereomeric ketals of (*R*, *R*)-2, 3-butanediol unless otherwise noted. The absolute configurations were determined by optical rotation (75 and 77: Posner, G. H.; Frye, L. *Isr. J. Chem.* 1984, 24, 88; 76: Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* 1986, 108, 7114; 68: Leyendecker, F.; Jessor, f.; Ruhland, B. *Tetrahedron Lett.* 1981, 22, 3601; 79: Tamura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* 1981, 22, 3601; 97 and 98: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* 1979, 44, 2250; 100 (determined by converting to the corresponding methyl ester 102): Gerlach, v. H. *Helv. Chim. Acta*, 1978, 61, 2773.) ^b Isolated yield of 1,4-addition product. ^c CuI · SMe₂ was used instead of CuI. ^d The absolute configuration was not determined. ^e Ee was determined by ¹H NMR of the corresponding methyl ester (104 and 105) in the presence of Eu(hfc)₃. ^f Optical yield. ^g Ee was determined by chiral HPLC (Daicel CHIRALPAK AD, iPrOH/hexane 1/100 for 100 and 1/20 for 101). ^h RMgBr was used.

基質とアルキル基の検討をおこなったところシクロヘキセノン、シクロヘプテノン、ペンテノライドに対して最高 92% ee という高い選択性で 1 級アルキル基が導入できた。しかしメチル、フェニル、ベンジル、イソプロピル基の導入は選択性、収率とも低かった。

高い選択性で得られた付加体のうちいくつかはさらに官能基化が可能であり、合成上有用な中間体に変換できた (Figure 14)。

Figure 14



12. ee のシュミレーション

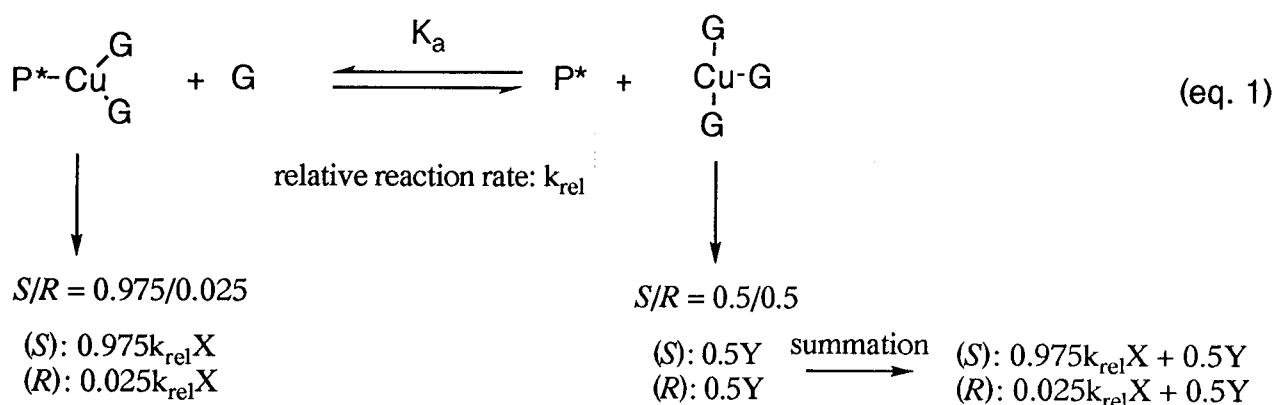
Table 31. Asymmetric Conjugate Addition of Butylmagnesium Cuprate by Stoichiometric 4

entry	CuI (mol%)	1/2 (mol%)	BuMgCl (mol%)	4 or 17/BuMgCl	ee/%		yield/%
					(observed)	(estimated)	
1	120	4 (150)	6000	0.025	18	17	62
2	120	4 (150)	1500	0.10	56	48	61
3	120	4 (150)	560	0.27	77	78	100
4	120	4 (150)	360	0.42	89	89	100
5	120	4 (150)	300	0.50	93	92	96
6	120	4 (150)	240	0.63	90	95	90
7	120	4 (480)	19200	0.025	9	16	35
8	120	4 (480)	4800	0.10	67	44	29
9	120	4 (480)	1800	0.27	70	69	95
10	120	4 (480)	960	0.50	84	81	100
11	120	4 (480)	360	1.3	95	93	97
12	120	17 (150)	1500	0.10	75	70	82
13	120	17 (150)	560	0.27	88	87	100
14	120	17 (150)	300	0.50	92	93	97

触媒の量を減らすと ee が低下する原因は、過剰のグリニャール試薬によりキラル配位

子が銅からキックアウトされアキラルなクプレートから反応が進行するためであることが示唆された。さらなる知見を得る目的で触媒回転を考慮する必要のない当量反応を系統的に検討した (Table 31)。120 モル%のよう化銅と150 モル%のキラル配位子の存在下、グリニャール試薬の当量を 6000 モル% から 240 モル% まで減らすと ee は 18% から 93% まで上昇した。120 モル%のよう化銅と 480 モル% もキラル配位子の存在下、グリニャール試薬を 19200 モル% から 360 モル% まで減らすと ee は 9% から 95% まで上昇した。150 モル%のキラル配位子と 480 モル%のキラル配位子を用いたときで、より少ないキラル配位子を用いたときのほうが ee が若干高いことがわかった。また、ee の変化率は銅への配位力の強い 17 の方が一定に近いことがわかった。

これらの知見は以下の仮定から説明できる (eq 1)。キラル配位子 (P^*) の配位した 95% ee を与えるキラルな活性種 ($P^*-\text{CuG}_2$) と、過剰のグリニャール試薬によりキラル配位子がキックアウトされたアキラルな活性種 (CuG_3) のあいだに結合定数 K_a の平衡が存在し、キラル活性種からの反応がアキラル活性種からの反応より k_{rel} だけ速いと仮定する。平衡における $P^*-\text{CuG}_2$ の濃度を X 、 CuG_3 の濃度を Y 、銅、 RMgCl 、 P^* の全濃度をそれぞれ C , G , P とおくと eq 2 が成立する。



$$K_a = \frac{[\text{P}^*-\text{CuG}_2][\text{G}]}{[\text{P}^*][\text{CuG}_3]} = \frac{(C-Y)(G-2C-Y)}{(P-C+Y)Y} \quad (\text{eq2})$$

$b = C/P$, $x = P/G$ の二つのパラメータを導入すると eq 2 は eq 3 のように変換できる。

$$K_a = \frac{(bP-Y)\left(\frac{P}{X}-2bP-Y\right)}{(P-bP+Y)Y} \quad (\text{eq3})$$

これを Y について解くと

$$Y = \frac{P\left(K_a(1-b)-b+\frac{1}{X}\right)}{2(K_a-1)} \left[\sqrt{1 + \frac{4b(K_a-1)\left(\frac{1}{X}-2b\right)}{\left(K_a(1-b)-b+\frac{1}{X}\right)^2}} - 1 \right] \quad (\text{eq4})$$

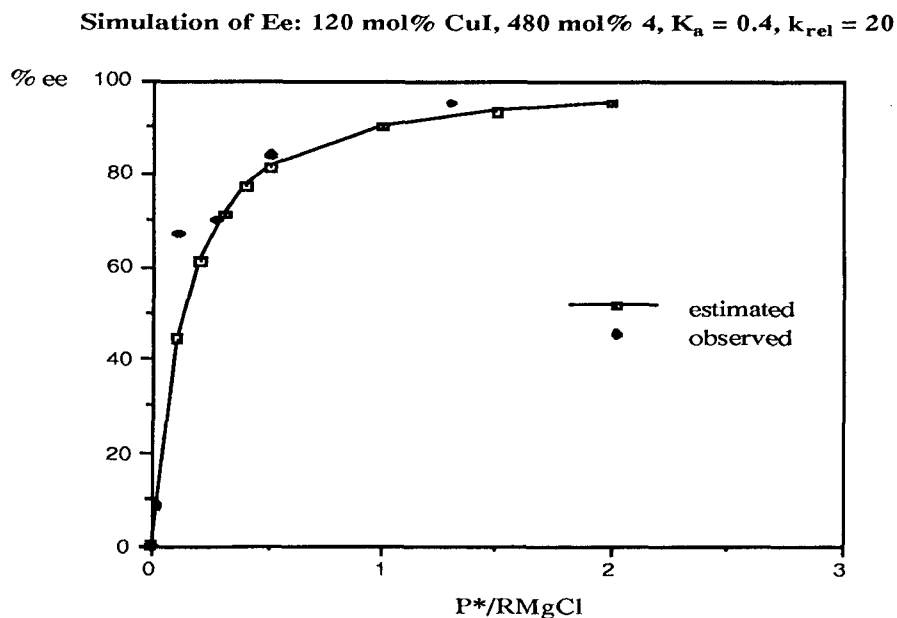
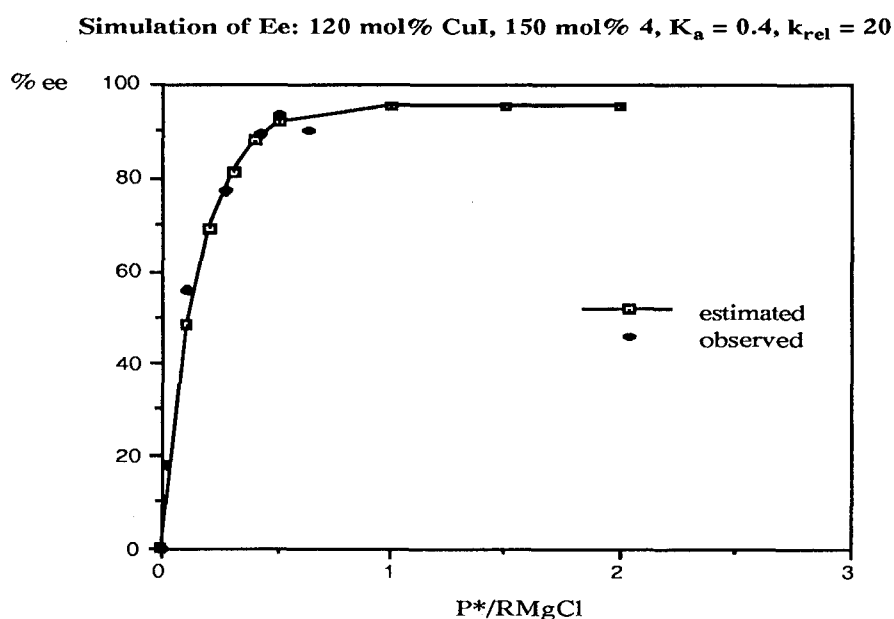
$$X = C - Y \quad (\text{eq5})$$

式1で $P^* - CuG_2$ からはS体とR体が 0.975/0.025 (95% ee)、相対速度 k_{rel} で生成し、 CuG_3 からは 0.5/0.5 (0% ee) で生成するので、合計、S/Rは $(0.975k_{rel}X + 0.5Y) / (0.025k_{rel}X + 0.5Y)$ となる。従って、ee は以下のように表わせる。

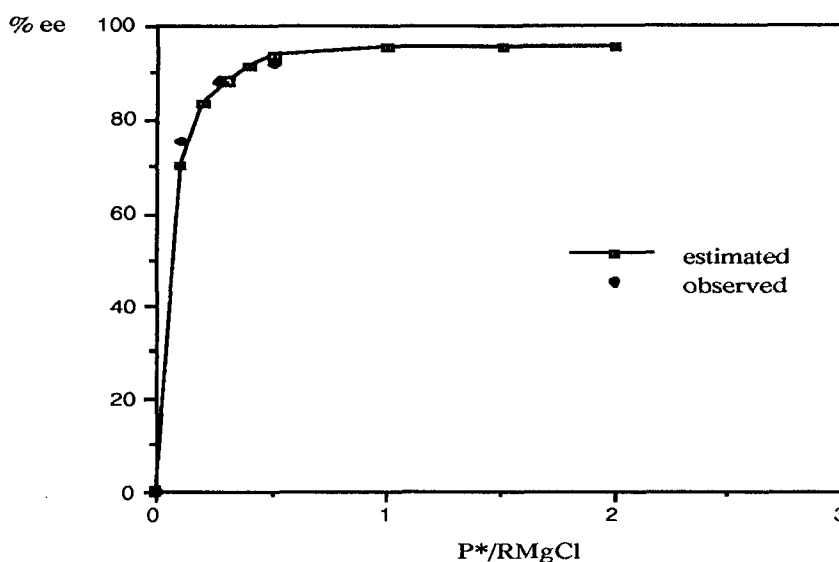
$$Ee = \left(\frac{0.95k_{rel}X}{k_{rel} + Y} \right) \times 100 \quad (eq6)$$

XとYが K_a の関数なので、ee は k_{rel} と K_a により表わされる。 k_{rel} と K_a の値は式6から計算した ee の値と Table 31 の実測の値を NEC PC-9801 VM personal computer 上で重ね合せて求めた (Figure 14)。

Figure 14. Simulation of Ee



Simulation of Ee: 120 mol% CuI, 150 mol% 17, $K_a = 1.2$, $k_{rel} = 20$



その結果、キラル配位子 4 では $K_a = 0.4$, $k_{rel} = 20$ 、17 では $K_a = 1.2$, $k_{rel} = 20$ のとき実験結果よく一致した。150 モル% の 4 を用いた反応での ee の実測値と計算値の標準偏差 (σ) は 4、最小二乗法では $ee_{observed} = 5.7 + 0.93ee_{estimated}$ で r 値は 0.992 であり、480 モル% の 17 を用いた反応では、 $\sigma = 11$, $ee_{observed} = 3.4 + 1.0ee_{estimated}$, $r = 0.94$ であった。150 モル% の 17 を用いた反応では、 $\sigma = 3$, $ee_{observed} = 23 + 0.74ee_{estimated}$, $r = 1$ であった。Table 31 に ee の実測値と計算値をともに示した。各場合でかなりよく ee の変化がシュミレートされている。また、150 モル% の 4 を用いた反応の方が 480 モル% 用いたときよりも ee が良いこと、17 より 4 の方が ee の変化率が小さいことも再現されている。

以上の知見をもとに触媒反応のシュミレーションを行った。式 6 から ee は x すなわちキラル配位子濃度とグリニャール試薬濃度の比の関数である。触媒条件では x の値が P/G_0 から $P/(G_0 - S_0)$ まで変化する。ここで G_0 と S_0 はグリニャール試薬と基質の初濃度を示す。すなわち、ee は反応の進行につれて変化する。ある時点での S 体の割合 $S(x)$ は反応の進行度 d により以下のように表わされる。

$$S(x) = \left(\frac{0.975k_{rel}X + 0.5Y}{k_{rel}X + Y} \right) \Delta d \quad (eq7)$$

ここで x と d の関係は

$$x = \frac{P}{G_0 - S_0 d} \quad (eq8)$$

よって

$$\Delta d = \frac{P}{S_0} \frac{1}{x^2} \Delta x \quad (eq9)$$

また、以下の関係がある。

$$d: 0 \rightarrow 1 \text{ is identical with } x: \frac{P}{G_0} \rightarrow \frac{P}{G_0 - S_0}$$

よって、反応終了後の全S体の割合は

$$S_{\text{total}} = \int_0^1 S(x) \, dd = \frac{P}{S_0} \int_{\frac{P}{G_0}}^{\frac{P}{G_0 - S_0}} S(x) \frac{1}{x^2} \, dx \quad (\text{eq10})$$

これは級数の和として次のように近似できる。

$$S_{\text{total}} = \sum_{i=0}^{1000} S \left(\frac{P}{G_0} + \frac{i}{1000} \left(\frac{P}{G_0 - S_0} - \frac{P}{G_0} \right) \right) \times \frac{1}{1000} \quad (\text{eq11})$$

よって ee は

$$ee = (2S_{\text{total}} - 1) \times 100 \quad (\text{eq12})$$

式12 からの ee の計算値と実測値を Table 32 に示す。計算値が実際の ee の変化を良く反映していることがわかる。

Table 32. Simulation of Conjugate Addition of Butylmagnesium Chloride Controlled by Catalytic 4

run	CuI/mol%	4 or 17 (mol%)	ee/%		yield/%
			(observed)	(estimated)	
1	2	4 (3)	67	63	78
2	2	4 (10)	74	80	69
3	8	4 (10)	67	93	89
4	8	4 (20)	80	91	83
5	8	4 (32)	90	92	92
6	2	17 (3)	75	79	70
7	8	17 (10)	80	92	74
8	8	17 (32)	87	94	18

さらにこの考え方は触媒反応における温度効果を説明できる。平衡定数と温度の関係式 ($K = \exp(-\Delta G/RT)$) およびアレニウスの式 ($k = A \exp(-E_a/RT)$) より -78 度で $K_a = 0.4$, $k_{\text{rel}} = 20$ であれば他の温度では Table 33 のようになる。また、-78 度での ee の最大値は 95% ($\Delta\Delta G^\ddagger = 1.42 \text{ kcal/mol}$) であったが、この活性化エネルギー差が他の温度でもそのまま保たれるとすれば各温度での最大 ee 値 (ee_{max}) は Table 33 のようになる。これらのパラメータから計算される ee 値は実測値とよく一致している。

Table 33. Simulation of Temperature Effect

temp/°C	K_a	k_{rel}	$ee_{max}/\%$	$ee_{estimated}/\%$	$ee_{observed}/\%$
-100	0.36	29	97	95	95
-78	0.4	20	95	92	90
-45	0.47	13	92	88	84
-20	0.49	10	89	85	76

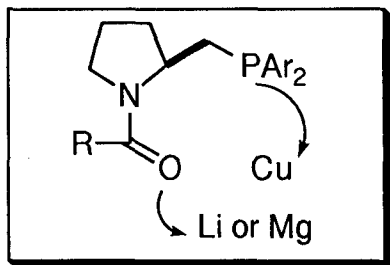
1.3. 考察

キラル外部配位子の制御によりグリニャール試薬の共役付加反応の立体化学が高選択的に制御できた。反応中、ホスフィン配位子は過剰に存在するグリニャール試薬と銅原子の配位座をめぐって競合しているが、32 mol% 用いることで当量反応に匹敵する選択性を示した。 ee の値はこの競合による平衡反応の定数 (K_a) と相対速度 (k_{rel}) により予測できた。本反応はキラル外部配位子-銅錯体制御によりグリニャール試薬の触媒的不斉共役付加反応を達成した初めての例である。しかし配位結合という比較的弱い結合を用いているため触媒の量を減らすと ee の低下がみられた。そこでリンの電子密度を高めて配位力を強めた配位子 **17** を設計し、3 mol% の制御で 75% ee が得られた。以上の結果は外部配位子制御というアプローチが本反応にも適用できることを示している。この程度の触媒の量で 95% ee 以上の選択性を発現するキラル配位子の設計を検討中である。

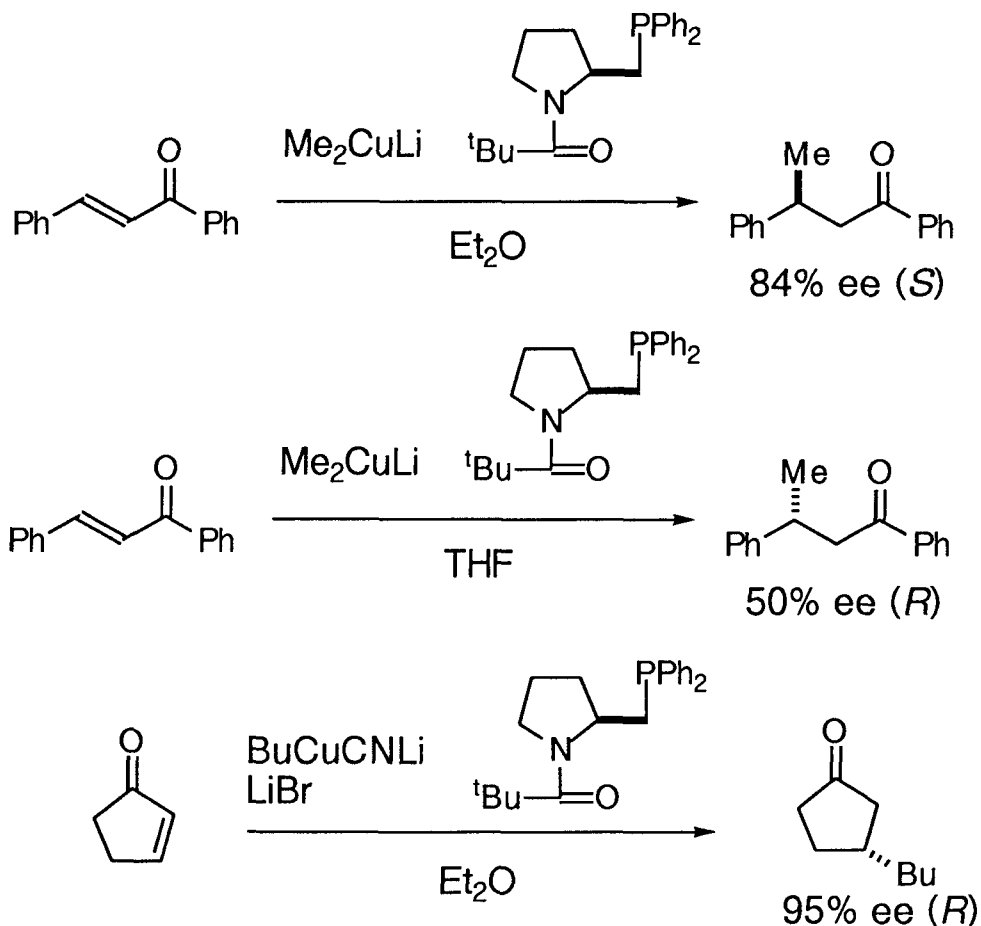
第7章 結論

金属選択的配位概念から設計したキラルアミドホスフィン配位子の制御により立体選択性の高い有機銅の不斉共役付加反応が達成できた (Figure 15)。キラル配位子の酸素とリンがリチウムあるいはマグネシウムと銅にそれぞれ選択的に配位することがNMR 実験により確かめられた。さらに、キラル配位子-銅錯体制御によるグリニャール試薬の触媒的共役付加反応をはじめて達成した。以上の知見をふまえ今後さらに効率の高い触媒反応系の設計に発展できると考えられる。

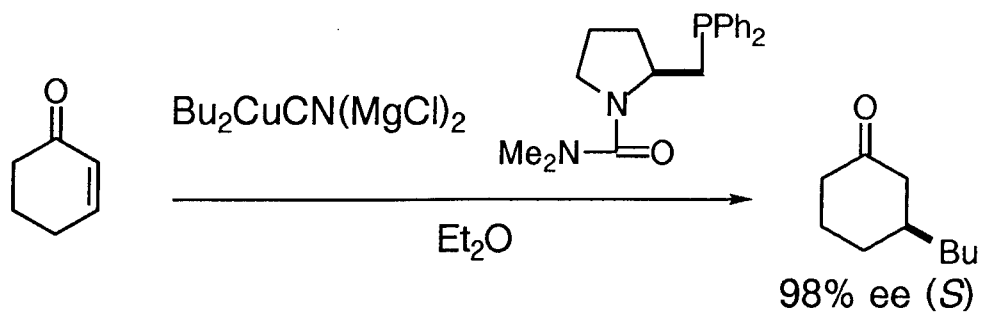
Figure 15.



