酸素を用いた触媒的酸化カップリングによるビナフトール類不斉合成法の開拓

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第１節　第１項　ビナフチル化合物の基本的特性、及び合成法

1,1'-ビナフタレン-2,2'-ジオール（ビナフトール）は 1,1'-結合のまわりの回転が阻害されているため、軸不斉による光学活性体が存在する。このような化合物は不斉配位子として非常に有用である。その理由には次のようなものが挙げられる。[1)]

1. 芳香環の堅固な構造により反応の際のコンフォメーションの数が制限される。
2. 立体的にかさ高く、大きな不斉空間を提供できる。
3. 対称なビナフチルでは C_1 対称の不斉源よりも反応に関与するジアステレオマーの数が減り、反応の制御、及び理解に有利である。
4. ２つのナフタレン残基のなす角度が、ある程度の自由度を有し反応相手によって立体反発を吸収できる。そのため基質選択性の広さ、遷移状態へのスムーズな移行などが考えられる。
5. 多くのビナフチル化合物の絶対配置が分かっている。

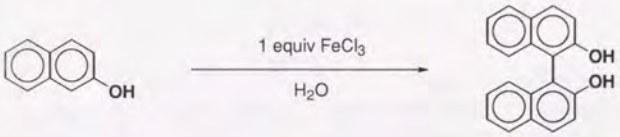
ビナフチル化合物の合成には、酸化的カップリング、Ullmann カップリング、ベンジジン転移、ニッケル-ホスフィン錯体を用いた Grignard 試薬とハライドとのクロスカップリング、オキサゾリンで活性化されたナフタレン環に対する求核置換反応、などが用いられてきた。ベンジジン転移はビナフチルジアミン合成に用いられる。ニッケル-ホスフィン錯体を用いた Grignard 試薬とハライドとのクロスカップリング、及びオキサゾリンで活性化されたナフタレン環に対する求核置換反応は非対称のビナフチル化合物の合成に優れている。[2)] 酸化的カップリングはビナフトール誘導体の合成に用いられる。

第１節　第２項　ビナフトール合成法、触媒的カップリングへの展開

先に述べたように、最も用いられるビナフトール誘導体合成法は、酸化的カップリングである。酸化剤として Fe(III)、 Mn(III)、 Cu(II) などを使用する。

R. Pummerer らは $FeCl_3$ を用いたカップリング[3)]により、ビナフトールを収率 90%で得た。この仕事（Dianin reaction）は、その後の多くの文献に引用されている。

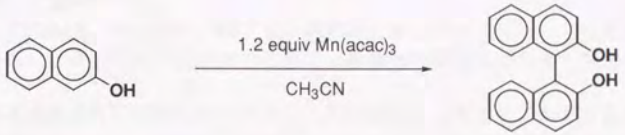
Scheme 1.



しかし、$FeCl_3$ は Friedel-Crafts 反応の触媒となるため副反応が起きることがあった。同じく酸化剤として用いられる $K_3Fe(CN)_6$ は、アルカリ水溶液中で反応を行うため、基質の制限があった。

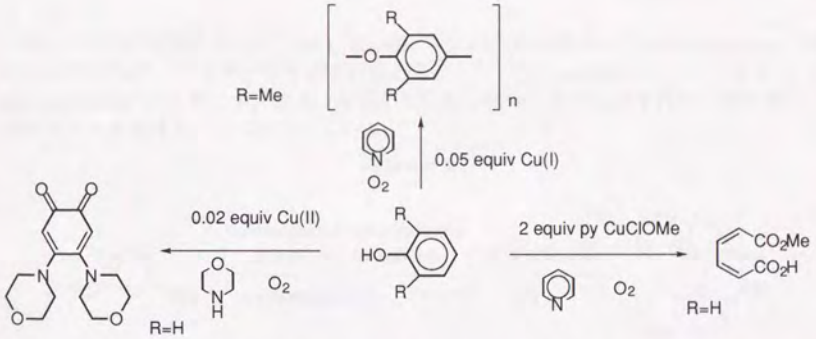
この点を改善すべく、T. Nakaya らは $Mn(acac)_3$ をフェノール誘導体のカップリング[4]に用い、ビナフトールを収率 69%で得た。

Scheme 2.