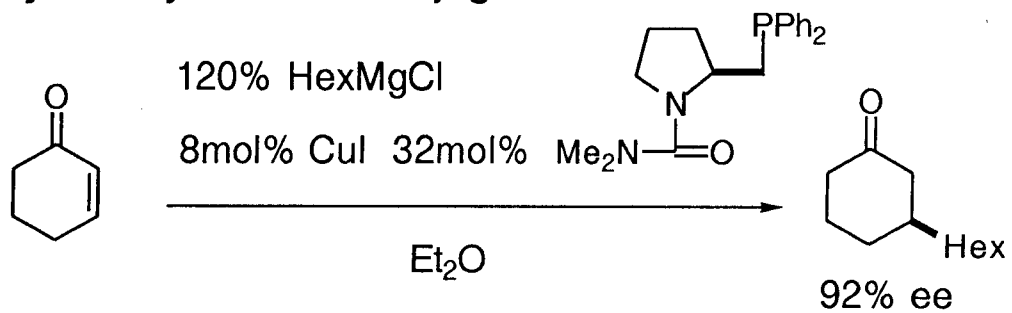
Asymmetric Conjugate Addition of Lithium Cuprate



Asymmetric Conjugate Addition of Magnesium Cuprate



Catalytic Asymmetric Conjugate Addition



References

1. Krause, N. *Kontakte* 1993, 1, 3; Lipshutz, B. H. *Synlett*, 1990, 119; Nakamura, E. *J. Synth. Org. Chem. Jpn.* 1990, 49, 902; Lipshutz, B. H. *Tetrahedron* 1989, 45, 349; Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* 1986, 25, 947; Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley; New York, 1980; Posner, G. H. *Org. React.* 1972, 19, 1.
2. Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* 1984, 23, 847.
3. Noyori, R. *Asymmetric Catalysis in Organic Synthesis* John Wiley and Sons, Inc. 1994; Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* 1992, 92, 771; Tomioka, K. *Synthesis* 1990, 541; Tomioka, K.; Koga, K. in *Asymmetric Synthesis*, Vol II, Academic Press, New York, 1983, chapter 7.
4. Kretschmer, R. A. *J. Org. Chem.* 1972, 37, 2744; Luche, J. L.; Barreiro, E.; Crabbe, P. *Tetrahedron Lett.* 1975, 2355; Imamoto, T.; Mukaiyama, T. *Chem. Lett.* 1980, 45; Huche, M.; Berlan, J.; Pourcelot, G.; Cresson, P. *Tetrahedron Lett.* 1981, 22, 1329; Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* 1983, 3517; *Idem*, *Nouv. J. Chim.* 1985, 9, 13.; Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* 1986, 108, 7114; Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* 1986, 51, 4953; Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* 1987, 109, 2040; Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *ibid.* 1988, 110, 3175; Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* 1990, 795; Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* 1990, 31, 965; Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *ibid.* 1990, 31, 4105; Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* 1990, 9, 3178; Rossiter, B. E.; Eguchi, M.; Hernandez, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heinis, D. *Tetrahedron Lett.* 1991, 32, 3973; Lambert, F.; Knotter, D. M.; Janssen, M. D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron Asymmetry* 1991, 1097; Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, M. *ibid.* 1992, 231; Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* 1992, 114, 3400; Quinkert, G.; Muller, T.; Koniger, A.; Schltheis, O.; Sickenberger, B.; Durner, G. *Tetrahedron Lett.* 1992, 33, 3469; Tanaka, K.; Matsui, J.; Suzuki, H.; Watanabe, A. *J. Chem. Soc. Perkin Trans. I* 1992, 1193; Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* 1993, 49, 965; Spescha, M.; Rihs, G. *Helv. Chim. Acta* 1993, 76, 1219; Pfaltz, A.; Zhou, Q.-L. *Tetrahedron Lett.* 1993, 34, 7725; Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* 1993, 4, 2427; Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* 1994, 50, 4455; Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* 1994, 50, 4467; *Idem*, *Tetrahedron* 1994, 50, 4467; van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* 1994, 35, 6135.
5. Power, P. P. *Progress in Inorg. Chem.* 1991, 39, 75; Olmstead, M.; Power, P. P. *J. Am. Chem. Soc.* 1990, 112, 8008; Knotter, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* 1990, 112, 5895; Stewart, K. R.; Lever, J. R.; Whangbo, M.-H. *J. Org. Chem.* 1982, 47, 1472.

6. Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, *26*, 6015; *Idem, ibid.* **1984**, *25*, 3063; Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395.
7. Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938.
8. Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032; Bertz, S. H. *ibid.* **1990**, *112*, 4031; *Idem, ibid.* **1991**, *113*, 5420; Snyder, J. P.; Spangler, D. P.; Behling, J. R.; Rossiter, B. E. *J. Org. Chem.* **1994**, *59*, 2665.
9. Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, *37*, 3601; Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040; Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* **1990**, *31*, 965.
10. Seebach, D. *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1624.
11. Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119; Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
12. Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. *ISr. J. Chem.* **1984**, *24*, 118.
13. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; *Idem, ibid.* **1985**, *26*, 6019; Alexakis, A.; Berlan, J.; Besace, Y. *ibid.* **1986**, *27*, 1047; Nakamura, E.; Matsuzawa, S. Horiguchi, Y.; Kuwajima, I. *ibid.* **1986**, *27*, 4029; Lipshutz, B. H.; Dimoch, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.
14. Miyashita, A.; Yamamoto, A. *Bull. Chem. Soc. Japan*, **1977**, *50*, 1102.
15. Kagaku-Binran, 3rd. Ed., II-452, Nihon-Kagakukai, Maruzen.
16. Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732; Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron, Lett.* **1991**, *32*, 3095.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a JEOL EX-270 (270 MHz for ^1H NMR and 67.8 MHz for ^{13}C NMR), HITACHI R-24B (60 MHz for ^1H NMR) or HITACHI R-90 (90 MHz for ^1H NMR) spectrometers in the solvent indicated. Chemical shifts were reported in δ values in ppm with tetramethylsilane (TMS) as an internal standard. Infrared spectra (IR) were recorded on a Jasco IR Report-100 Infrared Spectrometer, a Jasco DS-701G Diffraction Grating Infrared Spectrophotometer or HITACHI 260-10 Infrared Spectrophotometer. Mass spectra (MS) were recorded on a JEOL LMS-D300 and a JEOL JMS-DX300 mass spectrometer. Specific rotations were recorded on a Jasco DIP-370 Digital Polarimeter in the solvent indicated. Melting points were measured on a Büchi 510 melting point apparatus or Yamato melting point apparatus model MP-21 and uncorrected. Boiling points were uncorrected. High performance liquid chromatography (HPLC) was performed on a HITACHI 655A-11 Liquid Chromatograph with a HITACHI L-3000 Photo Diode Array Detector. Detection was performed at 250 nm. Column chromatography was performed on silica gel BW200 or BW300 (Fuji Silysia). All reactions were carried out under an argon atmosphere in dried glassware.

Chalcone, cyclohexenone, cyclopentenone and cycloheptenone are commercially available from Aldrich. Butyllithium was purchased from WAKO Ltd.. Ethyllithium¹⁷ and vinylolithium¹⁸ were prepared according to the reported procedure. Butylmagnesium chloride and benzylmagnesium chloride were purchased from Aldrich. Other Grignard reagents were prepared by general procedure. Titration of all the organometallic reagents was performed according to the reported method.¹⁹ Copper iodide, bromide, chloride and thiocyanate were purchased from Wako Ltd. and purified by the literature procedure²⁰ and stored under Ar over P_2O_5 and KOH. Copper cyanide was purchased from Kanto chemical Co., Inc. and dried in an Abderhalden at 50 °C over KOH and P_2O_5 then stored under Ar. Lithium cyanide was prepared by literature procedure.²¹

Chapter 2-2. Syntheses of Chiral Ligand

¹⁷ Gilman, H.; Moore, F. W.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2480.

¹⁸ Gassman, P. G.; Valcho, J. J.; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6524.

¹⁹ Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

²⁰ CuI: Kauffman, G. B; Teter, L. A. *Inorg. Synth.* **1963**, VII, 9. CuCl: Osterlof, J. *Acta Chem. Scand.* **1950**, *4*, 374. CuBr: Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040. CuCN: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.

²¹ Johns, I. B.; Dipietro, H. R. *J. Org. Chem.* **1964**, *29*, 1970.

(S)-N-tert-Butoxycarbonyl-2-pyrrolidinecarboxylic acid (22)²². To the suspension of L-proline (0.500 mol) in dioxane (1 l) and water (0.5 l), 500 ml of 1M sodium hydroxide in water (0.500 mol) and di-tert-butyl dicarbonate (0.490 mol) was added simultaneously under ice bath and the whole was stirred for 1 h at room temperature. The reaction mixture was evaporated and potassium carbonate was added to adjust the pH to 12. The water layer was washed by ether (200 ml x2) and acidified to pH 2 by citric acid. The water layer was extracted by chloroform (200 ml x3) and the organic layer was washed by water (100 ml), sat. NaCl aq. (100 ml), dried over MgSO₄, and concentrated in vacuo. Recrystallization from benzene (120 ml) and hexane (40 ml) gave a 91% yield: mp 133-135 °C; ¹H-NMR (CDCl₃) δ; 1.4 (s, 9H, tBu), 2.0 (m, 4H, CH₂CH₂), 3.4 (m, 2H, CH₂N), 4.2 (m, 1H, CHN), 11.2 (s, 1H, COOH); IR (nujol) 1740, 1640 cm⁻¹; [α]_D²⁵ -61.7 (c 2.20, AcOH).

(S)-N-tert-Butoxycarbonyl-2-pyrrolidinemethanol (23). To the solution of 22 (4.65 mmol) in THF (5 ml) was dropwise borane THF complex (9.30 mmol) in THF (9.3 ml) for 10 min under ice-salt bath and the whole was stirred for 2.5 h. Water (30 ml) was added to quench the reaction and water layer was extracted by ether (30 ml x3). The combined organic layer was washed (saturated sodium bicarbonate (10 ml), saturated sodium chloride (10 ml)), dried over MgSO₄, and concentrated to give crude oil which was purified by silica gel column chromatography (AcOEt/benzene 1:2). Pure alcohol was obtained as a colorless oil in 100% yield: ¹H-NMR (CDCl₃) δ; 1.47 (s, 9H, tBu), 1.63-2.03 (m, 4H (CH₂)₂), 3.33 (ddd, J=6.6, 6.6, 11.0 Hz, 1H, CH₂N), 3.45 (ddd, J=7.0, 7.0, 11.0 Hz, 1H, CH₂N), 3.60 (m, 2H CH₂OH), 3.97 (m, 2H, OH, CHN); IR (neat) 1680, 1660 cm⁻¹; MS m/z 201 (M⁺); [α]_D²⁵ -44.4 (c1.13, CHCl₃).

(S)-(-)-N-tert-Butoxycarbonyl-2-pyrrolidinemethanol 4-methylbenzenesulfonate (24)²³. To the solution of the alcohol (23) (67.1 mmol) in dry dichloromethane (MeOH free) (13 ml) was added the solution of tosyl chloride (80.6 mmol) in pyridine (71 ml) and the whole was stirred for 21 h at 4 °C. The reaction mixture became white suspension. Then cool saturated NaCl solution (50 ml) was added and extracted by dichloromethane (50 ml x3). The organic layer was washed by 10% CuSO₄ (50 ml x5), satd. NaHCO₃ (30 ml), H₂O (30 ml), and satd. NaCl (20 ml), successively, and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (ether / hexane 1/1) afforded 24 as a colorless oil in 100% yield: ¹H-NMR (CDCl₃) δ; 1.4 (s, 9H, tBu), 1.9 (m, 4H, (CH₂)₂), 2.4 (s, 3H, ArCH₃), 3.3 (m, 2H, CH₂N), 4.0 (m, 3H, CH₂OTs, CHN), 7.2 (d, J=8.0 Hz, 2H, Ar-H), 7.7 (d, J=8.0 Hz, 2H, Ar-H); IR (neat) 1690, 1390, 1360, 1180 cm⁻¹; MS m/z 355 (M⁺); [α]_D²⁵ -41.0 (c 0.400, CHCl₃)

(S)-(-)-N-tert-Butoxycarbonyl-2-[(diphenylphosphino)methyl]pyrrolidine (25)²⁴. To the solution of chlorodiphenylphosphine (2.1 mmol) in dioxane (3 ml) was added

²² Anderson, G. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, *79*, 6180.

²³ Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.

²⁴ Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

sodium (8.9 mmol) and the whole was refluxed under Ar for 6hr. The reaction mixture became yellow suspension. THF (2 ml) was added at rt and the solution of **24** in THF (2 ml) was added. After 1h the reaction mixture was filtrated through celite pad and washed with benzene. Concentration and purification by silica gel column chromatography (ether / benzene 1/19) afforded 77% yield of **25** as a colorless oil: $^1\text{H-NMR}$ (CDCl_3) δ ; 1.40 (s, 9H, tBu), 2.0 (m, 5H, $(\text{CH}_2)_2$, one of CH_2P), 2.7, 2.9 (m x2 (by amide configurational isomer) 1H one of CH_2P), 3.4 (m, 2H, CH_2N), 3.9 (m, 1H, CHN), 7.4 (m, 10H, C_6H_5 x2); $^{13}\text{C-NMR}$ (CDCl_3) δ ; 154.43(CO), 139.1 (d x2, Ar), 137.9 (d x2, Ar), 133 (m, Ar), 128.5 (m, Ar), 79.52, 79.01 ($(\text{CH}_3)_3\text{C}$), 55.62, 55.29 (CHN), 46.84, 46.33 (CH_2N), 34.09, 33.28 (CH_2P), 31.52, 31.39 (CH_2CHN), 28.75 ($(\text{CH}_3)_3$), 24.03, 23.17 ($\text{CH}_2\text{CH}_2\text{N}$); IR (neat) 1690, 1390, 1170, 1110 cm^{-1} ; MS m/z 369 (M^+); $[\alpha]^{20}_{\text{D}}$ -69.3 (c 1.09, CHCl_3); Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{P}$: C, 71.54; H, 7.59; N, 3.79. Found: C, 71.47; H, 7.73; N, 3.77.

(S)-(-)-2-[(Diphenylphosphino)methyl]pyrrolidine (14)²⁵. To the solution of **25** (27.6 mmol) in dichloromethane (60 ml) was added trifluoroaceticacid (276 mmol) under ice bath and the whole was stirred for 4h at rt. The reaction mixture was concentrated and dissolved in 6N HCl. NaOH (pellet) was added to pH 14 and the water layer was extracted by dichloromethane (200 ml x2 + 100 ml). The organic layer was washed by H_2O (50 ml) and satd. NaCl (100 ml), successively, and dried over Na_2SO_4 . Concentration and distillation (150 - 160 $^\circ\text{C}$ / 0.4 mmHg) gave pure **14** as a colorless oil in 78% yield: $^1\text{H-NMR}$ (CDCl_3) δ ; 1.40 (m, 1H one of $(\text{CH}_2)_2$), 1.63 ~ 2.00 (m, 3H, $(\text{CH}_2)_2$), 2.22 (dd, $J=7.7$, 13.8 Hz, 1H, one of CH_2P), 2.33 (dd, $J=6.9$, 13.8 Hz, 1H, one of CH_2P), 2.80 (ddd, $J=6.9$, 8.3, 10.8 Hz, 1H, one of CH_2N), 3.01 (m, 2H, CHN, one of CH_2N), 7.35 (m, 6H, Ar), 7.45 (m, 4H, Ar); $^{13}\text{C-NMR}$ (CDCl_3) δ ; 138.55 (d, $J=15.8$ Hz, *ipso*-Ar-C), 132.66 (d, $J=4.9$ Hz), 132.38 (d, $J=6.1$ Hz), 128.23, 56.27 (d, $J=15.9$ Hz, CHN), 46.08 (CH_2N), 35.59 (d, $J=13.5$ Hz, CH_2P), 32.38 (d, $J=7.3$ Hz, CH_2CHN), 25.03 ($\text{CH}_2\text{CH}_2\text{N}$); IR (neat) 3300, 1430, 740, 700 cm^{-1} ; MS m/z 269 (M^+); $[\alpha]^{20}_{\text{D}}$ -29.4 (c 4.86, EtOH); Anal. (hygroscopic) Calcd for $\text{C}_{17}\text{H}_{20}\text{NP}\cdot 1/2\text{H}_2\text{O}$: C, 73.38; H, 7.55; N, 5.04. Found: C, 73.41; H, 7.29; N, 4.95. HCl salt: colorless prisms; mp 124-125 $^\circ\text{C}$; MS m/z 269 ($\text{M}^+\text{-HCl}$); $[\alpha]^{25}_{\text{D}}$ -3.06 (c 0.620, EtOH); Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NPCl}\cdot 1/7\text{H}_2\text{O}$: C, 66.21; H, 6.90; N, 4.54. Found: C, 66.22; H, 6.77; N, 4.42.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-[(diphenylphosphino)methyl]pyrrolidine (2). To the solution of **14** (7.40 mmol) and triethylamine (18.5 mmol) in dichloromethane (7 ml) was added pivaloylchloride (11.1 mmol) under ice bath and the whole was stirred for 30 min. Satd. NaHCO_3 (20 ml) was added and extracted by dichloromethane (30 ml x3). The combined organic layer was washed by 10% HCl (20 ml), satd. NaHCO_3 (10 ml), H_2O (10 ml), and satd. NaCl (10 ml), successively, and dried over Na_2SO_4 . Concentration and recrystallization from ether (17 ml) gave pure **2** as colorless prisms in 68% yield: mp 97 - 97.5 $^\circ\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ ; 1.19

²⁵ Ogata, I.; Mizukami, F.; Ikeda, Y.; Tanaka, M. *Japan Patent, Kokai*, 1976, 76, 43754; *Chem. Abstr.*

(s, 9H, tBu), 1.74 ~ 2.03 (m, 5H, (CH₂)₂, one of CH₂P), 2.93 (brd, *J*=10 Hz, one of CH₂P), 3.52 (m, 1H, CH₂N), 3.71 (m, 1H, CH₂N), 4.31 (m, 1H, CHN), 7.27 ~ 7.39 (m, 8H, Ar), 7.63 (m, 2H, Ar); ¹³C-NMR (CDCl₃) δ; 176.30 (CO), 128.01 ~ 139.37 (Ar), 57.08 (d, *J*=18.3 Hz, CHN), 47.98 (CH₂N), 39.05 ((CH₃)₃C), 32.51 (d, *J*=13.4 Hz, CH₂P), 29.55 (d, *J*=11.0 Hz, CH₂CHN), 27.55 ((CH₃)₃), 25.48 (CH₂CH₂N); IR (KBr) 1610 cm⁻¹; MS *m/z* 353 (M⁺); [α]_D²⁵ -67.3 (c 1.45, CHCl₃); Anal. Calcd for C₂₂H₂₃NOP: C, 74.78; H, 7.93; N, 3.97. Found: C, 75.01; H, 8.02; N, 3.84.

(S)-(-)-N-Pentafluorobenzoyl-2-[(diphenylphosphino)methyl]pyrrolidine (5).

The same procedure as 2. Purification by alumina column chromatography (benzene / hexane 4/1) gave 96% yield. Recrystallization twice from pentane (40 ml) gave 5 as white powder in 86% yield: mp 84 – 85 °C; ¹H-NMR (CDCl₃) δ; 1.82 ~ 2.35 (m, 5H, (CH₂)₂, one of CH₂P), 3.16 ~ 3.76 (m, 3H, CH₂N, CHN, one of CH₂P), 4.35 (m, ca. 0.5H, CHN), 7.10 ~ 7.44 (m), 7.70 (m, 2H); ¹³C-NMR (CDCl₃) δ; 156.6, 156.1 (CO), 128.4 ~ 145 (Ar), 56.8 (d, *J*=23.1 Hz, CHN), 56.3 (d, *J*=21.9 Hz, CHN), 47.9, 45.7 (CH₂N), 34.8 (d, *J*=15.8 Hz, CH₂P), 32.2 (d, *J*=14.6 Hz, CH₂P), 30.8 (d, *J*=7.3 Hz, CH₂CHN), 24.0 (CH₂CH₂N), 22.1 (CH₂CH₂N) (Each carbon gave two signals by amide configurational isomer); IR (neat) 1650 cm⁻¹; MS *m/z* 463 (M⁺); [α]_D²⁵ -93.3 (c 0.845, CHCl₃); Anal. Calcd for C₂₄H₁₉NOF₅P: C, 62.20; H, 4.10; N, 3.02. Found: C, 62.37; H, 4.09; N, 3.29.

(S)-(-)-N-1'-Naphthoyl-2-[(diphenylphosphino)methyl]pyrrolidine (6). White amorphous. Yield 32%: mp 47 – 56 °C; ¹H-NMR (CDCl₃) δ; 1.59 ~ 2.25 (m, 6H, (CH₂)₂, CH₂P), 3.01 ~ 3.89 (m, 2H, CH₂N), 4.55 (m, 1H, CHN), 6.45, 6.87 ~ 7.48, 7.79 (m, Ar); ¹³C-NMR (CDCl₃) δ; 169.0, 168.9 (CO), 123.7 ~ 139.2 (Ar), 56.8 (d, *J*=22.5 Hz, CHN), 55.4 (d, *J*=19.5 Hz, CHN), 48.8 (CH₂N), 45.3 (CH₂N), 33.8 (d, *J*=15.7 Hz, CH₂P), 32.8 (d, *J*=13.5 Hz, CH₂P), 30.9 (d, *J*=8.6 Hz, CH₂CH), 30.6 (d, *J*=9.7 Hz, CH₂CHN), 24.4 (CH₂CH₂N), 22.1 (CH₂CH₂N) (Each carbon gave two signals by amide configurational isomer); IR (CHCl₃) 1610 cm⁻¹; MS *m/z* 423 (M⁺); [α]_D²⁵ -133.1 (c 1.03, CHCl₃); Anal. Calcd for C₂₈H₂₆NOP: C, 79.43; H, 6.15; N, 3.31. Found: C, 79.32; H, 6.26; N, 3.22.

(S)-(-)-N-Benzoyl-2-[(diphenylphosphino)methyl]pyrrolidine (7). White powder. Yield 95%: mp 92 – 92.5 °C (Et₂O / hexane 1:1); ¹H-NMR (CDCl₃) δ; 1.71 ~ 2.26 (m, 5H, (CH₂)₂, one of CH₂P), 3.12 (ddd, *J*=3.5 Hz, 3.5 Hz, 14.0 Hz, 1H, one of CH₂P), 3.43 (m, 2H, CH₂N), 4.41 (m, 1H, CHN), 7.26 ~ 7.45 (m, 13H, Ar), 7.70 (m, 2H, Ar); ¹³C-NMR (CDCl₃) δ; 169.9 (CO), 127.2 ~ 138.8 (Ar), 55.6 (d, *J*=19.5 Hz, CHN), 50.4 (CH₂N), 32.9 (d, *J*=12.2 Hz, CH₂P), 31.4 (d, *J*=8.5 Hz, CH₂CHN), 25.4 (CH₂CH₂N); IR (KBr) 1610 cm⁻¹; MS *m/z* 373 (M⁺); [α]_D²⁵ -114.9 (c 1.41, CHCl₃); Anal. Calcd. for C₂₄H₂₄NOP: C, 77.21; H, 6.43; N, 3.75. Found: C, 77.39; H, 6.53; N, 3.78.

(S)-(-)-N-Trifluoroacetyl-2-[(diphenylphosphino)methyl]pyrrolidine (8). Colorless prisms. Yield 88%: mp 72 – 74 °C; ¹H-NMR (CDCl₃) δ; 1.95 (m, 5H, (CH₂)₂, one of CH₂P), 2.92 (ddd, *J*=3.5 Hz, 3.5 Hz, 13.4 Hz, 1H, one of CH₂P), 3.53 (m, 2H, CH₂N), 4.14 (m,

1H, CHN), 7.3 (m, 10H, Ar); ¹³C-NMR (CDCl₃) δ; 155.38 (q, *J*=36.0 Hz, CO), 138.54 (d, *J*=11.0 Hz, *ipso*-Ar), 136.35 (d, *J*=6.8 Hz, *ipso*-Ar), 132.43 ~ 133.08 (Ar), 128.40 ~ 128.70 (Ar), 116.21 (q, *J*=288 Hz, CF₃), 57.62 (d, *J*=19.6 Hz, CHN), 46.80 (CH₂N), 31.56 (d, *J*=14.7 Hz, CH₂P), 29.63 (d, *J*=8.6 Hz, CH₂CHN), 24.51 (CH₂CH₂N); IR (CHCl₃) 1670, 1140 cm⁻¹; MS *m/z* 365 (M⁺); [α]²⁵_D -89.8 (c 1.24, CHCl₃); Anal. Calcd for C₁₉H₁₉NOF₃P: C, 62.47; H, 5.24; N, 3.83. Found: C, 62.43; H, 5.28; N, 4.04.

(S)-(-)-N, N, N', N'-Tetramethyl-2-[(diphenylphosphino)methyl]pyrrolidinyl phosphonic triamide (3). Colorless prisms. Yield 79%; mp 54 – 57 °C; ¹H-NMR (CDCl₃) δ; 1.76 ~ 2.01 (m, 5H, (CH₂)₂, one of CH₂P), 2.58 (dx2, *J*=9.3 Hz, 12H, (CH₃)₂Nx2), 2.80 (ddd, *J*=3.0, 5.0, 13.2 Hz, 1H, one of CH₂P), 3.15 (m, 2H, CH₂N), 3.71 (m, 1H, CHN), 7.27 ~ 7.44 (m, 8H, Ar), 7.55 ~ 7.61 (m, 2H, Ar); ¹³C-NMR (CDCl₃) δ; 139.10, 137.70, 133.26 ~ 132.29, 128.50 ~ 128.16 (Ar), 56.40 (d, *J*=20.7 Hz, CHN), 46.35 (CH₂N), 36.75 ((CH₃)₂N), 35.72 (d, *J*=13.4 Hz, CH₂P), 31.88 (CH₂CHN), 25.00 (CH₂CH₂N); IR (neat) 1480, 1455, 1430, 1200, 990; MS *m/z* 403 (M⁺); [α]²⁵_D -89.1 (c 1.16, CHCl₃); Anal. Calcd for C₂₁H₃₁N₃OP₂: C, 62.52; H, 7.75; N, 10.42. Found: C, 62.44; H, 7.56; N, 10.57

(S)-(+)-N-(N', N'-Dimethylcarbamoyl)-2-[(diphenylphosphino)methyl]pyrrolidine (4). Colorless prisms. Yield 95%; mp 64 ~ 65 °C (ether / hexane 1/20); ¹H-NMR (CDCl₃) δ; 1.64 (m, 1H, one of (CH₂)₂), 1.80 (m, 2H, two of (CH₂)₂), 2.16 (m, 1H, (CH₂)₂), 2.25 (dd, *J*=8.9, 13.6 Hz, 1H, CH₂P), 2.63 (s, 6H, (CH₃)₂), 2.68 (m, 1H, CH₂P), 3.28 (m, 2H, CH₂N), 4.18 (m, 1H, CHN), 7.26 ~ 7.56 (m, 10H, Ar); ¹³C-NMR (CDCl₃) δ; 163.05 (CO), 138.66 (dx2, *J*=56.2 Hz, 55.0 Hz, *ipso*-Ar), 132.33 ~ 132.79 (Ar), 128.00 ~ 128.32 (Ar), 56.28 (d, *J*=18.3 Hz, CHN), 50.75 (CH₂N), 37.59 (CH₃N), 33.59 (d, *J*=13.5 Hz, CH₂P), 31.97 (d, *J*=9.8 Hz, CH₂CHN), 25.54 (CH₂CH₂N); IR (CHCl₃) 1610 cm⁻¹; MS *m/z* 340 (M⁺); [α]²⁵_D +27.4 (c 1.14, CHCl₃); Anal. Calcd for C₂₀H₂₅NOP: C, 70.59; H, 7.35; N, 8.24. Found: C, 70.70; H, 7.49; N, 8.22. Melting point and optical rotation above was recorded in 1991. In 1993 ~ 1994, mp 76 – 78 °C and [α]²⁵_D +28.2 (c 1.24, CHCl₃)

(S)-(-)-N-(4-Methylphenylsulfonyl)-2-[(diphenylphosphinyl)methyl]pyrrolidine (70). To the solution of **14** (0.413 mmol) and triethylamine (1.03 mmol) in dichloromethane (1 ml) was added TsCl (0.619 mmol) under ice bath and the whole was stirred for 16h at rt. Usual workup and purification by silica gel column chromatography (AcOEt / hexane 4/1) gave white amorphous powder in 78% yield: mp 90 – 91 °C; ¹H-NMR (CDCl₃) δ; 1.46 (m, 1H, (CH₂)₂), 1.76 (m, 2H, (CH₂)₂), 2.14 (m, 1H, (CH₂)₂), 2.49 (ddd, *J*=11.7, 14.6, 14.6 Hz, 1H, CH₂P), 2.99 (m, 1H, CH₂N), 3.28 (ddd, *J*=2.0, 8.2, 14.6 Hz, 1H, CH₂P), 3.45 (m, 1H, CH₂N), 3.60 (m, 1H, CHN), 7.14 (d, *J*=8.2 Hz, 2H, Ts), 7.34 (d, overlapped with CHCl₃, 2H, Ts), 7.45 (m, 3H), 7.61 (m, 3H), 7.76 (m, 2H), 7.97 (m, 2H); ¹³C-NMR (CDCl₃) δ; 143.27 (CSO₂), 127.3 ~ 134.25 (Ar), 55.33 (s, CHN), 48.95 (CH₂N), 36.39 (d, *J*=66.0 Hz, CH₂P), 32.10 (CH₂CHN), 23.69 (CH₂CH₂N), 21.24 (CH₃Ph); IR (CHCl₃) 1335, 1475, 1160 cm⁻¹; MS *m/z* 438 (M⁺-1); [α]²⁵_D

-207.2 (c 0.695, CHCl₃); Anal. Calcd for C₂₄H₂₆NO₃PS: C, 65.60; H, 5.92; N, 3.19. Found: C, 65.48; H, 5.99; N, 3.41.

(S)-(-)-N-(4-Methylphenylsulfonyl)-2-[(diphenylphosphino)methyl]pyrrolidine (9). To the solution of **70** (1.38 mmol) and triethylamine (2.06 mmol) in acetonitrile (5 ml) was added trichlorosilane under ice bath and the whole was stirred for 4h at rt. Usual workup and recrystallization from ether-hexane (1:1) gave colorless prisms in 51% yield: mp 94 – 95 °C; ¹H-NMR (CDCl₃) δ; 1.40 ~ 1.89 (m, 4H, (CH₂)₂), 2.15 (ddd, *J*=4.5, 11.7, 13.5 Hz, 1H, CH₂P), 2.38 (s, 3H, CH₃Ph), 3.08 (m, 2H), 3.45 (m, 2H), 7.10 ~ 7.44 (m, 12H, Ar), 7.71 (m, 2H); ¹³C-NMR (CDCl₃) δ; 143.1 (CSO₂), 127.4 ~ 129.5 (Ar), 58.0 (d, *J*=20.7 Hz, CHN), 49.4 (CH₂N), 36.1 (d, *J*=13.4 Hz, CH₂P), 31.8 (d, *J*=8.6 Hz, CH₂CHN), 24.1 (CH₃Ph), 21.4 (CH₂CH₂N); IR (KBr) 1340, 1150 cm⁻¹; [α]_D²⁵ -289.9 (c 1.66, CHCl₃); Anal. Calcd for C₂₄H₂₆NO₂PS: C, 68.09; H, 6.15; N, 3.31. Found: C, 68.36; H, 6.19; N, 3.19.

(S)-(-)-N-Methyl-2-[(diphenylphosphino)methyl]pyrrolidine (1)²⁶. **25** (19.7 mmol) in THF (30 ml) was added to the suspension of lithium aluminum hydride (59.0 mmol) in THF (20 ml) under ice bath and the whole was refluxed for 1h. H₂O (2 ml), 15% NaOH (2 ml), and H₂O (1 ml) was added successively. Filtration and concentration followed by distillation gave colorless oil in 80% yield: ¹H-NMR (CDCl₃) δ; 1.53 ~ 1.76 (m, 3H, (CH₂)₂), 1.97 ~ 2.14 (m, 4H, one of (CH₂)₂, CHN, one of CH₂N, one of CH₂P), 2.27 (s, 3H, CH₃N), 2.55 (ddd, *J*=9.5, 3.0, 3.0 Hz, 1H, one of CH₂P), 3.03 (tlike, *J*=8.5 Hz, 1H, one of CH₂N), 7.27 ~ 7.47 (m, 10H, Ar); ¹³C-NMR (CDCl₃) δ; (*ipso*-Ar), 63.64 (d, *J*=19.5 Hz, CHN), 56.79 (CH₂N), 40.04 (CH₃N), 33.27 (d, *J*=13.4 Hz, CH₂P), 31.99 (d, *J*=7.4 Hz, CH₂CHN), 21.84 (CH₂CH₂N); IR (neat) 1430, 700 cm⁻¹; MS *m/z* 283 (M⁺); [α]_D²⁵ -131.5 (c 1.31, CHCl₃).

Di-(4-methoxyphenyl)phosphinous acid (27)²⁷. To the suspension of NaH (11.0 mmol) in ether (10 ml) was added diethyl phosphite (10.0 mmol) under ice bath and stirred at rt for 35 min. *p*-Methoxyphenylmagnesium bromide (21.0 mmol) in ether (11.7 ml) was added under ice bath and the whole was stirred at rt for 35 min and then refluxed for 2h. 10% HCl (20 ml) was added under ice bath and extracted by dichloromethane (50 ml x3). The organic layer was washed by satd. NaHCO₃, H₂O, and satd. NaCl (10 ml each), successively, and dried over Na₂SO₄. Concentration and recrystallization from AcOEt (7 ml) gave colorless needles in 58% yield: mp 121 – 122 °C; ¹H-NMR (CDCl₃) δ; 3.84 (s, 6H, CH₃O), 6.95 (dd, *J*=2.5, 7.9 Hz, 4H), 7.61 (dd, *J*=8.6, 13.0 Hz, 4H), 8.05 (d, *J*=447 Hz, PH); ¹³C-NMR (CDCl₃) δ; 162.75 (MeOC(*ipso*)), 132.52 (d, *J*=12.2 Hz, MeOCCH-Ar), 122.86 (d, *J*=117.4Hz, Ar-*ipso*CP), 114.32 (d, *J*=14.7 Hz, Ar-CHCP),

²⁶ Hayashi, T; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**,

48, 2195.

²⁷ Hunt, B. B.; Saunders, B. C. *J. Chem. Soc.* **1957**, 2413.

55.26 (CH₃O); IR (nujol) 1600, 1300, 1175 cm⁻¹; MS m/z 262 (M⁺), 246 (M⁺+1-CH₃), 231 (M⁺+1-(CH₃)₂).

Di-(4-methoxyphenyl)phosphine (28). To the solution of **27** (3.85 mmol) in toluene (7 ml) was added trichlorosilane (15.4 mmol) and the whole was stirred at rt for 75 min and at 40 °C for 7h. The reaction mixture was diluted with benzene (30 ml) and poured to 10% NaOH (30 ml), then filtrated through celite pad. The organic layer was separated, washed by 10 ml of satd. NaCl, dried over MgSO₄, and concentrated. ¹H-NMR analysis showed that this crude mixture was 1:1 mixture of the starting phosphine oxide and the target phosphine. This mixture was used without further purification.

(S)-(-)-N-tert-Butoxycarbonyl-2-[(di-(p-methoxyphenyl)phosphino)methyl]pyrrolidine (29). To the suspension of KH (5.51 mmol, washed twice by hexane) in THF (5 ml) was added **27** (1.84 mmol, 1:1 mixture of phspine oxide and phosphine) in THF (5 ml) under ice bath and the resulting deep red suspension was stirred at rt for 1h. **24** (3.30 mmol) in THF (4 ml) was added under ice bath and the whole was stirred for 30 min (red color disappered). Satd. NH₄Cl (20 ml) was added and extracted three times with 20 ml of AcOEt. The combined organic layer was successively washed with 10% HCl, satd. NaHCO₃, H₂O, and satd NaCl (10 ml each), then dried over Na₂SO₄. Concentration and purification by silica gel column chromatography gave 15% yield of target material as a colorless oil: ¹H-NMR (CDCl₃) δ; 1.42 (s, 9H, tBu), 1.93 (m, 5H), 2.64 (m, 1H), 3.33 (m, 2H, CH₂N), 3.78 (s, 6H, CH₃O), 3.85 (m, 1H, CHN), 6.90 (dd, *J*=2.5, 7.5 Hz, 4H), 7.4 (m, 4H); ¹³C-NMR (CDCl₃) δ; 160.15 (Ar-COMe), 160.00 (Ar-COMe), 154.23 (CO), 134.52 (d, *J*=9.6 Hz, Ar-CHCP), 133.62 (d, *J*=9.0 Hz, Ar-CHCP), 130.0 (d, *J*=11.3 Hz, Ar-CP), 126.8 (d, *J*=11.3 Hz, Ar-CP), 114.15 (d, *J*=7.6 Hz, Ar-CHCOMe), 79.08 ((CH₃)₃C), 55.31 (d, *J*=20.7 Hz, CHN), 55.12 (ArOCH₃), 46.33 (CH₂N), 34.10 (CH₂P), 31.12 (d, *J*=9.0 Hz, CH₂CHN), 28.63 ((CH₃)₃CO), 23.39 (CH₂CH₂N); IR (neat) 2960, 1675, 1590, 1500, 1395, 1280, 1245, 1175 cm⁻¹; MS m/z 429 (M⁺), 372 (M⁺-tBu); [α]_D²⁵ -51.2 (c 1.17, CHCl₃); Anal. Calcd. for C₂₄H₃₂NO₄P: C, 67.12; H, 7.51; N, 3.26. Found: C, 67.17; H, 7.36; N, 3.22. Unreacted **24** was recovered in 42%.

(S)-(+)-N-(N', N'-Dimethylcarbamoyl)-2-[(di-(p-methoxyphenyl)phosphino)methyl]pyrrolidine (16). To the solution of **29** (0.510 mmol) in dioxane (2 ml) was added 5.7N HCl in dioxane (1.8 ml, 10.2 mmol) and stirred at rt for 1.5h. Concentration gave white amorphous, which was dissolved in dichloromethane (1 ml). Triethylamine (2.55 mmol) and dimethylcarbamoyl chloride (0.765 mmol) was added under ice bath and the whole was stirred for 25 min. 10% Na₂CO₃ was added and extracted with dichloromethane (20 ml x3). The combined organic layer was washed successively with 10% HCl, satd. NaHCO₃, H₂O, and satd. NaCl (10 ml each), and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (AcOEt / hexane 4/1) gave pure **16** as a colorless oil in 67% yield: ¹H-NMR (CDCl₃) δ; 1.75 ~ 2.2 (m, 4H, (CH₂)₂), 2.65 (m, 2H, CH₂P), 2.66 (s, 6H, (CH₃)₂N), 3.25 (m, 2H, CH₂N), 3.73 (s, 6H, CH₃OAr), 4.10 (m, 1H, CHN), 6.86 (dd, *J*=5.0, 7.5 Hz, 4H), 7.4 (m, 4H); ¹³C-NMR

(CDCl₃) δ ; 162.96 (CO), 159.73 (Ar-COMe), 159.69 (Ar-COMe), 135.90 (d, J =20.5 Hz, Ar-CHCP), 133.60 (d, J =19.6 Hz, Ar-CHCP), 130.19 (d, J =9.7 Hz, Ar-CP), 128.91 (d, J =9.8 Hz, Ar-CP), 113.85 (d, J =7.3 Hz, Ar-CHCOMe), 56.30 (d, J =17.1 Hz, CHN), 54.83 (ArOCH₃), 54.79 (ArOCH₃), 37.54 ((CH₃)₂N), 34.09 (d, J =12.2 Hz, CH₂P), 31.90 (d, J =9.8 Hz, CH₂CHN), 25.45 (CH₂CH₂N); IR (neat) 2930, 1630, 1580, 1380, 1280, 1240 cm⁻¹; MS m/z 400 (M⁺), 356 (M⁺-Me₂N); [α]_D²⁵ +27.1 (c 0.590, CHCl₃); Anal. Calcd for C₂₂H₂₉N₂O₃P: C, 65.99; H, 7.30; N, 7.00. Found: C, 65.82; H, 7.23; N, 6.93.

Tri-(4-*N*, *N*-dimethylphenyl)phosphine (30)²⁸. *p*-Bromodimethylaniline (0.250 mol) in ether (180 ml) was added to lithium (0.555 mol) in ether (150 ml) for 80 min and the whole was refluxed for 3h. The concentration of *p*-*N*, *N*-dimethylaminophenyllithium was shown to be 0.770 M by titration with diphenylacetic acid²⁹. To the solution of *p*-*N*, *N*-dimethylaminophenyllithium (223 mmol) in ether (290 ml) was added the solution of phosphorous trichloride (72.0 mmol) in ether (50 ml) for 1.5h at -78 °C and the reaction temperature was elevated spontaneously to rt. After stirring for 16.5 h, satd. NH₄Cl (200 ml) was added under ice bath and extracted by chloroform (100 ml x3) after evaporating ether solvent. The organic layer was successively washed by H₂O and satd. NaCl (50 ml each) and dried over Na₂SO₄. Concentration and recrystallization from benzene (370 ml) afforded **30** as pale yellow needles: mp 254 – 256 °C (sealed); ¹H-NMR (CDCl₃) δ ; 2.92 (s, 18H, (CH₃)₂N x3), 6.68 (dd, J =1.0, 9.0 Hz, 6H), 7.18 (m, 6H); IR (nujol) 1580 cm⁻¹.

(*S*)-(-)-*N*-tert-Butoxycarbonyl-2-[(di-(*p*-*N*, *N*-dimethylaminophenyl)phosphino) methyl]pyrrolidine (31)³⁰. To the suspension of **30** (21.5 mmol) in THF (150 ml) was added K (50.1 mmol) and the resulting red suspension was stirred at rt for 17.5 h. **24** (7.16 mmol) in THF (20 ml) was added under ice bath, and after 30 min EtOH (10 ml) was added to quench the reaction. Satd. NH₄Cl (20 ml) was added and extracted by AcOEt (30 ml x3). The combined organic layer was washed successively by 10% citric acid, satd. NaHCO₃, H₂O, and satd. NaCl (10 ml each) and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (AcOEt / benzene 1/9) gave pure **31** as a cloudy oil in 96% yield: ¹H-NMR (CDCl₃) δ ; 1.45 (s, 9H, tBu), 1.87 (m, 5H, (CH₂)₂, one of CH₂P), 2.7 (m, 1H, CH₂P), 2.94 (s, 12H, (CH₃)₂N), 3.36 (m, 2H, CH₂N), 3.85 (m, 1H, CHN), 6.68 (brd, J =7.5 Hz, 4H), 7.33 (m, 4H); ¹³C-NMR (CDCl₃) δ ; 154.21 (CO), 150.57 (Ar-CNMe₂), 150.39 (Ar-CNMe₂), 133.84 (d, J =20.7 Hz, Ar-CHCP), 133.45 (d, J =20.8 Hz, Ar-CHCP), 124.56 (Ar-CP), 123.29 (Ar-CP), 112.21 (d, J =8.5 Hz, Ar-CHCN), 79.03 ((CH₃)₃C), 55.43 (d, J =20.8 Hz, CHN), 45.99 (CH₂N), 40.19 ((CH₃)₂N), 34.25 (CH₂P), 33.30 (CH₂P), 31.04 (CH₂CHN), 28.56 ((CH₃)₃C), 23.70 (CH₂CH₂N), 22.95 (CH₂CH₂N). Some carbons were assigned to two signals because of amide configurational isomer. IR (neat) 2950, 1680, 1590 cm⁻¹; MS m/z 455 (M⁺), 398 (M⁺-tBu); [α]_D²⁵ -61.3 (c 1.03, CHCl₃); HRMS m/z : Calcd for C₂₆H₃₈N₃O₂P (M⁺): 455.2704. Found: 455.2703.

²⁸ Schiemenz, G. P. *Chem. Ber.* **1965**, *98*, 65.

²⁹ Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

³⁰ Toth, I; Hanson, B. E. *Tetrahedron: Asymmetry* **1990**, *1*, 895.