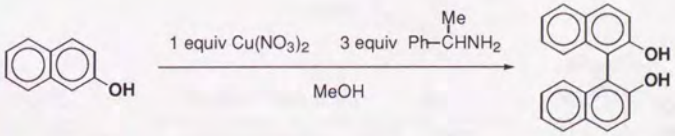
銅イオンは、チロシナーゼなどのフェノールを酸化する酵素に含まれており、その役割が注目を集めている。しかし、銅錯体をフェノールの酸化剤として使うことは、合成的には重要視されていなかった。好気的条件ではキノンやポリマー、炭素炭素結合の開裂した生成物を与えるためである。[5-7]

Scheme 3.



それに対して H. Wynberg らは、窒素雰囲気下銅アミン錯体を用いることで、収率 62%でビナフトールを得ることに成功した。[8]

Scheme 4.

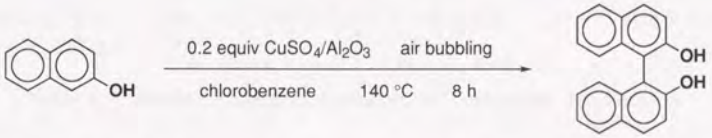


鉄を酸化剤として用いた反応では、溶媒、液性等の制限がある。その理由は無機塩の鉄と有機化合物のナフトールが、ともに溶解する条件が必要なためである。 $Mn(acac)_3$ は有機溶媒中での酸化カップッリングに適しているといえるが、引用例を調べるとアセトニトリル中のカップリングがほとんどである。一方、銅アミン錯体は多くの有機溶媒に可溶である。このため銅塩、アミンの選択の幅が広く、同様に適用可能なナフトール誘導体も多いと期待できる。

しかし、これら鉄、マンガン、銅-アミン錯体は、ナフトールに対して当量以上用いなければならない。そのため大量合成のときには廃棄物の問題などがあり実用的とは言い難かった。

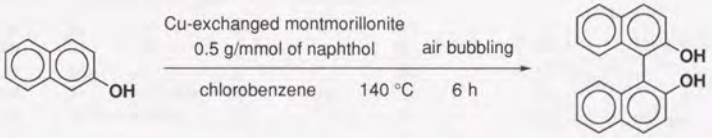
酸素を再酸化剤として利用したビナフトール合成法はこれまでにわずかな例が報告されているに過ぎない。T. Sakamoto らはアルミナに保持した硫酸銅を触媒として用い、ビナフトールを収率 99%で得ている。[9]不均一系の触媒であり後処理は濾過のみという利点がある。

Scheme 5.



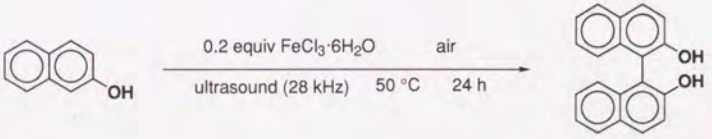
同じく不均一系反応として、M. L. Kantan らは Cu^{2+}を保持させた montmorillonite を用いて収率 95%でビナフトールを得ている。[10]ナフトール 1 mmol(0.14 g) につき 0.5g の montmorillonite が必要だが、濾過、回収した触媒を用いて再び反応を行い、収率 90%でビナフトールを得ることに成功している。

Scheme 6.

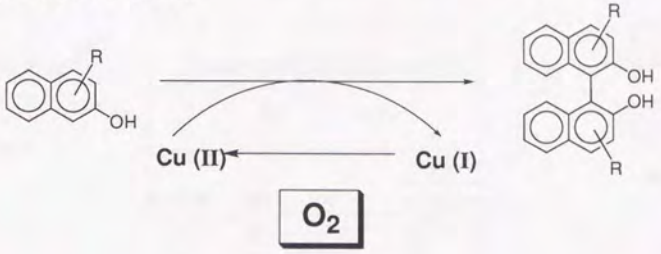


一方、F. Toda らは $FeCl_3 \cdot 6H_2O$ を用いて固相カップリングを行った。ナフトールに対して 2 当量の $FeCl_3 \cdot 6H_2O$ を用いて収率 95%にてビナフトールを得ている。さらに Scheme 7 に示した、超音波を用いた固相での触媒反応の試みも行っている。[11]

Scheme 7.

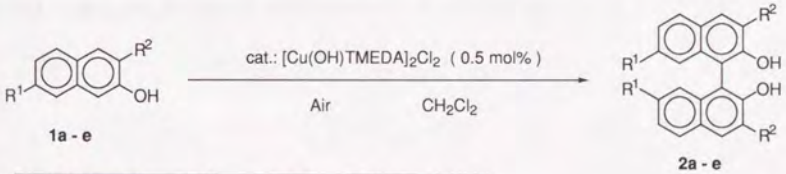


われわれは、過剰な酸化を引き起すために利用し難かった酸素を、カップリングに対する反応選択性を持たせながら利用可能ならば、触媒量の金属でナフトールのカップリングがおこなえると考えた。



検討の結果、CuCl と TMEDA から調製される二核錯体[12]が、非常に優れた触媒となることをみいだした。この系では，　空気中の酸素を効率よく利用でき、バブリングや激しい撹拌は必要ない。溶媒、反応温度の選択により各種置換ナフトール誘導体を高収率で得ることに成功した。[13a]

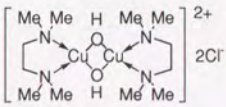
Table 1. Aerobic Oxidative Coupling of 2-Naphthol Derivatives



naphthol	R^1	R^2	time, h	T, °C	yield, %
1a	H	H	20	0	96
1b	H	Me	1	r.t.	96
1c	MeO	H	2	r.t.	95
1d	H	CO_2Me	90	53	99[a]
1e	9-Phenanthrol		1.5	r.t.	77

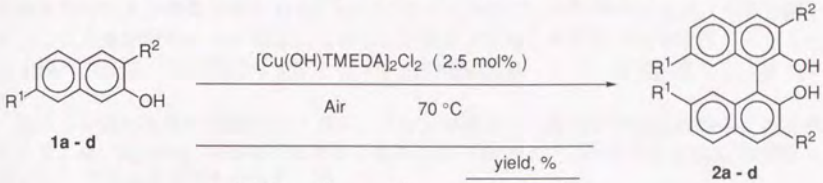
[a] Reaction was performed in MeOH.

cat:



さらに我々は$[Cu(OH)TMEDA]_2Cl_2$ が固相反応にも有効な事を見いだした。[13b)]

Table 2. Aerobic Oxidative Coupling of 2-Naphthol Derivatives in Solid State



naphthol	R^1	R^2	yield, % **2**	yield, % recovered **1**
1a	H	H	92	0
1b	H	Me	86	0
1c	MeO	H	63	37
1d[a]	H	CO_2Me	93	7

[a] Melted at 70 °C.

粉末にした触媒とナフトールを混合し、開放系で加熱した。銅として 2.5 mol% の使用で収率良くビナフトールを与えた。超音波や撹拌などの操作は必要なかった。昇華しやすいナフトール誘導体を用いたときは原料回収があった。

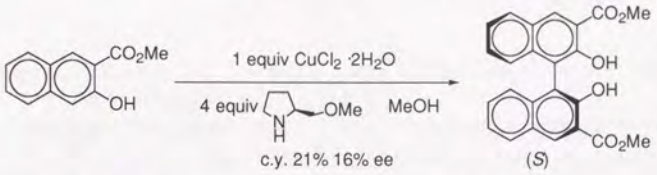
これらの触媒的反応にはそれぞれ利点があるが、我々の開発した銅アミン錯体を用いる方法は触媒的不斉反応への展開がしやすいという点で優れている。

第２節　不斉合成への応用

ビナフチル化合物の合成においては、その骨格を構築する事も重要であるが、光学活性体を得ることが最終目標となる。前節で述べた方法でラセミ体を合成後、光学分割を行うことも選択肢の一つである。しかし、不斉カップリング反応で光学活性ビナフトールを得る方法は、光学活性ビナフトールを直接得る方法として、非常に有効な方法となる。

銅アミン錯体を用いた酸化カップリングを、不斉反応へ展開する試みは数多く行われてきた。H. Wynberg らはキラルアミンまたはキラルアミノエーテルと $CuCl_2$ の錯体を用いカップリング反応を行った。[14]

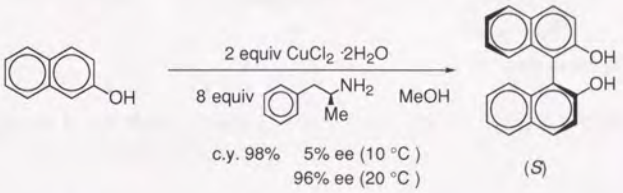
Scheme 8.