(S)-(+)-N-(N', N'-Dimethylcarbamoyl)-2-[(di-(p-N, N-dimethylaminophenyl)-phosphino)methyl]pyrrolidine (17). To the solution of **31** (2.46 mmol) in ethanol (9 ml) was added 5.7 N HCl in dioxane under ice bath and stirred for 3h at rt. White amorphous was obtained after concentration in vacuo and used in the next step without further purification. This crude amorphous was dissolved in the solution of dichloromethane (4 ml) and triethylamine (12.3 mmol) and *N, N*-dimethylcarbamoyl chloride (7.38 mmol) was added under ice bath. After 40 min the reaction mixture was directly charged to silica gel column chromatography (acetone / CHCl₃ 1/19) and purified to give white amorphous in 90% yield. This amorphous was further purified by recrystallization twice from benzene / hexane (1:3) to give pure **17** as white powder in 67% yield. Though **17** is not so labile to air, extraction by shaking (especially under basic condition) should be avoided: mp 98 – 99 °C (sealed); ¹H-NMR (CDCl₃) δ; 1.6 ~ 2.2 (m, 4H, (CH₂)₂), 2.58 ~ 3.0 (m, 2H, CH₂P), 2.97 (s, 6H, (CH₃)₂NCO), 2.92 (s, 12H, (CH₃)₂NAr), 3.25 (m, 2H, CH₂N), 4.12 (m, 1H, CHN), 6.69 (m, 4H), 7.35 (m, 4H); ¹³C-NMR (CDCl₃) δ; 163.05 (CO), 150.33 (ArCN), 133.65 (d, *J*=18.3 Hz, Ar-CHCP), 133.35 (d, *J*=18.3 Hz, Ar-CHCP), 125.12 (Ar-CP), 123.59 (Ar-CP), 112.23 (d, *J*=8.5 Hz, Ar-CHCN), 112.50 (d, *J*=8.5 Hz, Ar-CHCN), 56.45 (d, *J*=17.1 Hz, CHN), 50.39 (CH₂N), 40.13 ((CH₃)₂N), 40.07 ((CH₃)₂N), 37.68 (Ar-N(CH₃)₂), 34.28 (d, *J*=10.9 Hz, CH₂P), 31.93 (d, *J*=9.7 Hz, CH₂CHN), 25.47 (CH₂CH₂N); IR (neat) 1630, 1590 cm⁻¹; [α]_D²⁵ +29.2 (c 1.20, CHCl₃); HRMS *m/z* Calcd for C₂₄H₃₅N₄PO (M⁺): 426.2552. Found: 426.2554.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-pyrrolidinemethanol (33). To the solution of L-prolinol (**32**) (99.0 mmol) in dichloromethane (50 ml) was added triethylamine (119 mmol) and pivaloyl chloride (99.0 mmol) and the whole was stirred for 10 min under ice bath. Satd. NaHCO₃ (50 ml) was added and extracted by CH₂Cl₂ (50 ml x3). The organic layer was washed successively by 10% HCl (50 ml), satd. NaHCO₃, H₂O, and satd. NaCl (20 ml each) and dried over Na₂SO₄. Concentration and recrystallization from hexane (10 ml) gave colorless prisms in 82% yield: mp 79.5 ~ 81 °C; ¹H-NMR (CDCl₃) δ; 1.28 (s, 9H, tBu), 1.5 ~ 2.1 (m, 4H, (CH₂)₂), 3.2 ~ 3.91 (m, 4H, CH₂N, CH₂O), 4.25 (m, 1H, CHN), 4.80 (brs, 1H, OH); ¹³C-NMR (CDCl₃) δ; 179.19 (CO), 67.81 (CH₂O), 62.35 (CHN), 48.46 (CH₂N), 39.09 ((CH₃)₃CO), 27.51 ((CH₃)₃C), 27.32 (CH₂CHN), 25.34 (CH₂CH₂N); IR (neat) 3330, 1585 cm⁻¹; MS *m/z* 185 (M⁺); [α]_D²⁵ -70.9 (c 0.970, EtOH); Anal. Calcd. for C₁₀H₁₉NO₂: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.04; H, 10.21; N, 7.58.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-(methoxymethyl)pyrrolidine (13). To the suspension of NaH (32.4 mmol, washed three times by 3 ml of dry hexane) in THF (10 ml) was added **33** (16.2 mmol) in THF (20 ml) under ice bath. After 15 min, methyl iodide (81.0 mmol) was added and stirred for 1h. Satd. NH₄Cl (10 ml) was added and extracted by AcOEt (50 ml x3). The organic layer was washed successively by 10% HCl, satd. NaHCO₃, H₂O, and satd. NaCl (20 ml each) and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography gave **13** as a pale yellow oil in 94% yield: ¹H-NMR (CDCl₃) δ; 1.25 (s, 9H, tBu), 1.92 (m, 4H (CH₂)₂), 3.33 (s, 3H, OCH₃), 3.58 (m, 4H, CH₂N, CH₂O), 4.33 (m, 1H, CHN); ¹³C-NMR

(CDCl₃) δ ; 176.20 (CO), 72.24 (CH₂O), 58.63 (CHN), 57.81 (CH₃O), 47.86 (CH₂N), 38.92 ((CH₃)₃C), 27.38 ((CH₃)₃), 26.22 (CH₂CHN), 24.82 (CH₂CH₂N); IR (neat) 1620 cm⁻¹; MS *m/z* 199 (M⁺); [α]_D²⁵ -85.3 (c 1.03, EtOH); HRMS. Calcd for C₁₁H₂₁NO₂ (M⁺): 199.1573. Found: 199.1570.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-[(methylthio)methyl]pyrrolidine (10).

To the solution of dimethyl disulfide (67.5 mmol) and tributylphosphine (67.5 mmol) in pyridine (70 ml) was added **33** and the whole was stirred at rt for 2 days. H₂O (50 ml) was added to quench the reaction and extracted by AcOEt (50 ml x3). The organic layer was washed successively by H₂O (50 ml x6) and satd. NaCl (20 ml) then dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (AcOEt / hexane 1/9) gave **10** as a colorless oil in 64% yield: ¹H-NMR (CDCl₃) δ ; 1.24 (s, 9H, tBu), 1.87 (m, 4H, (CH₂)₂), 2.16 (s, 3H, SCH₃), 2.41 (dd, 1H, *J*=9.4, 13.0 Hz, CH₂S), 2.90 (dd, *J*=2.6, 13.0 Hz, 1H, CH₂S), 3.63 (m, 2H, CH₂N), 4.30 (m, 1H, CHN); ¹³C-NMR (CDCl₃) δ ; 176.39 (CO), 58.36 (CHN), 48.22 (CH₂N), 39.10 ((CH₃)₃CCO), 36.66 (CH₂S), 27.93 (CH₂CHN), 27.50 ((CH₃)₃), 24.94 (CH₂CH₂N), 15.60 (SCH₃); IR (neat) 1630 cm⁻¹; MS *m/z* 215 (M⁺); [α]_D²⁵ -64.1 (c 1.36, EtOH); Anal. Calcd for C₁₁H₂₁NOS: C, 61.35; H, 9.83; N, 6.50. Found: C, 61.26; H, 9.65; N, 6.76.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-[(phenylthio)methyl]pyrrolidine (11).

To the solution of diphenyl disulfide (9.89 mmol) and tributylphosphine (9.89 mmol) in pyridine (10 ml) was added **33** and the whole was stirred at rt for 4h. Workup as usual and purification by silica gel column chromatography (AcOEt / hexane 1/4) gave **11** as a colorless oil in 100% yield: ¹H-NMR (CDCl₃) δ ; 1.21 (s, 9H, tBu), 1.9 (m, 4H, (CH₂)₂), 2.88 (dd, *J*=6.0, 9.1 Hz, 1H, CH₂S), 3.51 (dd, 1H, *J*=2.1, 9.1 Hz, CH₂S), 3.60 (m, 2H, CH₂N), 4.40 (m, 1H, CHN), 7.10 ~ 7.50 (m, 5H, Ar); ¹³C-NMR (CDCl₃) δ ; 176.67 (CO), 136.43 (Ar-CS), 128.83 (Ar, *p*-CH), 128.17 (Ar, *o*-CH), 125.39 (Ar, *m*-CH), 58.21 (CHN), 48.48 (CH₂N), 39.09 ((CH₃)₃CCO), 35.16 (CH₂S), 28.03 (CH₂CHN), 27.49 ((CH₃)₃), 25.14 (CH₂CH₂N); IR (neat) 1620 cm⁻¹; MS *m/z* 277 (M⁺); [α]_D²⁵ -9.37 (c 1.20, EtOH); Anal. Calcd for C₁₆H₂₃NOS: C, 69.27; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.07; N, 4.97.

(S)-(+)-N-tert-Butoxycarbonyl-2-[(N', N'-diphenylamino)methyl]pyrrolidine (34). To the suspension of NaH (83.1 mmol, washed three times by 10 ml of dry hexane) in THF (80 ml) was added diphenylamine (83.1 mmol) and refluxed for 2.5h. **24** in THF 15 ml was added at rt and the whole was stirred for 2.5h. Satd. NH₄Cl (50 ml) was added and extracted by AcOEt (50 ml x3). The organic layer was washed successively by satd. NaHCO₃, H₂O, satd. NaCl and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (ether / hexane 1/9) gave pale yellow oil in 78% yield: ¹H-NMR (CDCl₃) δ ; 1.50 (s, 9H, tBu), 1.86 (m, 4H, (CH₂)₂), 3.3 ~ 4.3 (m, 5H), 6.87 ~ 7.35 (m, 10H, Ar); ¹³C-NMR (CDCl₃) δ ; 154.54 (CO), 148.65 (Ar-*ipso*C), 129.24 (Ar, *m*-CH), 121.43 (Ar, *p*-CH), 120.76 (Ar, *o*-CH), 79.78 ((CH₃)₃CO), 55.55 (CHN), 54.24 (CH₂NPh₂), 46.55 (CH₂NCO), 29.8 (CH₂CHN), 28.66 ((CH₃)₃), 22.68

(CH₂CH₂N); IR (neat) 1690 cm⁻¹; MS m/z 352 (M⁺); [α]²⁵_D +3.46 (c 2.05, EtOH); Anal. Calcd for C₂₂H₂₈N₂O₂: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.18; H, 8.06; N, 7.71.

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-[(N' N'-diphenylamino)methyl]pyrrolidine (12). To the solution of **34** (1.05 mmol) in CH₂Cl₂ (5 ml) was added trifluoroacetic acid (21.1 mmol) and stirred at rt for 26h. The reaction mixture was evaporated and the resulting black oil was dissolved in CH₂Cl₂ (1 ml) and triethylamine (10.5 mmol). Pivaloyl chloride (5.25 mmol) was added under ice bath and the whole was stirred for 20 min. The reaction was quenched by satd. NaHCO₃ (30 ml). Workup as usual and purification by silica gel column chromatography (AcOEt / hexane 1/9) gave **12** as a pale yellow oil in 73% yield. Recrystallization from hexane gave colorless needles: mp 78 – 79 °C; ¹H-NMR (CDCl₃) δ : 1.22 (s, 9H, tBu), 1.85 (m, 4H, (CH₂)₂), 3.48 (dd, *J*=9.5, 14.5 Hz, 1H, one of CH₂NPh₂), 3.60 (m, 2H, CH₂N), 4.20 (dd, *J*=4.0, 15.3 Hz, 1H, one of CH₂NPh₂), 4.63 (m, 1H, CHN), 6.83 ~ 7.40 (m, 10H, Ar); ¹³C-NMR (CDCl₃) δ : 176.94 (CO), 148.89 (Ar-*ipso*C), 129.24 (Ar, *m*-CH), 121.19 (Ar, *o*, *p*-CH), 57.93 (CHN), 53.35 (CH₂NPh₂), 48.04 (CH₂NCO), 39.16 ((CH₃)₃C), 27.66 ((CH₃)₃), 27.05 (CH₂CHN), 25.12 (CH₂CH₂N); IR (neat) 1620 cm⁻¹; MS m/z 336 (M⁺); [α]²⁵_D -41.0 (c 1.53, EtOH); Anal. Calcd for C₂₂H₂₈N₂O: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.31; H, 8.58; N, 8.49.

(S)-(-)-N-(Carbobenzyloxy)-N'-phenyl-2-pyrrolidinecarboxamide (36)³¹. To the solution of Z-L-proline (56.2 mmol) and triethylamine (61.8 mmol) in THF (160 ml) was added ethylchloroformate (61.8 mmol) under ice bath and the resulting white suspension was stirred for 3.5h. Aniline (61.8 mmol) was added at -5 °C and the whole was stirred for 1.8h. H₂O (100 ml) was added and extracted by AcOEt (100 ml x3). The combined organic layer was washed successively by 10% HCl, satd. NaHCO₃, H₂O, and satd. NaCl (50 ml each) and dried over Na₂SO₄. Concentration and recrystallization from AcOEt (50 ml) gave colorless prisms in 82% yield: mp 140 – 141 °C; ¹H-NMR (CDCl₃) δ : 1.8 ~ 2.6 (m, 4H, (CH₂)₂), 3.53 (m, 2H, CH₂N), 4.45 (m, 1H, CHN), 5.19 (m, 2H, PhCH₂), 7.3 (m, 10H, Ar); IR (CHCl₃) 3400, 3290, 1690 cm⁻¹; MS m/z 325 (M⁺+1); [α]²³_D -62.0 (c 1.05, EtOH).

(S)-(-)-N'-Phenyl-2-pyrrolidinecarboxamide (37)¹⁰. **36** (15.5 mmol) was dissolved in EtOH (100 ml) and 5% Pd on carbon (0.5g) was suspended. H₂ was bubbled for 100 min and diluted by EtOH. Filtration, concentration, and recrystallization from ether / hexane (20 ml/120ml) gave colorless plates in 87% yield: mp 78 – 78.5 °C; ¹H-NMR (CDCl₃) δ : 1.65 ~ 2.30 (m, 4H, (CH₂)₂), 3.01 (m, 2H, CH₂N), 3.85 (dd, *J*=5.6, 8.4 Hz, 1H, CHN), 6.98 ~ 7.66 (m, 5H, Ar), 9.7 (br, 1H, CONH); IR (CHCl₃) 3250, 1670 cm⁻¹; MS m/z 190 (M⁺); [α]²⁷_D -66.6 (c 1.14, EtOH).

(S)-(+)-2-[(N'-Phenylamino)methyl]pyrrolidine (38)¹⁰. To the suspension of lithium aluminum hydride (21.5 mmol) in THF (20 ml) was added **37** (10.7 mmol) under ice bath and stirred at rt for 21h. H₂O (0.8 ml), 15% NaOH (0.8 ml), and H₂O (1.6 ml) was dropped successively. Filtration, concentration, and distillation gave pale yellow oil in 93% yield: bp 200

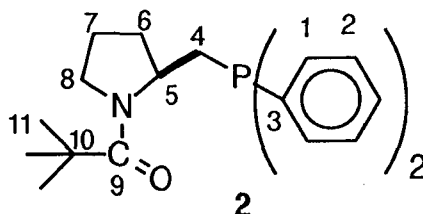
³¹ Mukaiyama, T.; Asami, M.; Hanna, J.; Kobayashi, S. *Chem. Lett.* 1977, 783.

°C/3mmHg; ¹H-NMR (CDCl₃) δ; 1.3 ~ 2.0 (m, 5H, (CH₂)₂, one of CH₂NHPh), 2.7 ~ 3.4 (m, 4H, CHN, CH₂N, one of CH₂NHPh), 4.0 (br, 1H, NH), 6.68 (m, 3H, Ar), 7.15 (m, 2H Ar); IR (neat) 3350, 1620 cm⁻¹; MS m/z 176 (M⁺); [α]²⁴_D +18.1 (c 1.59 EtOH).

(S)-(-)-N-(2', 2'-Dimethylpropionyl)-2-[(N'-phenylamino)methyl]pyrrolidine (20). To the solution of **38** (8.81 mmol) in CH₂Cl₂ (40 ml) was added triethylamine (13.2 mmol) and pivaloyl chloride (8.81 mmol) in CH₂Cl₂ (10 ml) at -78 °C and the reaction temperature was elevated spontaneously to -50 °C for 1.5h. Satd. NaHCO₃ (50 ml) was added and extracted by CH₂Cl₂ (30 ml x3). The organic layer was washed successively by satd. NaHCO₃ (20 ml), H₂O (10 ml), and satd. NaCl (10 ml) and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (ether / hexane 1/1) gave colorless oil in 92% yield: ¹H-NMR (CDCl₃) δ; 1.25 (s, 9H, tBu), 1.9 (m, 4H, (CH₂)₂), 3.09 (dd, *J*=6.4, 12.3 Hz, 1H, one of CH₂NHPh), 3.35 (dd, *J*=5.9, 12.3 Hz, 1H, one of CH₂NHPh), 3.6 (m, 2H, CH₂N), 4.53 (m, 2H, CHN, NH), 6.66 (m, 3H, Ar), 7.14 (m, 2H, Ar); IR (neat) 3350, 1600 cm⁻¹; MS m/z 260 (M⁺); [α]²⁵_D -25.8 (c 0.865, CHCl₃); Anal. Calcd for C₁₆H₂₄N₂O: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.97; H, 9.11; N, 10.66.

Chapter 2-3, 3-7. NMR Studies

^1H , ^{13}C , and ^{31}P -NMR chemical shift changes of **2** (0.04 mmol) by complexing with $\text{CuBr}\cdot\text{SMe}_2$ (0.04 mmol) in toluene- d_8 (0.6 ml) at 30 °C (ArCD_2H as internal standard for ^1H -NMR (2.10 ppm). ArCD_3 as internal standard for ^{13}C -NMR (20.4 ppm)). Chart 1~4.



#	^1H -NMR (ppm)		^{13}C -NMR (ppm)	
	control (δ)	+1eq $\text{CuBr}\cdot\text{SMe}_2$ ($\Delta\delta$)	control (δ)	+1eq $\text{CuBr}\cdot\text{SMe}_2$ ($\Delta\delta$)
1	7.87 (m) 7.42 (m)	+0.50 (m) +0.42 (m)	133.6 (d, 18.4 Hz) 133.3 (d, 21.8 Hz)	+1.2 (d, 15.9 Hz) - 0.1 (d, 13.5 Hz)
2	6.99~7.22 (m)	~ 0 (m)	127.6~129.2	~ 0
3	— —	— —	140.8 (d, 16.9 Hz) 138.4 (d, 13.5 Hz)	- 5.0 (d, 33.8 Hz) - 6.4 (d, 28.1 Hz)
4	3.14 (overlap) 1.88 (overlap)	+0.27 (brt, 12.1 Hz) +0.26 (overlap)	33.51 (d, 13.5 Hz) —	- 1.6 (d, 17.1 Hz) —
5	4.36 (m)	+0.06 (m)	57.50 (d, 19.5 Hz)	- 0.5 (d, 9.7 Hz)
6	1.22~1.87	1.32 (m), 1.73 (m)	29.91(d, 13.5 Hz)	+0.6 (d, 4.8 Hz)
7	1.22~1.87	1.97 (m), 2.52 (m)	25.59	+0.2
8	3.05, 3.20 (m)	- 0.02, - 0.07	47.95	- 0.2
9	—	—	175.2	+0.3
10	—	—	39.10	0
11	1.13 (s)	- 0.03	27.73	0

^{31}P -NMR (202.4 MHz, H_3PO_4 as external standard (0 ppm). Chart 5): Control: -20.5 ppm ($\Delta_{1/2}$ =45 Hz). +1eq $\text{CuBr}\cdot\text{SMe}_2$: $\Delta\delta$ =+4.0 ppm ($\Delta_{1/2}$ =90 Hz).

^1H -NMR chemical shift changes of **2** (0.04 mmol) by complexing with LiClO_4 (0.04 mmol) in ether-toluene- d_8 (0.2 ml – 0.4 ml) at 30 °C (ArCD_2H as internal standard for ^1H -NMR (2.10 ppm)). Chart 6,7.

#	Control (δ ppm)	1eq LiClO ₄ ($\Delta\delta$ ppm)
1, 2	7.75 (m) 7.33 (m) 7.17 (m) 7.1 (m)	- 0.3 (m) +0.1 (m) 0 0
4	3.1 (overlap) 1.8 (overlap)	- 0.7 (br) - 0.1 (br)
5	4.26 (m)	+0.4
6, 7	1.0~1.7 (overlap)	0 (overlap)
8	3.2 (overlap)	- 0.4 (br), 0 (overlap)
11	1.1 (overlap)	- 0.1 (overlap)

¹³C and ³¹P-NMR chemical shift changes of 2 (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04mmol) in ether-toluene-*d*₈ (0.2 ml - 0.4 ml) at 30 °C (ArCD₃ as internal standard for ¹³C-NMR (20.4 ppm)). Chart 8~10.

#	Control (δ ppm)	+1eq LiClO ₄ ($\Delta\delta$ ppm)	+1eq CuBr•SMe ₂ ($\Delta\delta$ ppm)
1	133.6 (d, 19.5 Hz) 133.4 (d, 19.5 Hz)	0 (d, 19.5 Hz) - 0.2 (d, 19.5 Hz)	+1.3 (d, 15.8 Hz) - 0.2 (d, 15.7 Hz)
2	127.6~129.2	0	0
3	140.9 (d, 16.9 Hz) 138.6 (overlap)	- 1.1 (d, 16.9 Hz) - 0.7	- 4.6 (d, 31.5 Hz) - 6.1 (d, 31.5 Hz)
4	33.6 (d, 13.4 Hz)	- 0.8 (d, 14.7 Hz)	- 1.7 (d, 17.1 Hz)
5	57.6 (d, 19.5 Hz)	+0.4 (br)	- 0.5 (d, 9.7 Hz)
6	29.98 (d, 9.8 Hz)	- 0.1 (d, 9.8 Hz)	+0.5 (d, 5.5 Hz)
7	25.7	0	+0.2
8	48.1	+1.0 (br)	- 0.2
9	175.2	+2.6	+0.3
10	39.2	+0.2	0
11	27.8	- 0.3	0

³¹P-NMR (202.4 MHz, H₃PO₄ as external standard (0 ppm). Chart 11): Control; -20.7 ppm ($\Delta_{1/2}$ =36 Hz). +1eq LiClO₄; $\Delta\delta$ =-2.9 ppm ($\Delta_{1/2}$ =48 Hz). +1eq CuBr•SMe₂; $\Delta\delta$ =+3.6 ppm ($\Delta_{1/2}$ =95 Hz).

¹H, ¹³C, and ³¹P-NMR chemical shift changes of 2 by complexing with Me₂CuLi in ether-toluene-*d*₈ (1:12) at -20 °C. (ArCD₂H as internal standard for ¹H-NMR (2.10 ppm). ArCD₃ as internal standard for ¹³C-NMR (20.4 ppm).). To the suspension of CuI (0.40 mmol) in toluene-*d*₈ (4 ml) was dropped MeLi (0.80 mmol) in ether (0.53 ml) at -20 °C. After 15 min, 2 (0.43 mmol) in toluene-*d*₈ (2.1 ml) was added at -78 °C. The resulting colorless clear solution was transferred to 5φ NMR tube under Ar by canule at -78 °C. Chart 12~17.

#	¹ H-NMR (ppm)		¹³ C-NMR (ppm)	
	Control (δ)	+1eq Me ₂ CuLi (Δδ)	Control (δ)	+1eq Me ₂ CuLi (Δδ)
1, 2	7.31 (t, 7.5 Hz) 7.44 (m) 8.29 (t, 7.3 Hz)	- 0.1 (m) +0.13 (m) - 0.61(m)	133.44 (d, 15.6 Hz) 133.29 (d, 10.8 Hz)	+0.02 (d, 23.4 Hz) - 0.41 (d, 23.4 Hz)
3	—	—	140.29 (d, 16.9 Hz)	- 2.16 (br)
4	3.50 (m) 1.88 (m)	- 0.9 (m) - 0.3 (m)	32.88 (d, 11.0 Hz)	- 0.22 (br)
5	4.39 (m)	+0.5 (m)	56.94 (d, 18.3 Hz)	+0.89 (br)
6	1.0~1.5	0	29.24(d, 9.8 Hz)	+0.59 (br)
7	1.0~1.5	0	25.23	- 0.23(br)
8	2.88 (m)	- 0.3	47.52	+0.81 (br)
9	—	—	174.79	+2.05
10	—	—	38.94	- 0.10
11	1.2 (s)	- 0.26	27.23	- 0.41

¹H-NMR of Me₂CuLi: control; -0.26 (s, major), +0.29, +0.65, +0.86 (minor) ppm. +1eq ligand; -0.36 ppm (s) (Δδ=-0.10 ppm). ¹³C-NMR of Me₂CuLi: control; -8.12 ppm. +1eq ligand; -8.35 ppm (Δδ=-0.23 ppm). ³¹P-NMR (145 MHz, H₃PO₄ in D₂O as external standard (0 ppm).): control; -20.59 ppm (Δ_{1/2}=11 Hz). +1eq Me₂CuLi (-78 °C); -6.80, -10.80, -11.27, -15.60, -16.00, -19.40, -22.80 (major), -25.40 ppm; (-20 °C) -23.20 ppm (Δ_{1/2}=43 Hz).

¹H-NMR chemical shift changes of 2 (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04 mmol) in THF-*d*₈ (0.6 ml) at 30 °C (3-CH of THF-*d*₈ as internal standard (1.70 ppm)). Chart 19~22.

#	Control (δ)	+1eq LiClO ₄ (Δδ)	+1eq CuBr•SMe ₂ (Δδ)	+1eq LiClO ₄ (Δδ) +1eq CuBr•SMe ₂ (Δδ)
1	7.67 (m)	0 (m)	+0.4 (m)	+0.3 (m)

	7.35 (overlap)	0 (m)	+0.3 (m)	+0.3 (m)
2	7.19~7.32 (m)	0(m)	δ : 7.25 (m), 7.38 (m)	δ : 7.26 (m), 7.35 (m)
4	2.94 (ddd, 3.0, 5.1, 13.2 Hz) 1.9 (overlap)	- 0.1 (m) 0 (overlap)	+0.2 (brt, 13.5 Hz) +0.4 (m)	+0.2 (brt, 12.0 Hz) +0.2 (overlap)
5	4.19 (m)	0 (m)	+0.1 (m)	+0.1 (m)
6, 7	1.74~2.01 (m)	0 (m)	$\sim$ +0.1 (m)	δ : 1.59~2.18 (m)
8	3.67 (m) 3.50 (m)	0 (m) 0	- 0.1 0	- 0.1 0
11	1.14	0	0	0

^1H -NMR chemical shift changes of 2 by complexing with Me_2CuLi in ether-THF- d_8 (1:12) at $-78\text{ }^\circ\text{C}$. (3-CH of THF- d_8 as internal standard (1.70 ppm). Chart 23)

#	Control (ppm)	+1eq Me_2CuLi (ppm)
1,2	7.95 (t like, $J=7.1\text{ Hz}$)	- 0.1 (t like, $J=7.3\text{ Hz}$)
4	3.14 (m) 1.66 (ddd, $J=5.5, 12.6, 12.6\text{ Hz}$)	- 0.1 (m) +0.2 (m)
5	4.19 (m)	0
6, 7	1.88~2.10 (m)	0 (m)
8	3.68~3.76 (m)	0 (m)
11	1.21 (s)	0 (s)
$(\text{CH}_3)_2\text{CuLi}$	-1.46 (s, major), - 0.34 (s), +0.26 (s)	δ : -1.43 (s), -1.12 (br, major), -0.32 (s), +0.27 (s)

^{13}C -NMR chemical shift changes of 2 (0.04 mmol) by complexing with LiClO_4 (0.04 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (0.04 mmol) in THF- d_8 (0.6 ml) at $30\text{ }^\circ\text{C}$ (3-C of THF- d_8 as internal standard (25.3 ppm)). Chart 24~27.

#	Control (δ)	+1eq LiClO_4 ($\Delta\delta$)	+1eq $\text{CuBr}\cdot\text{SMe}_2$ ($\Delta\delta$)	+1eq LiClO_4 ($\Delta\delta$) +1eq $\text{CuBr}\cdot\text{SMe}_2$ ($\Delta\delta$)
1	133.9 (d, 19.6 Hz) 133.5 (d, 21.5 Hz)	0 0	+1.2 +0.1	+1.0 +0.3
2	128.9~129.1	0	δ : 129.1~130.8	δ : 129.1~130.7
3	138.8	+0.1 (d, 11.2 Hz)	- 6.0 (d, 32.6 Hz)	- 5.7 (d, 28.1 Hz)

	141.3	- 0.1 (d, 14.6 Hz)	- 4.9 (d, 33.8 Hz)	- 4.9 (d, 31.5 Hz)
4	33.7 (d, 13.4 Hz)	- 0.1 (d, 13.4 Hz)	- 1.7 (d, 17.1 Hz)	- 1.8 (d, 18.7 Hz)
5	58.1 (d, 19.5 Hz)	+0.1 (d, 21.5 Hz)	- 0.6 (d, 11.0 Hz)	- 0.4 (d, 9.8 Hz)
6	30.4 (d, 9.8 Hz)	0 (d, 8.5 Hz)	+0.5 (d, 3.7 Hz)	+0.5
7	26.2	- 0.1	+0.1	0
8	48.7	+0.1	- 0.2	- 0.2
9	175.7	+0.3	+0.3	+0.5
10	39.6	+0.1	+0.1	+0.1
11	28.0	- 0.1	- 0.1	0

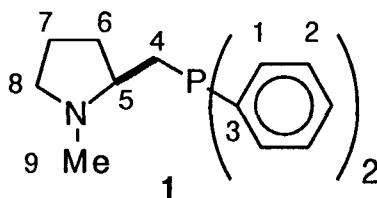
¹³C-NMR chemical shift changes of 2 by complexing with Me₂CuLi in ether-THF-*d*₈ (1:12) at -78 °C. (3-C of THF-*d*₈ as internal standard (26.5 ppm). Chart 28)

#	Control (δ ppm)	+1eq Me ₂ CuLi (Δδ ppm)
1	135.2 (d, 18.2 Hz) 134.5 (d, 19.5 Hz)	- 0.1 (d, 17.9 Hz) +0.1 (d, 18.2 Hz)
2	130.6, 130.3	±0.1
3	142.6 (d, 12.8 Hz) 138.6 (d, 12.1 Hz)	- 0.8 (brs) 0
4	34.4 (d, 21.5Hz)	- 0.4 (brs)
5	58.9 (d, 17.8 Hz)	+0.1 (d, 17.7 Hz)
6	31.3 (d, 9.2Hz)	0 (d, J=7.3 Hz)
7	27.5	- 0.1
8	50.0	0
9	176.6	+0.3
10	40.9	0
11	28.8	0
(CH ₃) ₂ CuLi	-8.53	0 (br)

³¹P-NMR (145 MHz, H₃PO₄ in D₂O as external standard (0 ppm), 30 °C, Chart 29): control; -20.0 ppm (Δ_{1/2}=28 Hz). +1eq LiClO₄; -20.2 ppm (Δδ=-0.2 ppm, Δ_{1/2}=38 Hz). +1eq CuBr•SMe₂;

-16.0 ppm ($\Delta\delta=+4.0$ ppm, $\Delta_{1/2}=94$ Hz). (-78 °C, Chart 30) Control; -20.03 ppm ($\Delta_{1/2}=4.3$ Hz). +1eq Me₂CuLi; -20.22 ppm (br, $\Delta\delta=-0.2$ ppm, $\Delta_{1/2}=49$ Hz).

¹H-NMR chemical shift changes of **1** (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04 mmol) in ether-toluene-*d*₈ (0.3 ml – 0.5 ml) at 30 °C (ArCD₂H as internal standard (2.10 ppm)). Chart 31~33.



#	Control (δ ppm)	+1eq LiClO ₄ ($\Delta\delta$)	+1eq CuBr•SMe ₂ ($\Delta\delta$)
1	7.40 (ddd, 2.0, 7.4, 7.4 Hz) 7.36 (ddd, 2.0, 7.4, 7.4 Hz)	0 (ddd, 1.8, 7.0, 7.0 Hz) 0 (ddd, 1.5, 7.4, 7.4 Hz)	+0.4 (t like, 8.6 Hz) +0.3 (t like, 8.1 Hz)
2	7.1 (m)	0 (m)	0 (m)
4	2.45 (ddd, 2.5, 2.5, 12.8 Hz) 1.93 (overlap)	0 (ddd, 2.7, 2.7, 13.0 Hz) 0 (overlap)	0 +0.2 (overlap)
5	2.01 (m)	0 (overlap)	0 (overlap)
6	1.4~2.0 (m)	0 (m)	0 (m)\
7	1.4~2.0 (m)	0 (m)	0 (m)
8	2.88 (br t, 7.7 Hz) 1.4~2.0 (overlap)	0 (br t, 7.1 Hz) 0 (overlap)	+0.8 (m) 0 (overlap)
9	2.10 (s)	0 (s)	+0.3 (s)

¹³C-NMR chemical shift changes of **1** (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04 mmol) in ether-toluene-*d*₈ (0.3 ml – 0.5 ml) at 30 °C (ArCD₃ as internal standard (20.4 ppm)). Chart 34~36. In the presence of LiClO₄, all the signals were too broad to be detected.

#	Control (δ ppm)	+1eq CuBr•SMe ₂ ($\Delta\delta$)
1	133.41 (d, 19.6 Hz) 133.20 (d, 19.6 Hz)	+0.9 (d, 14.2 Hz) +0.3 (d, 15.9 Hz)
2	124.9~129.1	0 (m)

3	141.02 (d, 14.3 Hz) 140.18 (d, 14.3 Hz)	- 4.3 (d, 25.8 Hz) - 5.0 (d, 24.5 Hz)
4	34.61 (d, 13.3 Hz)	- 1.3 (d, 18.3 Hz)
5	64.11 (d, 18.3 Hz)	+0.9 (overlap)
6	32.80 (d, 7.3 Hz)	- 2.1
7	22.65	- 0.7
8	57.41	+1.3
9	40.23	+4.5

³¹P-NMR (145 MHz, H₃PO₄ in D₂O as external standard (0 ppm), 30 °C, Chart 37): control; -19.5 ppm. +1eq LiClO₄; -19.0 ppm (Δδ=+0.5 ppm). +1eq CuBr•SMe₂; No signal was observed.

¹H-NMR chemical shift changes of 1 (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04 mmol) in THF-*d*₈ (0.6 ml) at 30 °C (2-H of THF-*d*₈ as internal standard (3.55 ppm)). Chart 38~41.

#	Control (δ)	+1eq LiClO ₄ (Δδ)	+1eq CuBr•SMe ₂ (Δδ)	+1eq LiClO ₄ (Δδ) +1eq CuBr•SMe ₂ (Δδ)
1, 2	7.37 (m) 7.15 (m)	0 (br) 0 (br)	+0.5 (m), +0.4 (m) 0	+0.5 (m), +0.4 (m) 0
4	2.44 (ddd, 3.0, 3.0, 13.2 Hz)	+0.2 (br)	+0.4 (ddd, 2.4, 9.8, 14.9)	+0.4 (m)
5	~2.0 (overlap)	+1.6 (m)	+0.7 (m)	+0.7 (m)
6, 7	1.32~1.99 (m)	0 (br)	1.42~1.58	1.42~1.58
8	2.86 (brt, 8.2 Hz)	+0.1 (br)	+1.1 (brt, 8.5 Hz)	+1.1 (brt, 8.5 Hz)
9	2.09 (s)	0 (s)	+0.4 (s)	+0.4 (s)

¹³C-NMR chemical shift changes of 1 (0.04 mmol) by complexing with LiClO₄ (0.04 mmol) and CuBr•SMe₂ (0.04 mmol) in THF-*d*₈ (0.6 ml) at 30 °C (3-C of THF-*d*₈ as internal standard (25.3 ppm)). Chart 42~45.

#	Control (δ)	+1eq LiClO ₄ (Δδ)	+1eq CuBr•SMe ₂ (Δδ)	+1eq LiClO ₄ (Δδ) +1eq CuBr•SMe ₂ (Δδ)
1	133.39~133.87	0	δ; 133.86~134.69	δ; 133.83~134.75
2	128.88~129.49	0 (br)	δ; 129.05~130.49	δ; 129.07~130.54

3	141.31 (d, 13.1 Hz) 140.37 (d, 15.8 Hz)	- 0.1 (d, 13.1 Hz) - 0.1 (d, 15.8 Hz)	- 4.6 (d, 28.1 Hz) - 4.7 (d, 24.4 Hz)	- 4.5 (d, 26.8 Hz) - 4.7 (d, 25.6 Hz)
4	34.63 (d, 13.4 Hz)	- 0.1 (d, 12.2 Hz)	- 1.6 (d, 18.3)	- 1.6 (d, 18.3 Hz)
5	64.55 (d, 18.3 Hz)	+0.1 (d, 18.3 Hz)	+2.2 (overlap)	+2.2 (overlap)
6	33.09 (d, 7.3 Hz)	0 (d, 7.3 Hz)	- 2.0 (s)	- 2.1 (s)
7	22.92	0	- 0.7	- 0.7
8	57.79	0	+1.4	+1.3
9	40.39	0	+4.3	+4.2

³¹P-NMR (145 MHz, H₃PO₄ in D₂O as external standard (0 ppm), 30 °C, Chart 46): control; -20.5 ppm. +1eq LiClO₄; -20.5 ppm ($\Delta\delta=0$ ppm). +1eq CuBr•SMe₂; -23.5 ppm ($\Delta\delta=-3.0$ ppm, br). +1eq LiClO₄+1eq CuBr•SMe₂; -23.4 ppm ($\Delta\delta=-2.9$ ppm, br).

Chapter 3. Asymmetric Addition Reaction of Lithium Diorganocuprate

Conjugate addition of lithium dimethylcuprate to chalcone controlled by 2 in ether solvent (*S*-(+)-3-phenylbutylophenone 47) (Table 2, run 2). A solution of methyllithium (low halide, 1.3 ml, 1.88 mmol) in ether was added dropwise to a suspension of CuI (179 mg, 0.94 mmol) in dry ether 8ml under Ar at -20 °C. The resulting colorless clear solution was stirred for 25 min, and then cooled to -78 °C. A solution of 2 (351 mg, 0.99 mmol) in ether 3ml was added and the resulting white suspension was stirred at -78 °C for 20 min. A solution of chalcone (130 mg, 0.63 mmol) in ether 5ml was added dropwise over a period of 5 min at -20 °C and the resulting red suspension was stirred for 1h. Satd. NH₄Cl (10 ml) and 10% NH₃ aq. (10 ml) was added, vigorously stirred for 30 min in air, and extracted by ether (20 ml x3). The organic layer was washed successively by 10% HCl (10 ml), satd. NaHCO₃ (10 ml), H₂O (10 ml), and satd. NaCl (10 ml), then dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (benzene / hexane 4/1) gave the adduct (110 mg, 79% yield) as a colorless oil. The ee was determined to be 84% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/30, 0.5 ml/min, (*S*) 14 min, (*R*) 17 min). Absolute configuration was determined to be *S* by optical rotation ($[\alpha]^{25}_{\text{D}} +12.6$ (c 2.62, CCl₄))³². ¹H-NMR (CDCl₃) δ; 1.2 (d, *J*=6.4 Hz, 3H, CH₃), 3.0 ~ 3.5 (m, 3H, CHPh, CH₂CO), 7.0 ~ 7.8 (m, 10H, Ar); IR (CCl₄); 1690 cm⁻¹; MS *m/z* 224 (M⁺). 2 was recovered in 67% as colorless prisms.

Conjugate addition of lithium diviylcuprate to chalcone controlled by 2 ((*R*)-(+)-3-phenyl-4-pentenophenone 49) (Table 2, run 4). To the solution of tetravinyltin (0.540 mmol) in ether (5.5 ml) was added ether solution of methyllithium (1.62 mmol, 1.7 ml, low halide) under ice bath and transmetalated for 1h. This solution of vinylolithium was added to the suspension of CuI (0.810 mmol) in ether (7 ml) by canule at -20 °C and after 20 min, 2 (0.864 mmol) in ether (6 ml) was added at -78 °C. The reaction mixture was black suspension. After 20 min, chalcone (0.54 mmol) in ether (4 ml) was added at -20 °C and the whole was stirred for 1h. Usual workup and purification by silica gel column chromatography (benzene / hexane 4/1) gave the adduct in 67% yield as a colorless oil. The ee was determined to be 73% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane, 1/30, 0.5 ml/min, (*R*) 16 min, (*S*) 18 min). ¹H-NMR (CDCl₃) δ; 3.36 (dd, *J*=6.0, 16.5 Hz, 1H, one of CH₂CO), 3.42 (dd, *J*=7.7, 16.8 Hz, 1H, one of CH₂CO), 4.14 (ddd, *J*=0, 6.9, 13.7 Hz, 1H, PhCH), 5.04 (m, 2H, CH₂=CH), 6.04 (ddd, *J*=6.6, 10.3, 17.0 Hz, 1H, CH₂=CH), 7.17 ~ 7.54 (m, 8H, Ar), 7.91 (d, *J*=8.2 Hz, 2H, Ar); IR (neat) 1680, 1635 cm⁻¹; MS *m/z* 236 (M⁺); $[\alpha]^{25}_{\text{D}} +9.07$ (c 3.27, CCl₄).

³² Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011.

Determination of absolute configuration of vinyl adduct (49). To the mixture of 49 (0.233 mmol) and 10% Pd on carbon (5 mg), H₂ was bubbled for 20 min. Filtration, concentration, and purification by silica gel column chromatography (ether / hexane, 1/9) gave ethyl derivative in 63% yield as a colorless oil in 63% yield: ¹H-NMR (CDCl₃) δ; 1.0 (t, *J*=7.0 Hz, 3H, CH₃), 1.8 (m, 2H, CH₃CH₂), 3.2 (m, 3H, CHCH₂CO), 7.0 ~ 7.3 (m, 8H, Ar), 7.8 (m, 2H, Ar); IR (neat) 1675 cm⁻¹; MS *m/z* 238 (M⁺); [α]_D²⁵ +105.5 (c 1.27, EtOH) (Alarm lamp lighted.), (*S*)-(+)³³; HPLC (Waters Opti Pak TA, *i*-propylalcohol / hexane, 1/36, 0.5 ml/min, (*S*) 31 min, (*R*) 36 min) analysis showed 76% ee.

Cojugate addition of lithium dibutylcuprate to chalcone controlled by 2 ((*S*)-(+)-3-phenyl-heptanophenone 48) (Table 2, run 5). A solution of butyllithium (1.0 ml, 1.59 mmol) in hexane was added dropwise to a suspension of CuI (152 mg, 0.797 mmol) in dry ether 7 ml under Ar at -40 °C. The resulting black solution was stirred for 20 min, and then cooled to -78 °C. A solution of 2 (300 mg, 0.850 mmol) in ether 4 ml was added and stirred at -78 °C for 20 min. A solution of chalcone (110 mg, 0.531 mmol) in ether 5 ml was added dropwise over a period of 5 min at -20 °C and the resulting blackish orange suspension was stirred for 1h. Usual workup and purification by silica gel column chromatography (benzene / hexane 4/1) gave the adduct (137 mg, 97% yield) as a colorless oil. The ee was determined to be 24% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane, 1/30, 0.5 ml/min, (*S*) 12 min, (*R*) 13 min). Absolute configuration was determined to be *S* by optical rotation ([α]_D²⁵ +2.80 (c 4.28 CCl₄)³⁴). ¹H-NMR (CDCl₃) δ; 0.82 (t, *J*=7.3 Hz, 3H, CH₃), 1.24 (m, 4H), 1.66 (m, 2H), 3.2 ~ 3.3 (m, 3H, CHCH₂CO), 7.16 ~ 7.54 (m, 8H, Ar), 7.87 (d, 2H, Ar); IR (neat) 1680 cm⁻¹; MS *m/z* 266 (M⁺). 2 was recovered in 72% as a colorless oil.

Cojugate addition of lithium dimethylcuprate to 2-heptenophenone (50) controlled by 2 ((*R*)-(-)-3-methyl-heptanophenone 52) (Table 4). ¹H-NMR (CDCl₃) δ; 0.89 (m, 3H, CH₃CH₂), 0.95 (d, *J*=6.6 Hz, 3H, CH₃CH), 1.30 (m, 6H, (CH₂)₃), 2.17 (m, 1H, CHCH₃), 2.74 (dd, *J*=7.9, 15.8 Hz, 1H, one of CH₂COPh), 2.94 (dd, *J*=5.6, 15.8 Hz, 1H, one of CH₂COPh), 7.41 ~ 7.56 (m, 3H, Ar), 7.94 (m, 2H, Ar); IR (neat) 1690 cm⁻¹; MS *m/z* 204 (M⁺); [α]_D²⁵ -2.83 (c 7.13, benzene); 55% oy (*R*) (see below). 2 was recovered in 68% as white powder.

Determination of absolute configuration and optical yield of 52. To the solution of 52 (1.40 mmol) in CCl₄ (5.7 ml), CH₃CN (5.7 ml), and H₂O (11.2 ml) was added sodium periodate (25.1 mmol) and ruthenium (III) trichloride hydrate (0.0308 mmol) and the whole was stirred for 30h³⁵. The reaction mixture was filtrated and extracted by CH₂Cl₂ (20 ml x3). The combined organic layer was washed by satd. NaCl (10 ml) and dried over Na₂SO₄. Concentration gave a crude oil which was showed that the starting ketone still remained. The crude mixture was oxidated in the same procedure for 14h and workuped as above. The resulting oil was dissolved in

³³ Soai, K.; Hayasaka, T.; Ugajin, S.; yokoyama, S. *Chem. Lett.* 1571, 1988.

³⁴ Ahllerecht, H.; Sommer, H. *Chem. Ber.* 1990, 123, 829.

³⁵ Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* 1981, 46, 3936.

ether (20 ml) and filtrated by celite pad. The organic layer was extracted by 10% NaOH (10 ml x3) and the combined water layer was washed by ether (10 ml). It was acidified by 6N HCl to pH 1 and extracted by CH₂Cl₂ (20 ml x3). The organic layer was washed by satd. NaCl (10 ml) and dried over Na₂SO₄. Concentration and short path distillation gave the acid in 68% yield as a colorless oil. The absolute configuration and optical yield was determined to be *R* in 55% oy from its optical rotation³⁶: $[\alpha]^{25}_{\text{D}} +2.31$ (l 0.1, neat); $[\alpha]^{25}_{\text{D}} +2.21$ (c 4.07, benzene); bp 200 °C/15 mmHg; ¹H-NMR (CDCl₃) δ; 0.88 (brt, *J*=6.0 Hz, 3H, CH₃CH₂), 0.97 (d, *J*=6.8 Hz, 3H, CH₃CH), 1.3 (m, 6H, (CH₂)₃), 1.85 (m, 1H, CHCH₃), 2.14 (dd, *J*=8.3, 15.0 Hz, 1H, one of CH₂CO), 2.25 (dd, 1H, *J*=6.0, 15.0 Hz, one of CH₂CO); IR (neat) 1710 cm⁻¹; MS *m/z* 144 (M⁺), 145 (M⁺+1).

Cojugate addition of lithium divinylcuprate to 2-heptenophenone (50) controlled by 2 ((*S*)-(-)-3-ethenyl-heptanophenone 53) (Table 4). ¹H-NMR (CDCl₃) δ; 0.88 (m, 3H, CH₃), 1.3 (m, 6H, (CH₂)₃), 2.73 (m, 1H, CHCH₂CO), 2.98 (dlike, *J*=7.0 Hz, 2H, CH₂CO), 4.98 (m, 2H, CH₂=CH), 5.68 (m, 1H, CH=CH₂), 7.42 ~ 7.51 (m, 3H, Ar), 7.94 (d, *J*=8.3 Hz, 2H, Ar); IR (neat) 1680, 1640 cm⁻¹; MS *m/z* 216 (M⁺); $[\alpha]^{25}_{\text{D}} -0.424$ (c 5.19, CCl₄); $[\alpha]^{25}_{435} -0.478$ (c 5.45, CCl₄); 50% oy (*S*) (see below). 2 was recovered in 80% as white powder.