化学収率、不斉収率ともにそれほど高くはないが、不斉誘起を行った初めての例として重要である。反応機構については記されていない。

その後、J. Brussee らによりアンフェタミンを配位子として用いたカップリングが報告された。[15]非常に高い不斉収率を示した初めての例である。

Scheme 9.



不斉誘起の機構は次のように説明されている。

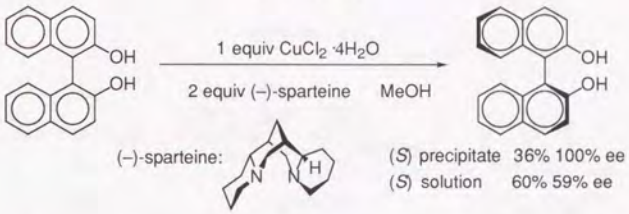
1. 室温程度の温度にて、銅アンフェタミン錯体はラセミ体ビナフトールの各エナンチオマーの相互変換を促進する。
2. 銅アンフェタミン錯体とビナフトールは塩を生成する。そのうち *S* 体と銅アンフェタミン錯体との塩はメタノールに難溶で、析出し反応系外に出る。（ジアステレオ選択的結晶化）
3. 残った *R* 体は *S* 体ビナフトールへ不斉変換され（平衡が存在する）、次第に *S* 体の塩が蓄積していく。

10 ℃にて低い不斉誘起しか示さないのはエナンチオマーの相互変換（不斉変換）の速度が遅いためである。

銅アミン錯体を用いた酸化カップリングにおいてはこのようなエナンチオマーの相互変換（不斉変換）とジアステレオ選択的結晶化はいくつか報告されている。

M. Smrčina らはラセミ体ビナフトールの不斉変換とジアステレオ選択的結晶化により 100%ee にてビナフトールを得た。[16]

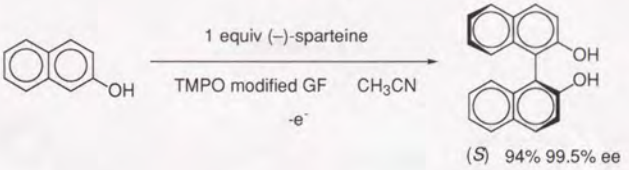
Scheme 10.



溶液、結晶から得られたビナフトールはともに *S* 体であり、銅スパルテイン錯体が(*R*)-ビナフトールを *S* 体に不斉変換することがわかる。

ナフトールと当量の不斉源を用いた例としては、これらの他に電解酸化を用いた方法がある。T. Osa らは 4-amino-TMPO (TMPO =2,2,6,6,-tetramethylpiperidin-1-yloxy) 基で修飾したグラファイト電極を用いて、スパルテイン存在下ナフトール誘導体の酸化カップリングを行った。[17]

Scheme 11.



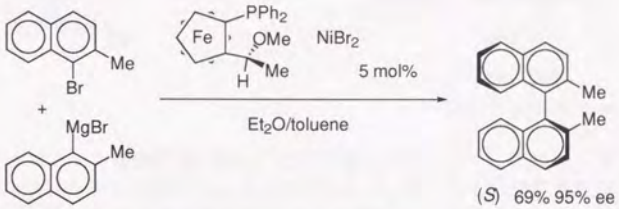
4-amino-TMPO により修飾した電極とアミンを使うことで、反応進行の妨げとなる電極上のポリマーの生成を防いでいる。

最後の例は特殊であるが、光学活性ビナフトールを酸化カップリングにより得るためには、当量以上の不斉源を必要とする反応が多い。この理由には、各エナンチオマー間の相互変換と、ジアステレオ選択的結晶化が不斉誘起の機構であることが挙げられる。

カップリング時に不斉誘起することは、ビナフチル化合物の不斉合成を触媒的な反応に展開するために重要な点である。この“不斉カップリング”を実現した、触媒的なビナフチル化合物不斉合成法はいくつか報告されている。

T. Hayashi らはキラルなフェロセニルホスフィンをニッケルの配位子として用い、アリールブロマイドとアリールグリニャール化合物のクロスカップリングを行った。[18]

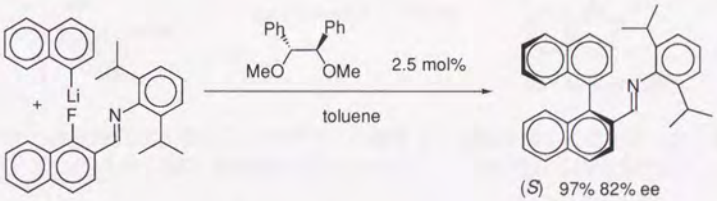
Scheme 12.