Determination of absolute configuration and optical yield of 53. To the mixture of 53 (0.778 mmol) and Raney Ni (W4) (1ml) in EtOH (8 ml), H₂ was bubbled for 5h. The reaction mixture was diluted by EtOH, filtrated, and concentrated: ¹H-NMR (CDCl₃) δ; 0.89 (m, 6H, CH₃ x2), 1.28 (m, 8H, (CH₂)₃, CH₂CH₃), 2.87 (dlike, *J*=6.6 Hz, 2H, CH₂CO), 4.79 (dd, *J*=5.3, 8.2 Hz, PhCHOH of overreduced alcohol), 7.26 ~ 7.58 (m, 3H, Ar), 7.94 (d, *J*=6.9 Hz, 2H, Ar). 3.8:1 mixture of the targeted ketone and overreduced alcohol. IR (neat) 1680 cm⁻¹; MS *m/z* 218 (M⁺), 220 (M⁺ of overreduced alcohol). This crude mixture was dissolved in CCl₄ (3 ml)–CH₃CN (3 ml)–H₂O (6 ml) and added sodium periodate (14.0 mmol) and ruthenium (III) trichloride hydrate⁴. The whole was stirred at rt for 2.5 days. Workup as usual and purification by short path distillation gave the acid as a purple oil in 72% yield. The absolute configuration and optical yield was determined as *S* in 50% oy from optical rotation³⁷: $[\alpha]^{25}_{\text{D}} -1.47$ (l 0.1, neat); $[\alpha]^{25}_{\text{D}} -0.14$ (c 3.51, benzene), $[\alpha]^{25}_{435} -0.20$ (c 3.51, benzene); ¹H-NMR (CDCl₃) δ; 0.885 (m, 6H, CH₃ x2), 1.31 (m, 8H, (CH₂)₃, CH₂CH₃), 1.81 (m, 1H, CHCH₂CO), 2.28 (d like, *J*=6.9 Hz, 2H, CH₂CO); IR (neat) 1700 cm⁻¹; MS 158 (M⁺).

Cojugate addition of lithium divinylcuprate to 2-butenophenone (51) controlled by 2 ((*S*)-(+)-3-methyl-4-pentenophenone 54) (Table 4). The same procedure as for 53. Yield 46%: ¹H-NMR (CDCl₃) δ; 1.10 (d, *J*=6.3 Hz, 3H, CH₃), 3.00 (m, 3H, CHCH₂CO), 5.00 (m, 2H, CH₂=CH), 5.85 (ddd, *J*=6.7, 10.9, 17.0 Hz, 1H, CH=CH₂), 7.43 ~ 7.59 (m, 3H, Ar), 7.95 (d, *J*=6.9 Hz, 2H, Ar); IR (neat) 1680, 1640 cm⁻¹; MS *m/z* 174 (M⁺); $[\alpha]^{25}_{\text{D}} +0.36$ (c 4.72, CCl₄), $[\alpha]^{25}_{435} +1.23$ (c 4.72, CCl₄); 7% oy (*S*) (see below). The 1,2-adduct was obtained in 19% yield: ¹H-NMR (CDCl₃) δ; 1.74 (d, *J*=5.6 Hz, 3H, CH₃), 5.27 (m, 2H), 5.74 (m, 2H, CH=CH₂),

³⁶ Levene, P. A.; Marker, R. E. *Biol. Chem.* 1932. 95, 1.

³⁷ Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* 1979, 44, 2250.

6.18 (dd, $J=10.4$ Hz, 17.3 Hz, 1H), 7.21 ~ 7.45 (m, 5H, Ar); IR (neat), 3420 cm^{-1} ; MS m/z 174 (M^+). **2** was recovered as white powder in 60%.

Determination of absolute configuration and optical yield of 54. To the mixture of **54** (0.632 mmol) and Raney Ni (W4) (0.5 ml) was bubbled H_2 for 15 min. The reaction mixture was filtrated through celite pad. Concentration and purification by silica gel column chromatography gave ethyl derivative as colorless oil in 77% yield. The absolute configuration and optical yield was determined as *R* in 7% oy from optical rotation³⁸: $[\alpha]^{25}_{\text{D}} -1.28$ (l 0.1, neat), $[\alpha]^{25}_{\text{D}} -1.40$ (c 3.37, CCl_4). $^1\text{H-NMR}$ (CDCl_3) δ ; 0.93 (t, $J=7.4$ Hz, CH_3CH_2), 0.96 (d, $J=6.9$ Hz, 3H, CH_3CH), 1.23 ~ 1.49 (m, 2H, CH_2CH_3), 2.10 (m, 1H, CHCH_2CO), 2.74 (dd, $J=7.9$, 15.8 Hz, 1H, one of CH_2CO), 2.95 (dd, $J=5.6$, 15.5 Hz, 1H, one of CH_2CO), 7.43 ~ 7.58 (m, 3H, Ar), 7.96 (d, $J=7.2$ Hz, 2H, Ar); IR (neat) 1680 cm^{-1} ; MS m/z 176 (M^+).

Conjugate addition of lithium dimethylcuprate to benzalacetone (55) controlled by 2 ((*R*)-(-)-4-phenyl-pentan-2-one 58) (Table 4). The procedure was the same as the procedure of **47**. The reaction was run at -20°C for 1.5h. Purification by silica gel column chromatography (ether / benzene 1/19) gave **58** as a colorless oil in 10% yield. The ee was determined to be 14% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/100, 0.2 ml/min, (*R*) 30 min, (*S*) 31 min). Absolute configuration was determined to be *R* by optical rotation³⁹ ($[\alpha]^{25}_{\text{D}} -9.49$ (c 0.295, benzene)). $^1\text{H-NMR}$ (CDCl_3) δ ; 1.26 (d, $J=6.9$ Hz, 3H, CH_3CH), 2.06 (s, 3H, CH_3CO), 2.66 (dd, $J=7.7$, 16.1 Hz, 1H, one of CH_2CO), 2.75 (dd, $J=6.6$, 16.1 Hz, 1H, one of CH_2CO), 3.29 (sectet, $J=6.0$ Hz, 1H, CHPh), 7.2 (m, 5H, Ar); IR (neat) 1720 cm^{-1} ; MS m/z 162 (M^+). **2** was recovered as white powder in 46%.

Conjugate addition of lithium dimethylcuprate to 1, 1, 1, 4-tetraphenyl-buten-2-one (56) controlled by 2 (1, 1, 1, 4-tetraphenyl-pentan-2-one 59) (Table 4). The same procedure as **47**. Yield 96%. The ee was determined to be 2% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/30, 0.5 ml/min, 9 min and 10 min). $^1\text{H-NMR}$ (CDCl_3) δ ; 1.02 (d, $J=6.9$ Hz, 1H, CH_3), 2.58 (dd, $J=7.1$, 16.8 Hz, 1H, one of CH_2CO), 2.87 (dd, $J=6.6$, 16.8 Hz, 1H, one of CH_2CO), 3.10 (q like, $J=7.0$ HZ, 1H, CHPh), 7.2 (m, 20H, Ar); IR (neat) 1710 cm^{-1} ; MS 391 (M^+); $[\alpha]^{25}_{\text{D}} 0$ (c 7.85, CHCl_3). **2** was recovered as white powder in 46%.

Conjugate addition of lithium dibutylcuprate to benzalacetone (55) controlled by 2 ((-)-4-phenyl-octan-2-one 61) (Table 4). The same procedure as **48**. Yield 31%. The ee was determined to be 4% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/100, 0.3 ml/min, 18.5 min and 19.4 min). $^1\text{H-NMR}$ (CDCl_3) δ ; 0.82 (t, $J=7.1$ Hz, 3H, CH_3), 1.0 ~ 1.3 (m, 4H), 1.58 (m, 2H), 1.99 (s, 3H, CH_3), 2.70 (dd x2, $J=6.9$, 16.9 Hz, 2H, CH_2CO), 3.10 (quintet like, $J=7.3$ Hz, 1H, CHPh), 7.2 (m, 5H, Ar); IR (neat) 1720 cm^{-1} ; MS m/z 204 (M^+);

³⁸ Hoppka, G.; Marschall, H.; Numberg, P.; Oestreicher, F.; Scherowsky, G. *Chem. Ber.* **1981**, 114,

2501

³⁹ Gustafsson, B. *Tetrahedron* **1978**, 34, 3023.

$[\alpha]^{25}_{\text{D}} -3.06$ (c 0.915, benzene). Starting 55 was recovered in 44%. 2 was recovered as white powder in 41%.

Conjugate addition of lithium dibutylcuprate to 1, 1, 1, 4-tetraphenyl-buten-2-one (56) controlled by 2 ((+)-1, 1, 1, 4-tetraphenyl-octan-2-one 62) (Table 4). The same procedure as 48. Yield 89%. The ee was determined to be 6% by HPLC analysis (Opti Pak XC, *i*-propylalcohol / hexane 1/100, 0.3 ml/min, 16 min and 18 min). $^1\text{H-NMR}$ (CDCl_3) δ : 0.72 (t, $J=7.3$ Hz, 3H, CH_3), 0.93 (m, 2H), 1.09 (m, 2H), 1.31 (m, 2H), 2.58 (dd, $J=5.6, 16.9$ Hz, 1H, one of CH_2CO), 2.89 (m, 2H, CHPh , one of CH_2CO), 7.2 (m, 20H, Ar); IR (neat) 1710 cm^{-1} ; MS m/z (M^+); $[\alpha]^{25}_{\text{D}} +0.32$ (c 2.51, CHCl_3). 2 was recovered as white powder in 43%.

Conjugate addition of lithium dibutylcuprate to ethyl cinnamate (57) controlled by 2 (ethyl-(+)-3-phenylheptanoic acid 63) (Table 4). The same procedure as 48. The reaction was run at $-20\text{ }^\circ\text{C}$ for 4.5h. Yield 40%. The ee was determined to be 4% by HPLC analysis (Opti Pak XC, *i*-propylalcohol / hexane 1/60, 0.5 ml/min, 15 min and 17 min). $^1\text{H-NMR}$ (CDCl_3) δ : 0.82 (t, $J=7.1$ Hz, CH_3), 1.06 ~ 1.32 (m, 7H, 1.13 (t, $J=7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$)), 1.61 (m, 2H), 2.53 (dd, $J=8.0, 15.0$ Hz, one of CH_2COO), 2.61 (dd, $J=15.0, 7.1$ Hz, 1H, one of CH_2COO), 3.07 (quintet, $J=7.5$ Hz, CHPh), 4.02 (q, $J=7.2$ Hz, 2H, COOCH_2), 7.2 (m, 5H, Ar); IR (neat) 1730 cm^{-1} ; MS m/z 234 (M^+); $[\alpha]^{25}_{\text{D}} +0.08$ (c 1.20, CHCl_3). 2 was recovered as white powder in 40%.

Conjugate addition of lithium dimethylcuprate to ethyl 2-(ethoxycarbonyl)-cinnamate (64) controlled by 2 (ethyl 2-(ethoxycarbonyl)-3-phenylbutanate 65⁴⁰) (Table 4). The same procedure as 47. The reaction was run at $-78\text{ }^\circ\text{C}$ for 1h. Yield 95%. The ee was determined to be 2% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/30, 0.5 ml/min, 13 min and 15 min). : $^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (t, $J=7.1$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$), 1.31 (t, $J=7.1$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$), 1.35 (d, $J=6.2$ Hz, 3H, CH_3CHPh), 3.6 (m, 2H, CHPh , CHCOO), 3.93 (q, $J=7.1$ Hz, 2H, COOCH_2), 4.26 (q, $J=7.1$ Hz, 2H, COOCH_2), 7.3 (m, 5H, Ar); IR (neat) $1750, 1730\text{ cm}^{-1}$; $[\alpha]^{25}_{\text{D}} +0.682$ (c 5.58, benzene). 2 was recovered as white powder in 57%.

Conjugate addition of lithium dibutylcuprate to ethyl 2-(ethoxycarbonyl)-cinnamate (64) controlled by 2 (ethyl 2-(ethoxycarbonyl)-3-phenylheptanate 66⁹) (Table 4). The same procedure as 48. The reaction was run at $-40\text{ }^\circ\text{C}$ for 1h. Yield 90%. The ee was determined to be 0% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/30, 0.5 ml/min, 13 min and 15 min). : $^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (t, $J=7.3$ Hz, 3H, CH_3CH_2), 1.03 (t, $J=7.0$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$), 1.2 ~ 1.4 (m, 4H), 1.40 (t, $J=7.1$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$), 1.79 (m, 2H), 3.47 (ddd, $J=3.8, 10.5, 10.5$ Hz, 1H, CHPh), 3.74 (d $J=10.9$ Hz, CHCOO), 3.96 (q, $J=7.2$ Hz, COOCH_2), 4.34 (q, $J=7.1$ Hz, 2H, COOCH_2), 7.3 (m, Ar); IR (neat) $1750, 1730\text{ cm}^{-1}$; $[\alpha]^{25}_{\text{D}} +0.350$ (c 4.57, benzene). 2 was recovered as a colorless oil in 53%.

⁴⁰ Cahiez, G.; Alami, M. *Tetrahedron* 1989, 45, 4163.

Conjugate addition of lithium dimethylcuprate to 2-cyclohexen-1-one (67) controlled by 2 ((R)-(+)-3-methyl-cyclohexan-1-one 68) (Table 4). The same procedure as 47. The reaction was run at -78 °C for 80 min. Yield 63%. The absolute configuration and optical yield was determined to be *R* in 16% oy from optical rotation⁴¹: $[\alpha]^{25}_D +2.37$ (c 1.48, CHCl₃); bp 150 °C / 70 mmHg (cugel); ¹H-NMR (CDCl₃) δ ; 1.02 (d, *J*=5.9 Hz, 3H, CH₃), 1.34 (m, 1H), 1.69 (m, 1H), 1.8 ~ 2.05 (m, 4H), 2.17 ~ 2.40 (m, 3H); IR (neat) 1710 cm⁻¹; 112 (M⁺), 111 (M⁺-1). 2 was recovered as colorless prisms in 61%.

Conjugate addition of lithium dibutylcuprate to 2-cyclohexen-1-one (67) controlled by 2 ((S)-(-)-3-butyl-cyclohexan-1-one 69) (Table 4). The same procedure as 48. The reaction was run at -78 °C. Yield 98%. The absolute configuration and optical yield was determined to be *S* in 7% oy from optical rotation⁴²: $[\alpha]^{23}_D -0.572$ (c 5.07, toluene); bp 200 °C / 60 mmHg (cugel); ¹H-NMR (CDCl₃) δ ; 0.89 (brt, *J*=6.6 Hz, 3H, CH₃), 1.3 (m, 7H), 1.55 ~ 1.8 (m, 2H), 1.85 ~ 2.01 (m, 3H), 2.24 ~ 2.44 (m, 3H); IR (neat) 1710 cm⁻¹; MS *m/z* 154 (M⁺), 153 (M⁺-1).

Conjugate addition of lithium methyl-2-trimethylsilylacetylenylcuprate to chalcone (46) controlled by 2 (47) (Table 5, run 2). To the solution of trimethylsilylacetylene (1.12 mmol) in ether (8 ml) was dropped methyllithium (halide free, 1.12 mmol) in ether (1.2 ml) under ice bath and stirred for 15 min. This colorless clear solution of trimethylsilylacetylenyllithium was transferred to the suspension of CuI (1.12 mmol) in ether (8 ml) under ice bath and the white suspension was stirred for 20 min. Methyllithium (halide free, 1.12 mmol) in ether (1.2 ml) was added at -20 °C and the resulting yellow clear solution was stirred for 15 min. 2 in ether (8 ml) was added at -78 °C and after 15 min chalcone (0.223 mmol) in ether (11 ml) was dropped at -20 °C. The resulting red suspension was stirred for 2 h. Workup and purification as usual gave a colorless oil in 82% yield. The ee was determined to be 54% from HPLC analysis ($[\alpha]^{25}_D +8.94$ (c 1.56, CCl₄)). 2 was recovered as a colorless oil in 75%.

Conjugate addition of lithium butyl-2-trimethylsilylacetylenylcuprate to chalcone (46) controlled by 2 (48) (Table 5, run 3). The same procedure as above. The reaction was run at -20 °C for 1 h. Yield 80%. The ee was determined to be 36% from HPLC analysis ($[\alpha]^{22}_D +4.40$ (c 1.46, CCl₄)). 2 was recovered as a colorless oil in 56%.

Conjugate addition of lithium butylthiophenolatocuprate to chalcone (46) controlled by 2 (48) (Table 5, run 4). To the solution of thiophenol (1.22 mmol) in ether (8.5 ml) was added butyllithium (1.22 mmol) in hexane (0.75 ml) under ice bath and after 15 min this lithium thiophenolate was transferred to the suspension of CuI (1.22 mmol) in ether (8.5 ml) under ice bath. After 25 min butyllithium (1.22 mmol) in hexane (0.75 ml) was added at -40 °C then the deep green suspension was stirred at -20 °C for 25 min. 2 in ether 9 ml was added at -78 °C and

⁴¹ Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* 1989, 30, 6349.

⁴² Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* 1986, 108, 7144.

after 15 min chalcone (0.243 mmol) in ether (11 ml) was dropped. The reaction was run for 1 h. Workup and purification as usual gave a colorless oil in 82% yield. The ee was determined to be 23% from HPLC analysis ($[\alpha]^{25}_{\text{D}} +2.47$ (c 1.38, CCl_4)). **2** was recovered as colorless prisms in 33%.

Conjugate addition of lithium *N*-L-2-[(diphenylphosphino)methyl]pyrrolidinyl-methylcuprate to chalcone (46) (Table 7, run 1). To the solution of **14** (2.04 ml) in ether (9 ml) was dropped methyllithium (2.04 ml) in ether (1.5 ml) at $-78\text{ }^{\circ}\text{C}$ and stirred for 20 min (lithium amide). To the suspension of CuI (2.04 mmol) in ether (9 ml) was added methyllithium (2.04 mmol) in ether (1.5 ml) at $-50\text{ }^{\circ}\text{C}$ and stirred for 20 min (methylcopper). Lithium amide was transferred to methylcopper at $-78\text{ }^{\circ}\text{C}$ and the vessel was washed with 9 ml of ether. After 25 min to the resulting pale yellow suspension was added chalcone (0.340 mmol) in ether (3.5 ml) at $-78\text{ }^{\circ}\text{C}$ and stirred for 4 h. Workup and purification as usual gave a colorless oil in 28%. HPLC analysis ($\mu\text{Porasil}$, AcOEt / hexane 1/20, 1.0 ml/min) showed 32% yield of the adduct and 45% of starting enone. The ee was determined to be 87% from HPLC analysis ($[\alpha]^{25}_{\text{D}} +11.7$ (c 0.92, CCl_4)).

Conjugate addition of lithium dimethylcuprate to chalcone (46) controlled by 20 (Table 7, run 8). Lithium dimethylcuprate was prepared as usual (0.965 mmol). **20** (0.985 mmol) in ether (7 ml) was added at $-78\text{ }^{\circ}\text{C}$ and stirred at $-20\text{ }^{\circ}\text{C}$ for 35 min. To the resulting colorless clear solution was added chalcone (0.193 mmol) in ether (4 ml) and the whole was stirred for 1 h at $-20\text{ }^{\circ}\text{C}$. Workup and purification as usual gave a colorless oil in 45% yield. The ee was determined to be 61% from HPLC analysis ($[\alpha]^{25}_{\text{D}} -8.66$ (c 1.27, CCl_4)). The starting ketone was recovered in 55%. **20** was recovered as a colorless oil in 85%.

Conjugate addition of lithium dimethylcuprate to chalcone controlled by 2 in THF solvent (47) (Table 8, run 4). A solution of methyllithium (low halide, 1.2 ml, 1.60 mmol) in ether was added dropwise to a suspension of CuI (153 mg, 0.801 mmol) in dry THF 8ml under Ar at $-20\text{ }^{\circ}\text{C}$. The resulting colorless clear solution was stirred for 25 min, and then cooled to $-78\text{ }^{\circ}\text{C}$. A solution of **2** (300 mg, 0.855 mmol) in THF 4 ml was added and the resulting colorless clear solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min. A solution of chalcone (111 mg, 0.534 mmol) in THF 5ml was added dropwise over a period of 5 min at $-20\text{ }^{\circ}\text{C}$ and the resulting red solution was stirred for 4 h. Workup and purification as usual gave the adduct (86 mg, 72% yield) as a colorless oil. The ee was determined to be 50% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol / hexane 1/30, 0.5 ml/min, (*S*) 14 min, (*R*) 17 min). Absolute configuration was determined to be *R* by optical rotation ($[\alpha]^{25}_{\text{D}} -7.59$ (c 2.62, CCl_4)).

Chapter 4. Asymmetric Addition Reaction of Lithium Cyanocuprate

Preparation of ethyllithium⁴³. Bromoethane was washed successively with conc. H₂SO₄ (x2), H₂O, satd. Na₂CO₃, H₂O, and satd. NaCl, and dried over MgSO₄, followed by distillation from P₂O₅. To lithium (100mmol) in ether (50 ml) was added bromoethane (50 mmol) in ether (50 ml). First thirty drops were added at rt and the rest was added at -10°C for 30 min. The resulting purple suspension was stirred at 0 ~ 10 °C for 2h. Titration with diphenylacetic acid (DPPA)⁴⁵ revealed the concentration of ethyllithium was 0.457M.

Preparation of Sn-free vinylolithium in ether⁴⁴. To the solution of tetravinyltin (33.0 mmol) in pentane (36 ml) was added butyllithium (67.0 mmol) in hexane (44 ml) at rt and the whole was stirred for 1h. The reaction mixture was filtrated by glass filter and the residue was washed by pentane (25 ml x2). The residue was dissolved with 40 ml of ether. Titration by DPPA method⁴⁵ showed 1.51N (yield 90%).

Preparation of lithium cyanide⁴⁶. To the solution of acetone cyanohydrine (0.100 mol) in toluene (100 ml) was added butyllithium (0.100 mol) in hexane (62 ml) under ice bath and the resulting white suspension was vigorously stirred at rt for 20 min. Filtration and recrystallization from THF gave colorless needles in 68% yield: mp 157~160 °C; IR (nujol) 2090, 2200, 2270 cm⁻¹; ¹³C-NMR (D₂O) δ; 165.2

Conjugate addition of lithium cyanoethylcuprate to 2-cyclopenten-1-one controlled by 2 (*R*-(+)-3-ethylcyclopentan-1-one 78) (Table 16, run 1). To the solution of CuCN (1.53 mmol) and LiBr (12.2 mmol) in ether (30 ml) was dropped ethyllithium (1.53 mmol) in ether (3.3 ml) at -78 °C and the resulting colorless clear solution plus yellow precipitation was stirred for 20 min. 2 (4.59 mmol) in ether (16 ml) was added and the resulting bright yellow suspension (sometimes it was yellow clear solution) was stirred for 15 min. 2-Cyclopenten-1-one (1.02 mmol) in ether (4 ml) was added at -78 °C and stirred for 1h. Workup as usual and purification by silica gel column chromatography (CH₂Cl₂ / hexane 4/1) gave a colorless oil in 90% yield. Short path distillation (bp 200 °C / 50 mmHg) gave 70% yield. The ee was determined to be 94% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁴⁷: [α]_D²⁵ +147 (c 0.845, CHCl₃); ¹H-NMR (CDCl₃) δ; 0.952 (t like J=7.0

⁴³ Gilman, H.; Moore, F. W.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2480.

⁴⁴ Gassman, P.G.; Valcho, J. J; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6524.

⁴⁵ Kodron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

⁴⁶ Johns, I. B.; DiPietro, H. R. *J. Org. Chem.* **1964**, *29*, 1970.

⁴⁷ Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401.

Hz, 3H, CH₃), 1.3 ~ 2.5 (m, 9H); IR (neat) 1740 cm⁻¹. **2** was recovered as colorless prisms in 92%.

Determination of the ee of 78 (Table 16, run 1)⁴⁸. **78** (0.375 mmol), (*R, R*)-2, 3-butanediol (0.714 mmol), and *p*-toluenesulfonate monohydrate (cat.) was dissolved in benzene (15 ml) and refluxed with MS 4A trap for 4h. 10% Na₂CO₃ (10 ml) was added and extracted with benzene (20 ml x3). The organic layer was washed successively by H₂O and satd. NaCl (10 ml each) and dried over Na₂SO₄. Concentration gave a colorless oil in 90% yield: ¹H-NMR (CDCl₃) δ; 0.88 (t like, J=7.2 Hz, 3H), 1.2 ~ 2.1 (m, 15H), 3.55 (m, 2H, CHO x2); IR (neat) 2950, 1110 cm⁻¹; ¹³C-NMR (CDCl₃, Observed frequency was set in 3000Hz. Data point was 30000.) δ; 117.2 (OCO), 78.17 (CHO), 78.11 (CHO), 44.53 (CHCH₂, major), 44.23 (CHCH₂, minor), 39.78 (OCCH₂CH, major), 39.25 (OCCH₂CH, minor), 38.01 (CH₂CH₂CH, major), 37.56 (CH₂CH₂CH, minor), 30.13 (CH₂CH₂CH), 28.85 (CH₂CH₃), 16.94, 16.91 (CH₃CH), 12.53 (CH₃CH₂); From three integration ratios (major / minor=36/1.0, 36/1.1, 37/1.2), The ee was determined to be 94%.

Conjugate addition of lithium butylcyanocuprate to 2-cyclopenten-1-one controlled by 2 (*R*-(+)-3-butylcyclopentan-1-one 79) (Table 16, run 2). The same procedure as **78**. Lithium butylcyanocuprate–lithium bromide complex in ether was pink clear solution. Lithium butylcyanocuprate–lithium bromide–**2** complex was dark yellow clear solution. Yield 99% (column chromatography); 89% (cugel distillation. bp 200 °C / 35 mmHg). The ee was determined to be 95% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁴⁹: [α]_D²⁵ +124.3 (c 1.29, CHCl₃); ¹H-NMR (CDCl₃) δ; 0.90 (t like, J=5.0 Hz, 3H, CH₃), 1.3 ~ 2.5 (m, 13H); IR (neat) 2950, 2920, 2850, 1735, 1150 cm⁻¹; MS m/z 140 (M⁺). **2** was recovered in 79% as colorless prisms.

Determination of the ee of 79 (Table 16, run 2). The same procedure as **78**. Yield 85%: ¹H-NMR (CDCl₃) δ; 0.88 (t like, J=6.8 Hz, 3H, CH₃), 1.22 ~ 1.41 (m, 14H), 1.8 ~ 2.1 (m, 5H), 3.55 (m, 2H, CHO x2); IR (neat) 2950, 2900, 2840, 1100 cm⁻¹; MS m/z 212 (M⁺); ¹³C-NMR (CDCl₃) δ; 117.2 (OCO), 78.15 (CHO), 78.11 (CHO), 44.93 (CHCH₂, major), 44.61 (CHCH₂, minor), 38.03 (OCCH₂CH), 37.97 (OCCH₂CH₂CH), 35.56 (OCCH₂CH₂), 30.53 (CH₂ of side chain), 30.41 (CH₂ of side chain), 22.79 (CH₂CH₃), 16.95 (CH₃CH), 16.89 (CH₃CH), 14.04 (CH₃CH₂); From integration ratio (35.3/1) the ee was determined to be 95%.

Conjugate addition of lithium cyanomethylcuprate to 2-cyclohexen-1-one controlled by 2 (*R*-(+)-3-methylcyclohexan-1-one 68) (Table 16, run 3). The preparation of lithium cyano-methylcuprate (1.59 mmol) –lithium bromide (12.8 mmol) –**2** (4.77mmol) complex was the same procedure as **78**. Lithium cyanomethylcuprate–lithium bromide complex in ether solvent was yellow clear solution at -78 °C. Lithium cyanomethylcuprate–lithium

⁴⁸ Hiemstra, H.; Wynberg, H. *Tetrahedron, Lett.* 1977, 2183.

⁴⁹ Tamura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* 1989, 30, 4349.

bromide-2 complex was bright yellow ~ cream yellow suspension. To this suspension was added HMPA (3.18 mmol) at -78 °C and after 15 min, was added the solution of 2-cyclohexen-1-one (1.06 mmol) and TMSCl (3.18 mmol) in ether (4ml). The reaction was run at -78 °C for 1.5h. Crude oil which was obtained by usual workup was dissolved in THF (20 ml) and was added 10% HCl (5 ml) at rt. After stirring for 10 min, the water layer was extracted by CH₂Cl₂ (20 ml x3). The organic layer was washed successively by satd. NaHCO₃ and satd. NaCl (10 ml each) and dried over Na₂SO₄. Concentration and purification by silica gel column chromatography (CH₂Cl₂ / hexane, 1/1) gave a colorless oil in 66% yield. Short path distillation gave 19% yield. The ee was determined to be 96% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁵⁰: [α]_D²⁵ +13.7 (c 0.590, CHCl₃). 2 was recovered in 82%. Data was shown at experimental section of chapter 3.

Determination of the ee of 68 (Table 16, run 3). The same procedure as 78. Yield 72%: ¹H-NMR (CDCl₃) δ ; 0.89 (d like J=6.3 Hz, 3H, CH₃), 1.15 ~ 1.8 (m, 15H), 3.62 (m, 2H, CHO x2); IR (neat) 2920, 2850, 1090 cm⁻¹; ¹³C-NMR (CDCl₃) δ ; 108.5 (OCO), 78.10 (CHO), 77.01 (CHO), 44.85 (CHCH₃, major), 45.78 (CHCH₃, minor) 36.77 (OCCH₂CH), 33.91 (OCCH₂CH₂), 30.57 (OCCH₂CH₂), 23.00 (CHCH₂CH₂), 22.25 (CH₃), 17.11 (CH₃), 16.98 (CH₃); From integration ratio (53/1) the ee was determined to be 96%.

Conjugate addition of lithium cyanoethylcuprate to 2-cyclohexen-1-one controlled by 2 (*R*-(+)-3-ethylcyclohexan-1-one 75) (Table 16, run 4). The same procedure as 78. Yield 89%. Cugel distillation (bp 220 °C /40 mmHg) gave 74% yield. The ee was determined to be 91% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁵¹: [α]_D²⁵ +168 (c 0.640, CHCl₃): ¹H-NMR (CDCl₃) δ ; 0.91 (t, J=7.1 Hz, 3H), 1.22 ~ 2.38 (m, 11H); IR (neat) 1710 cm⁻¹; MS m/z 126 (M⁺). 2 was recovered in 89%.

Determination of the ee of 75 (Table 16, run 4). The same procedure as 78. Yield 79%: ¹H-NMR (CDCl₃) δ ; 0.9 (t like J=6.8 Hz, CH₃), 1.15 ~ 1.8 (m, 17H), 3.63 (m, 2H, CHO x2); IR (neat) 2920, 2850, 1100 cm⁻¹; MS m/z 198 (M⁺); ¹³C-NMR (CDCl₃) δ ; 108.5 (OCO), 78.04 (CHO), 77.61 (CHO), 43.58 (CHCH₂, minor) 42.61 (CHCH₂, major), 37.13 (OCCH₂CH), 37.09 (OCCH₂CH₂), 31.31, 29.53, 22.86 (CH₂CH₃), 17.02 (CH₃CH), 16.98 (CH₃CH), 11.18 (CH₃CH₂); From integration ratio (22/1) the ee was determined to be 91%.

Conjugate addition of lithium butylcyanocuprate to 2-cyclohexen-1-one controlled by 2 (*R*-(+)-3-butylcyclohexan-1-one 76) (Table 16, run 5). The same procedure as 78. Yield 97%. After short path distillation yield 86%. The ee was determined to be 90% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁵²: [α]_D²³ +7.21 (c 1.04, toluene). 2 was recovered as colorless prisms in 93%.

⁵⁰ Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, *22*, 3601.

⁵¹ Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88.

⁵² Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114.

Determination of the ee of 76 (Table 16, run 5). The same procedure as 78. Yield 98%: $^1\text{H-NMR}$ (CDCl_3) δ ; 0.8 (m, 4H), 1.1 ~ 1.8 (m, 20H), 3.6 (m, 2H); IR (neat) 2925 cm^{-1} ; $^{13}\text{C-NMR}$ (CDCl_3) δ ; From integration ratio (20:1) of 43.04 (CHCH_2 , major), 43.97 (CHCH_2 , minor), the ee was determined to be 90%.

Conjugate addition of lithium cyanophenylcuprate to 2-cyclohexen-1-one controlled by 2 (*R*-(+)-3-phenylcyclohexan-1-one 77) (Table 16, run 6). The same procedure as 78. Lithium cyanophenylcuprate–lithium bromide complex in ether was pale yellow clear solution. Lithium cyanophenylcuprate–lithium bromide–2 complex was cream yellow suspension. Yield 63%. After short path distillation (bp $200\text{ }^\circ\text{C}$ / 0.2 mmHg) yield 56%. The ee was determined to be 60% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁷: $[\alpha]^{25}_{\text{D}} +10.5$ (c 0.660, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) δ ; 1.6 ~ 3.0 (m, 9H), 7.2 (m, 5H); IR (neat) 1715 cm^{-1} ; MS m/z 174 (M^+). 2 was recovered as colorless prisms in 95%.

Determination of the ee of 77 (Table 16, run 6). The same procedure as 78. Yield 80%: $^1\text{H-NMR}$ (CDCl_3) δ ; 1.16 ~ 1.88 (m, 14H), 2.87 (m, 1H, CHPh), 3.65 (m, 2H, $\text{CHO} \times 2$), 7.24 (m, 5H, C_6H_5); IR (neat) $2930, 1090\text{ cm}^{-1}$; MS m/z 246 (M^+); $^{13}\text{C-NMR}$ (CDCl_3) δ ; 146.2 (*Ar-*ipso** C), 128.3 (*Ar*), 126.8(*Ar*), 125.9(*Ar*), 108.3 (OCO), 78.11(CHO), 77.85 (CHO), 43.20 (CHPh , major), 44.22 (CHPh , minor), 41.82 (CH_2 , major), 41.19 (CH_2 , minor), 36.77 (CH_2), 33.48 (CH_2), 23.33 (CH_2), 17.11 (CH_3), 16.88 (CH_3); From integration ratio (4.1/1, 4.4/1), the ee was determined to be 60%.

Conjugate addition of lithium cyanovinylcuprate to 2-cyclohexen-1-one controlled by 2 (*R*-(+)-3-vinylcyclohexan-1-one 80) (Table 16, run 7). The same procedure as 78. Lithium cyanovinylcuprate–lithium bromide complex in ether was green suspension. Lithium cyanovinylcuprate–lithium bromide–2 complex was green-yellow suspension. Yield 60%. After short path distillation (bp $200\text{ }^\circ\text{C}$ / 20 mmHg) yield 48%. The ee was determined to be 44% by diastereomeric ketal (*vide infra*). Absolute configuration was determined to be *R* by optical rotation⁷: $[\alpha]^{25}_{365} +101$ (c 0.540, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) δ ; 1.5 ~ 2.5 (m, 9H), 5.0 (m, 2H), 5.8 (ddd, $J=3.3, 10.0, 17.5\text{ Hz}$, 1H); IR (neat) $1710, 1640\text{ cm}^{-1}$. 2 was recovered in 94%.

Determination of the ee of 80 (Table 16, run 7). The same procedure as 78. Yield 74%: $^1\text{H-NMR}$ (CDCl_3) δ ; 1.0 ~ 2.3 (m, 15H), 3.62 (m, 2H, $\text{CHO} \times 2$), 4.95 (m, 2H, $\text{CH}_2=\text{CH}$), 5.75 (ddd, $J=6.4, 10.6, 16.6\text{ Hz}$, 1H, $\text{CH}=\text{CH}_2$); IR (neat) $2980, 2950, 2880, 1640, 1100\text{ cm}^{-1}$; $^{13}\text{C-NMR}$ (CDCl_3) δ ; 143.3 ($\text{CH}=\text{CH}_2$), 112.09 ($\text{CH}_2=\text{CH}$), 108.1 (OCO), 78.10 (CHO), 77.81 (CHO), 41.71 (CHCH_2 , major), 42.70 (CHCH_2 , minor), 39.46 (CH_2), 36.77 (CH_2 , major), 35.73 (CH_2 , minor), 31.31 (CH_2), 22.74 (CH_2), 17.06 (CH_3), 16.89 (CH_3). From integration ratio (2.6/1, 2.6/1), the ee was determined to be 44%.

Conjugate addition of lithium cyanomethylcuprate to 2-cyclohepten-1-one controlled by 2 (*R*-(+)-3-methylcycloheptan-1-one 81) (Table 16, run 8). The same

procedure as 78. Yield 46%. After short path distillation (bp 200 °C / 60 mmHg) yield 31%. Absolute configuration and ee was determined to be *R* in 68% oy by optical rotation⁵³: $[\alpha]^{26}_D +43.3$ (c 0.480, MeOH). ¹H-NMR (CDCl₃) δ; 0.98 (d, J=6.0 Hz, 3H, CH₃), 1.2 ~ 1.9 (m, 7H), 2.41 (m, 4H). **2** was recovered as colorless prisms in 76%.

Conjugate addition of lithium butylcyanocuprate to 2-cyclohepten-1-one controlled by 2 ((+)-3-butylcycloheptan-1-one 82) (Table 16, run 9). The same procedure as 78. Yield 92%. After short path distillation (bp 200 °C / 20 mmHg) yield 79%. The ee was determined to be 74% by diastereomeric ketal (*vide infra*). Absolute configuration was not determined: $[\alpha]^{25}_D +34.0$ (c 1.03, CHCl₃). ¹H-NMR (CDCl₃) δ; 0.89 (m, 3H, CH₃), 1.25 ~ 1.94 (m, 15H), 2.46 (m, 4H); IR (neat) 2940, 2860, 1710 cm⁻¹; MS m/z 168 (M⁺); ¹³C-NMR (CDCl₃) δ; 214.59 (CO), 49.92 (CH), 43.85 (CH₂), 36.91 (CH₂), 36.82 (CH₂), 35.98 (CH₂), 29.08 (CH₂), 28.43 (CH₂), 24.37 (CH₂), 22.70 (CH₂), 13.96 (CH₃). **2** was recovered in 90%.

Determination of the ee of 82 (Table 16, run 9). The same procedure as 78. Yield 99%; ¹H-NMR (CDCl₃) δ; 0.92 (t like, J=6.8 Hz, 3H, CH₃), 1.2 ~ 2.0 (m, 23H), 3.58 (m, 2H, CHO x2); IR (neat) 2930, 2850, 1450, 1100 cm⁻¹; MS m/z 240 (M⁺); ¹³C-NMR (CDCl₃) δ; 111.63 (OCO), 77.45 (CHO), 77.27 (CHO), 46.65 (CH, major), 46.04 (CH, minor), 40.34 (CH₂), 38.22 (CH₂, major), 37.88 (CH₂, minor), 36.75 (CH₂, major), 34.97 (CH₂, minor), 33.95 (CH₂, major), 32.61 (CH₂, minor), 29.45 (CH₂), 29.09 (CH₂), 22.84 (CH₂), 22.64 (CH₃), 16.43 (CH₃), 14.05 (CH₃); From integration ratio (5.9/1, 6.0/0.92, 6.4/0.98, 6.3/ 0.90), the ee was determined to be 74%.

Conjugate addition of lithium butylcyanocuprate to 2-butenophenone controlled by 2 (*S*-(+)-3-methyl-heptanophenone 52) (Table 16). The same procedure as 78. The reaction was run at -78 °C for 25 min followed by at -50 °C for 45 min. Yield 87%. Absolute configuration and ee was determined to be *S* in 44% oy by optical rotation: $[\alpha]^{25}_D +2.27$ (c 6.96, benzene). **2** was recovered in 93%.

⁵³ Djerassi, C.; Burrows, B. F.; Overberger, C. G.; Takekoshi, T.; Gutsche, C. D.; Chang, C. T. *J. Am. Chem. Soc.* 1963, 85, 949.

Chapter 5. Asymmetric Addition Reaction of Magnesium Cuprate

Conjugate addition of magnesium dibutyl-cyanocuprate to 2-cyclohexen-1-one controlled by 2 (*S*-(-)-3-butylcyclohexan-1-one 76) (Table 20, run 6). To the mixture of CuCN (0.784 mmol) and 4 (0.979 mmol) in ether (15 ml) was added dropwise butylmagnesium chloride (1.57 mmol) in ether (0.90 ml) at -78 °C and the resulting white suspension was stirred for 20 min. 2-Cyclohexenone (0.653 mmol) in ether (4 ml) was added at -78 °C and stirred for 35 min. Workup as usual and purification by silica gel column chromatography (ether / hexane, 1/2) gave a colorless oil in 98% yield. Short path distillation gave 86% yield. The ee was determined to be 98% by diastereomeric ketal. Absolute configuration was determined to be *S* by optical rotation⁵⁴: $[\alpha]_{405}^{25} -81.1$ (c 1.08, CHCl₃). 4 was recovered as colorless oil in 98%.

Conjugate addition of magnesium cyano-di-*iso*-propylcuprate to 2-cyclohexen-1-one controlled by 2 ((-)-3-propylcyclohexan-1-one 86) (Table 20, run 5). The same procedure as 76. From crude ¹H-NMR, the ratio of 1,4-adduct to 1,2-adduct was 7. Yield 63%. Short path distillation (200 °C / 20 mmHg) gave 60% yield. The ee was determined to be 83% by diastereomeric ketal (*vide infra*). Absolute configuration was not determined: $[\alpha]_{405}^{25} -74.3$ (c 0.990, CHCl₃); ¹H-NMR (CDCl₃) δ; 0.90 (br t, *J*=5.0 Hz, 3H, CH₃), 1.2 ~ 2.4 (m, 13H); IR (neat) 2930, 2850, 1705 cm⁻¹. 1,2-Adduct: ¹H-NMR (CDCl₃) δ; 0.93 (m, 3H, CH₃), 1.26 ~ 1.7 (m, 9H), 1.98 (m, 2H, CH₂CH=CH), 5.63 (br d, *J*=10.0 Hz, 1H, HOCCH=CH), 5.77 (ddd, *J*=3.0, 3.0, 10.0 Hz, 1H, CH=CHCH₂); IR (neat) 3330, 2930 cm⁻¹; MS *m/z* 140 (M⁺), 122 (M⁺-H₂O), 97 (M⁺-Pr). 4 was recovered as a colorless oil in 96%.

Determination of the ee of 86 (Table 20, run 5). The same procedure as 78. Yield 64%. ¹H-NMR (CDCl₃) δ; 0.88 (br t, *J*=6.2 Hz, 3H, CH₃), 1.15 ~ 1.7 (m, 19H), 3.26 (m, 2H, CHO x2); IR (neat) 2930, 2860 cm⁻¹; ¹³C-NMR (CDCl₃) δ; 108.57 (OCO), 78.02 (CHO), 77.65 (CHO), 43.92 (CHCH₂, major), 43.00 (CHCH₂, minor), 39.36 (OCCH₂), 37.16 (OCCH₂, minor), 36.12 (OCCH₂, major), 35.22 (CH₂, minor), 34.18 (CH₂, major), 31.75 (CH₂), 23.33 (CH₂, major), 22.95 (CH₂, minor), 19.80 (CH₂), 17.09 (CH₃), 16.95 (CH₃), 14.31 (CH₃); From four integration ratios, the ee was determined to be 83%.

Conjugate addition of magnesium cyano-di-hexylcuprate to 2-cyclohexen-1-one controlled by 2 ((-)-3-hexylcyclohexan-1-one 87) (Table 20, run 7). The same procedure as 76. From crude ¹H-NMR, the ratio of 1,4-adduct to 1,2-adduct was 32. Yield 73%. Short path distillation (260 °C / 20 mmHg) gave 76% yield. The ee was determined to be 94% by diastereomeric ketal (*vide infra*). Absolute configuration was not determined: $[\alpha]_{405}^{25} -69.8$ (c 1.08,

⁵⁴ Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114.

CHCl₃); ¹H-NMR (CDCl₃) δ; 0.86 (br t, *J*=5.0 Hz, 3H, CH₃), 1.25 ~ 2.47 (m, 19H); IR (neat) 2920, 2850, 1710 cm⁻¹; MS *m/z* 182 (M⁺), 97 (M⁺-Hex); ¹³C-NMR (CDCl₃) δ; 212.02 (CO), 48.14, 41.42, 39.00, 36.52, 31.70, 31.23, 29.24, 26.53, 25.23, 22.52, 13.98. 1,2-Adduct: ¹H-NMR (CDCl₃) δ; 0.86 (m, 3H, CH₃), 1.26 ~ 1.65 (m, 14H), 1.96 (m, 2H, CH₂CH=CH), 5.70 (m, 2H, CH=CH); IR (neat) 3450, 2920 cm⁻¹; MS *m/z* 182 (M⁺), 97 (M⁺-Hex). **4** was recovered as a colorless oil in 97%.

Determination of the ee of 87 (Table 20, run 7). The same procedure as **78**. Yield 100%. ¹H-NMR (CDCl₃) δ; 0.87 (m, 3H, CH₃), 1.20 ~ 1.72 (m, 25H), 3.63 (m, 2H, CHO x2); IR (neat) 2930, 2850, 1100 cm⁻¹; ¹³C-NMR (CDCl₃) δ; 108.57 (OCO), 78.02 (CHO), 77.65 (CHO), 43.96 (CHCH₂, major), 43.04 (CHCH₂, minor), 37.07 (OCCH₂), 36.12 (OCCH₂, major), 35.49 (CH₂, minor), 34.99 (CH₂), 31.86 (CH₂), 31.81 (CH₂), 29.54 (CH₂), 26.67 (CH₂), 23.33 (CH₂, major), 22.99 (CH₂, minor), 19.80 (CH₂), 17.07 (CH₃), 16.93 (CH₃), 14.05 (CH₃); From three integration ratios, the ee was determined to be 94%.

Conjugate addition of magnesium di-benzylcyanocuprate to 2-cyclohexen-1-one controlled by 2 ((+)-3-benzylcyclohexan-1-one 88) (Table 20, run 8). The same procedure as **76**. Yield 61%. The ee was determined to be 53% by diastereomeric ketal (*vide infra*). Absolute configuration was not determined: [α]_D²⁵₄₀₅ +64.1 (c 1.31, CHCl₃); ¹H-NMR (CDCl₃) δ; 1.28 ~ 2.47 (m, 9H), 2.63 (d like, *J*=6.3 Hz, 2H, CH₂Ph), 7.09 ~ 7.38 (m, 5H); IR (neat) 2920, 1705 cm⁻¹; MS *m/z* 188 (M⁺); ¹³C-NMR (CDCl₃) δ; 211.20 (CO), 139.34, 129.00, 128.26, 126.10, 47.74, 42.91, 41.33, 40.78, 30.86, 25.03. 1,2-Adduct (yield 26%): ¹H-NMR (CDCl₃) δ; 1.65 (m, 5H), 1.97 (m, 2H), 2.83 (s, 2HCH₂Ph), 5.59 (d like, *J*=10.0 Hz, 1H, HOCCH=CH), 5.80 (m, 1H, HOCCH=CH), 7.26 (s, 5H, Ar); IR (neat) 3400, 2920 cm⁻¹; MS *m/z* 188 (M⁺). **4** was recovered as a colorless oil in 68%.

Determination of the ee of 88 (Table 20, run 8). The same procedure as **78**. Yield 100%. ¹H-NMR (CDCl₃) δ; 7.2 (m, 5H), 3.49 (m, 2H), 2.45 (d like, *J*=7.2 Hz, 2H), 0.9 ~ 1.75 (m, 15H); IR (neat) 2920 cm⁻¹; MS *m/z* 260 (M⁺), 169 (M⁺-PhCH₂); ¹³C-NMR (CDCl₃) δ; 140.47 (Ar-*ipso* C), 129.11 (Ar), 127.96 (Ar), 125.59 (Ar, *p*-CH), 108.28 (OCO), 77.97 (CHO), 77.63 (CHO), 43.42 (CH₂), 42.68 (CH₂), 37.23 (CHCH₂, major), 36.66 (CHCH₂, minor), 37.00 (CH₂, major), 35.96 (CH₂, minor), 31.36 (CH₂), 23.02 (CH₂, minor), 22.63 (CH₂, major), 16.93 (CH₃).

Conjugate addition of magnesium cyano-di-*iso*-propylcuprate to 2-cyclohexenone controlled by 2 ((-)-3-(1'-methyl)-ethylcyclohexanone 89) (Table 20, run 9). The same procedure as **76**. Yield 40%. The ee was determined to be 15% by diastereomeric ketal (*vide infra*). Absolute configuration was not determined: [α]_D²⁵₄₀₅ -38.6 (c 1.39, CHCl₃); ¹H-NMR (CDCl₃) δ; 0.91 (d, *J*=6.3 Hz, 6H), 1.22 ~ 2.43 (m, 10H); IR (neat) 2950, 1705 cm⁻¹; MS *m/z* 140 (M⁺). 1,2-Adduct (yield 4%): ¹H-NMR (CDCl₃) δ; 0.90 (d, *J*=6.2 Hz, 3H, CH₃), 0.98 (d, *J*=6.2 Hz, 3H, CH₃), 1.52 ~ 2.25 (m, 8H), 5.65 (br d, *J*=10.0 Hz, 1H, HOCCH=CH), 5.87 (m, 1H, HOCCH=CH); IR (neat) 3430, 2940 cm⁻¹; MS *m/z* 140 (M⁺). **4** was recovered as a colorless oil in 99%.

Determination of the ee of 89 (Table 20, run 9). The same procedure as 78. Yield 100%. ¹H-NMR (CDCl₃) δ; 0.82 (d like, *J*=6.3 Hz, 6H, CH₃), 1.2 ~ 1.68 (m, 16H), 3.60 (m, 2H, CHO x2); IR (neat) 2950, 1450, 1100 cm⁻¹; ¹³C-NMR (CDCl₃) δ; 108.90 (OCO), 78.06 (CHO), 78.02 (CHO), 41.46 (CHCH₂, major), 40.94 (CHCH₂, minor), 40.74 (CHCH₃, major), 39.77 (CHCH₃, minor), 37.16 (OCCH₂, major), 36.10 (OCCH₂, minor), 32.44 (CH₂), 32.40 (CH₂), 28.14 (CH₂), 23.36 (CH₂), 22.95 (CH₂), 19.61 (CH₃), 19.37 (CH₃), 19.34 (CH₃), 17.07 (CH₃), 17.02 (CH₃), 16.91 (CH₃); From two integration ratio, the ee was determined to be 15%.

Chapter 6. Catalytic Asymmetric Conjugate Addition Reaction

Preparation of copper iodide–dimethyl sulfide complex⁵⁵. CuI (0.105 mol) was packed in column tube and washed successively by the flow of methanol (100 ml), ether (50 ml), and hexane (50 ml). Then CuI was dissolved in dimethyl sulfide (60 ml) and to this orange solution was added hexane (50 ml). The resulting colorless needles was filtrated, washed successively by dimethyl sulfide / hexane (20 ml / 30 ml, 10 ml / 30 ml), and hexane (80 ml) and dried in vacuo: Yield 36%; dp ~100 °C (smell of DMS), ~118 °C (slightly brown); Anal. Calcd. for CuI• 3/4 SMe₂: C, 7.62; H, 1.91; S, 10.14. Found: C, 7.62, H; 1.84; S, 9.88.

Conjugate addition of butylmagnesium chloride to 2-cyclohexenone controlled by catalytic amount of CuI–4 complex (*S*-(*-*)-3-butylcyclohexanone 76) (Table 30, run 3). Copper iodide (0.134 mmol) and **1** (0.538 mmol) was suspended in ether (13ml) at room temperature for 20 min. Then the suspension was cooled to -78 °C and butylmagnesium chloride (2.02 mmol) in ether (1.2 ml) was added. After 15 min, a solution of 2-cyclohexenone (1.68 mmol) in ether was dropwised for 20 min and the whole was stirred for 20 min at -78 °C. Usual workup and purification by silica gel column chromatography (dichloromethane/hexane 4:1) followed by short path distillation afforded (*S*)-3-butylcyclohexanone ($[\alpha]^{25}_{365}$ -146.3 ° (c 1.18, CHCl₃), $[\alpha]^{25}_{405}$ -73.2 ° (c 1.25, CHCl₃), $[\alpha]^{25}_D$ -7.38 ° (c 1.13, toluene)) in 92% isolated yield. The ee was determined to be 90% by ¹³C NMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol (*p*-TsOH in benzene at reflux). The ligand **4** was recovered in 61% yield for reuse without any racemization.

Conjugate addition of hexylmagnesium chloride to 5, 6-dihydro-2H-pyran-2-one controlled by catalytic amount of CuI–4 complex (*S*-(*-*)-hexyl-valerolactone 99) (Table 30, run 11). The same procedure as **76**. CuI•SMe₂ was used. Isolated yield 70%. The ee was determined to be 90% by converting to **105** and ¹H-NMR analysis in the presence of shift reagent (*vide infra*). The absolute configuration was not determined. ¹H-NMR (CDCl₃) δ; 0.89 (m, 3H), 1.3 ~ 2.18 (m, 12H), 2.70 (m, 1H), 4.36 (m, 2H, CH₂O); ¹³C-NMR (CDCl₃) δ; 171.32 (CO), 68.34 (CH₂O), 36.39 (CH₂CH₂O), 35.96 (CH₂CO), 31.50 (CH₂), 31.23 (CH), 28.97 (CH₂), 28.74 (CH₂), 26.15 (CH₂), , 22.36 (CH₂), 13.84 (CH₃); IR (neat) 2920, 2850, 1730 cm⁻¹; MS m/z 185 (M⁺+1); $[\alpha]^{25}_{405}$ -47.1 (c 2.63, CHCl₃); HRMS m/z Calcd for C₁₁H₂₀O (M⁺): . Found: . The ligand **4** was recovered in 84% yield as a colorless oil.

Determination of the ee of 99 (Table 30, run 11). To the solution of **99** (0.592 mmol) in ethanol (1 ml) was added NaOH (0.529 mmol) in H₂O (1 ml) and the whole was stirred for

⁵⁵ Wuts, P. G. M. *Synth. Commun.* **1981**, *11* (2), 139.

20 min at rt. Concentration and azeotropic distillation with benzene gave sodium 3-(2'-hydroxyethyl)-nonanoate as white powder: $^1\text{H-NMR}$ (CD_3OD) δ ; 0.9 (m, 3H, CH_3), 1.33 ~ 2.11 (m, 15H), 3.61 (t like, $J=7.5$ Hz, 2H, CH_2O); IR (neat) 1650, 1550 cm^{-1} . This hydroxy acid was dissolved in THF (2 ml) and added NaH (1.18 mmol) at rt. After 15 min methyl iodide (5.92 mmol) was added. After methyl etherification was completed (confirmed by TLC), DMF (2 ml) was added and the whole was stirred for 35 min. Satd. NH_4Cl (20 ml) was added and extracted by AcOEt (20 ml x3). The organic layer was washed successively by 10% HCl, satd. NaHCO_3 , H_2O , 20% $\text{Na}_2\text{S}_2\text{O}_3$, and satd. NaCl (10 ml each) then dried over Na_2SO_4 . Concentration and purification by silica gel column chromatography (AcOEt / hexane 1/9) gave **105** as a colorless oil in 85% yield. The ee was determined to be 90% by $^1\text{H-NMR}$ analysis in the presence of $\text{Eu}(\text{hfc})_3$ (**105** / $\text{Eu}(\text{hfc})_3$, 20 mg / 20 mg, singlet signal of methyl ether, δ ; 4.14 ppm (major) and 4.09 ppm (minor), integration ratio 19/1): $^1\text{H-NMR}$ (CDCl_3) δ ; 0.86 (t like, $J=6.7$ Hz, 3H, CH_3CH_2), 1.25 (m, 10H), 1.55 (m, 2H), 1.95 (m, 1H), 2.27 (m, 2H, CH_2CO), 3.29 (s, 3H, CH_3O), 3.38 (t like, CH_2O), 3.64 (s, 3H, CH_3OCO); $^{13}\text{C-NMR}$ (CDCl_3) δ ; 173.69 (CO), 70.73 (CH_2O), 58.48 (CH_3OCO), 51.34 (CH_3O), 38.91 (CH_2COO), 34.09 (CH_3O), 33.62 (CH_2), 32.40 (CH), 31.75 (CH_2), 29.44 (CH_2), 26.44 (CH_2), 22.59 (CH_2), 14.04 (CH_3CH_2); IR (neat) 2910, 2840, 1730 cm^{-1} ; MS m/z 215 (M^+-CH_3), 199 ($\text{M}^+-1-\text{CH}_3 \times 2$); Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{O}_3$: C, 67.79; H, 11.38. Found: C, 68.00; H, 11.16. $[\alpha]^{25}_{405} +0.33$ (c 3.02, CHCl_3).

Conjugate addition of butylmagnesium chloride to 5, 6-dihydro-2H-pyrane-2-one controlled by catalytic amount of CuI-4 complex (S-(-)-3-butyl-valerolactone 98) (Table 30, run 10). The same procedure as **76**. NMR yield 70%. Isolated yield 57%. The ee was determined to be 90% by converting to **104**⁵⁶ and $^1\text{H-NMR}$ analysis in the presence of shift reagent (*vide infra*). The absolute configuration and optical yield was determined to be *S* in 90% oy from optical rotation⁵⁶: $[\alpha]^{25}_{\text{D}} -21.1$ (c 4.53, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ ; 0.90 (m, 3H), 1.3 ~ 2.17 (m, 11H), 2.7 (m, 1H), 4.35 (m, 2H, CH_2CO); IR (neat) 2910, 1730 cm^{-1} ; MS m/z 156 (M^+).

Determination of the ee of 98 (Table 30, run 10). The same procedure as **99**. Yield 60%. The ee was determined to be 91% by $^1\text{H-NMR}$ analysis in the presence of $\text{Eu}(\text{hfc})_3$ (**104** / $\text{Eu}(\text{hfc})_3$, 30 mg / 20 mg, singlet signal of methyl ether, δ ; 3.68 ppm (major) and 3.65 ppm (minor), integration ratio 22/1): $^1\text{H-NMR}$ (CDCl_3) δ ; 0.89 (m, 3H, CH_3), 1.26 ~ 2.0 (m, 11H), 2.25 (m, 2H, CH_2CO), 3.31 (s, 3H, CH_3O), 3.40 (t, 7.0 Hz, 2H, CH_2O), 3.66 (s, 3H, CH_3OCO); IR (neat) 2910, 1730 cm^{-1} ; MS m/z 202 (M^+).

Conjugate addition of propylmagnesium chloride to 5, 6-dihydro-2H-pyrane-2-one controlled by catalytic amount of CuI-4 complex (S-(-)-3-propyl-valerolactone 97⁵⁶) (Table 30, run 9). The same procedure as **76**. $\text{CuI} \cdot \text{SMe}_2$ complex was used. NMR yield 66%. Isolated yield 34%. The absolute configuration and optical yield was determined to be *S* in 76% oy from optical rotation⁵⁶: $[\alpha]^{25}_{\text{D}} -18.8$ (c 6.05, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ ; 0.92 (m, 3H, CH_3), 1.35 (m, 4H), 1.54 (m, 1H), 1.98 (m, 2H), 2.14 (dd, $J=9.9, 17.0$ Hz, 1H, one of

⁵⁶ Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

CH₂CO), 2.69 (dd, J=5.7, 17.0 Hz, 1H, one of CH₂CO), 4.26 (ddd, J=3.6, 11.4, 11.4 Hz, 1H, one of CH₂O), 4.41 (ddd, J=4.5, 4.5, 11.4 Hz, 1H, one of CH₂O); ¹³C-NMR (CDCl₃) δ; 171.32 (CO), 68.32 (CH₂O), 38.08 (CH), 36.28 (CH₂CO), 30.89 (CH₂), 28.59 (CH₂), 19.27 (CH₂), 13.71 (CH₃); IR (neat) 2950, 1730, 1245, 1215, 1065 cm⁻¹; MS m/z 142 (M⁺), 99 (M⁺-Pr). The ligand **4** was recovered in 100% as a colorless oil.

(-)-3-(2-Phenylethyl)cyclohexan-1-one (100)⁵⁷: [α]_D²⁵₄₀₅ -68.7° (c 1.41, CHCl₃) (84% ee); ¹H-NMR (CDCl₃) δ; 7.20 (m, 5H), 1.4-2.73 (m, 13H); IR (neat) 2940, 1710 cm⁻¹; MS m/z 202 (M⁺).

(-)-3-(2-Phenylethyl)cycloheptan-1-one (101): [α]_D²⁵₄₀₅ -105.1° (c 1.34, CHCl₃) (83% ee); ¹H-NMR (CDCl₃) δ; 7.20 (m, 5H), 2.4-2.73 (m, 6H), 1.4-1.98 (m, 9H); ¹³C-NMR (CDCl₃) δ; 214.2, 142.0, 128.3, 125.7, 49.67, 43.79, 38.92, 36.64, 35.38, 33.16, 28.30, 24.30; IR (neat) 2920, 1695 cm⁻¹; MS m/z 216 (M⁺); HRMS m/z Calcd for C₁₅H₂₀O (M⁺): 216.1515. Found: 216.1513.

Oxidation of 100 to Methy Ester 102⁵⁸ (**(R)-(-)-Methyl 3-(3-oxocyclohexyl)-propionate**). To the solution of **100** (1.01 mmol) in a mixed solvent of carbon tetrachloride (4 mL), acetonitrile (4 mL) and H₂O (8 mL) was added sodium metaperiodate (18.3 mmol) and ruthenium trichloride n-hydrate (0.022 mmol) and the whole was stirred for 18.5 h at rt. Usual workup gave the corresponding carboxylic acid in 63% yield, which was methylated by diazomethane in ether under ice bath. Purification by silica gel column chromatography (ether/hexane 1/1) gave **102** in 75% yield as a colorless oil: [α]_D²⁵ -9.28 (c 1.73, cyclohexane) (87% ee); ¹H-NMR (CDCl₃) δ; 3.69 (s, 3H), 1.4-2.52 (m, 13H); IR (neat) 2950, 1730, 1705 cm⁻¹; MS m/z 184 (M⁺). Ee was determined by ¹³C NMR analysis of the corresponding diastereomeric ketals of (*R,R*)-2,3-butanediol.

(-)-Methyl 3-(3-oxocycloheptyl)-propionate (103): [α]_D²⁵ -35.1 (c 0.875, CHCl₃) (83% ee); ¹H-NMR (CDCl₃) δ; 3.66 (s, 3H), 2.41 (m, 6H), 1.4-1.94 (m, 9H); ¹³C-NMR (CDCl₃) δ; 213.76, 173.76, 51.56, 49.29, 43.78, 36.39, 35.37, 31.90, 31.50, 28.20, 24.21; IR (neat) 2925, 1735, 1695 cm⁻¹; MS m/z 198 (M⁺), 167 (M⁺-CH₃); HRMS m/z Calcd for C₁₁H₁₈O₃(M⁺): 198.1256. Found: 198.1252.

Typical Procedure of the Asymmetric Conjugate Addition Reaction in Stoichiometric Conditions. (Table 31, entry 11): Copper iodide (0.794 mmol) and **1** (3.18 mmol) was suspended in ether (28 mL) at room temperature for 20 min. Then the suspension was cooled to -78 °C and butylmagnesium chloride (2.38 mmol) in ether was added. After 15 min, a solution of 2-cyclohexenone (0.662 mmol) in ether (4 mL) was added dropwise for 20 min and the whole was stirred for 20 min at -78 °C: [α]_D²⁵₃₆₅ -155.1° (c 1.20, CHCl₃) (95% ee).

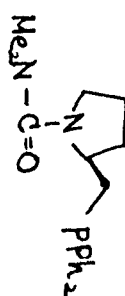
⁵⁷ Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1993**, *58*, 3455.

⁵⁸ Gerlach, v. H. *Helv. Chim. Acta*, **1978**, *61*, 2773.

Basic Program for Ee Simulation of Stoichiometric Reaction.

— Estimation of K_a and k_{rel} .

STOE

$$K = 0.4, \quad k = 20, \quad k = 0.8$$


Load "3:STOEE

〇天

15

10 CLS:CLS 3:L=1

20 DEEDBL A,B,C,D,E,X,Y,K

```
30 SCREEN 3:A#=0:B#=0:C#=0:D#=0:E#=0:X#=0:Y#=0:K#=0:S=0
```

```
40 DEFDBL A,B,C,D,E,X,Y,K
```

```
50 INPUT "K=":M:INPUT "K=":K#:INPUT "B=":B#
```

```
55 PSET(0,0);7:DRAW"D4OR1OL1OD4OR1OL1OD4OR1OL1OD4OR1OL1OD4OR1OL1OD4OR1O
```

L10D4OR1QL10D4OR1OL10D39R1O7U1OD1OR1O7U1OD1OR1O7U1OD1OR1O7U1OD1OR1O7U1

0010

```
60 RESTORE 110:A(0)=0:B(0)=0:FOR I=1 TO 6:READ A(I),B(I):LINE(A(I-1)*200,400-B(I
```

```
-1)*400)-(A(I)*200,400-B(I)*400),6:NEXT I
```

```
70 FOR I=.01 TO 3 STEP .01
```

$$30 \text{ A\#} = \text{M}*(1-\text{B\#})-\text{B\#}+1/\text{I}:\text{C\#} = 1+4*\text{B\#}*(\text{M}-1)*(1/\text{I}-2*\text{B})/(\text{A\#}*\text{A\#}):\text{D\#} = \text{SQR}(\text{C\#})-1:\text{Y\#} =$$
$$A \# * D \# / (2 * (M - 1)) : X \# = B \# - Y \# : E \# = .95 * K \# * X \# / (K \# * X \# + Y \#)$$

```
85 IF E# > .95 THEN E# = .95
```

90 PRINT #

```
100 S=INT(400-#*400):PSET(I*200,S),3:NEXT I
```

```
110 DATA .025, .18, .1, .50, .26, .77, .42, .89, .65, .9, 5, .95
```

120 RUN 20

四

300

Basic Program for E_e Simulation of Catalytic Reaction

- Estimation of E_e .

CATEVAL

```
OK
list
10 CLS
20 SCREEN 3
25 CONSOLE,,1:COLOR 7
30 INPUT"K=":K:INPUT"C=":C:INPUT"P=":P:INPUT"G0=":G0:INPUT"S0=":S0
35 B=C/P:D=P/G0:E=P/(G0-S0):F=(E-D)/1000:FOR I=D TO E STEP F
40 Y1=M*(1-B)-B+1/I:Y2=1+(4*B*(M-1)*(1/I-2*B))/(Y1*Y1):Y=P*Y1*(SQR(Y2)-1)/(2*(M-1))
50 X=C-Y
60 A=(.975*K*X+.5*Y)/(K*X+Y):IF A>.975 THEN A(I)=.975 ELSE A(I)=A:B(I)=A(I)*.001
: NEXT I
70 FOR J=D TO E STEP F:Z=Z+B(J):NEXT J:COLOR 2:PRINT:Z:COLOR 7
80 H=2*Z-1:COLOR 6:PRINT:H
90 RUN 20
OK
COPY 3
```

load " auto go to list run save " key print edit . cont

報文リスト

1. Enantioselective Conjugate Addition of Organocuprate Using a Chiral Amidophosphine Ligand
M. Kanai, K. Koga and K. Tomioka
Tetrahedron Lett. **1992**, *33*, 7193.
2. Solvent Effect and NMR Behaviour in a Chiral Amidophosphine Mediated Reaction of Organocuprate with Chalcone
M. Kanai, K. Koga and K. Tomioka
J. Chem. Soc., Chem. Commun. **1993**, 1248.
3. Asymmetric Conjugate Addition of Organocopper–Amidophosphine Reagents to Cycloalkenones
M. Kanai and K. Tomioka
Tetrahedron Lett. **1994**, *35*, 895.
4. Asymmetric Conjugate Addition of Grignard reagents Controlled by Catalytic Copper(I)-Chiral Ligand Complex
M. Kanai and K. Tomioka
in preparation.
5. Asymmetric Conjugate Addition of Magnesiumcuprate Controlled by Chiral Amidophosphine Ligand
M. Kanai and K. Tomioka
in preparation.

本研究以外の報文リスト

1. An Expedient Synthesis of Dolastatin 10
K. Tomioka, M. Kanai and K. Koga
Tetrahedron Lett. **1991**, *32*, 2395.
2. Origin of Regioselectivity in Electrophilic Reaction of Ambident Enal dimines
Tomioka, K., T. Okamoto, M. Kanai and H. Yamataka
Tetrahedron Lett. **1994**, *35*, 1891.