このカップリング機構は次のように説明されている。ニッケル上にトランスメタレーションと酸化的付加をした２つのナフチル基が不斉配位子の効果で配位方向の規制を受ける。これらが還元的脱離によりビアリール結合を生成し、そのときに *S* 体が生成する。

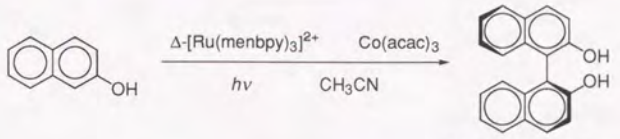
また、K. Tomioka らはナフタレン環への求核置換反応を用い、ビナフチル骨格を形成している。[19]

Scheme 13.



触媒的酸化カップリングによりビナフトールを不斉合成する試みは今までに３例が報告されているに過ぎない。K. Ohkubo らはナフトールの酸化剤に C_3 対称なキラルルテニウム錯体を用い、その再酸化剤として Co(III) を用いたカップリングをおこなっている。[20]

Scheme 14.

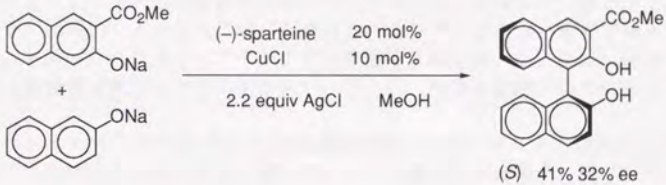


(*S*) TON 66 16% ee

Ru(III) がナフトールを酸化し、生成したラジカルがナフトールとカップリングしビナフチルオキシラジカルを生成する。これがさらに Ru(III) により酸化され、ビナフトールを生成し、そのとき *S* の軸不斉を誘起すると説明している。光は Ru(II) を活性化し Co(III) へ電子を与える役目をしている。

M. Smrčina らは銅アミン錯体を用いて、ナフトールの酸化的カップリングを検討し、不斉カップリングが起こることを報告した。[21]

Scheme 15.

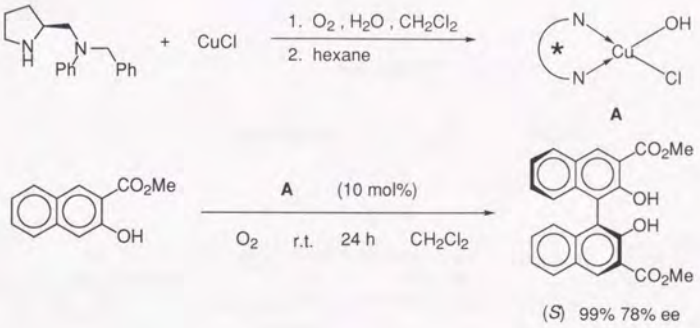


(*S*) 41% 32% ee

ナフトールを酸化後１価になった銅アミン錯体を、再酸化剤するために AgCl を用いている。また生成する HCl を中和するためナフトール塩を用いて反応を行っている。

M. Nakajima ら[22] は野地、中島、古賀らにより報告された触媒的ビナフトール合成法[13] を不斉カップリングへ展開し成功を収めている。

Scheme 16.



ビナフトール誘導体の不斉合成を中心に紹介したが、以上をまとめると次のようになる。

銅キラルアミン錯体を用いるカップリングではエナンチオマー間の相互変換（不斉変換）、ジアステレオ選択的結晶化の機構が存在するため、不斉源が当量必要である。ビナフトールの触媒的な不斉合成には“不斉カップリング”の実現が重要である。

ニッケルを用いたクロスカップリングや求核置換反応を用いた方法は、無水、低温、不活性ガス雰囲気下反応を行う必要があり、さらに、強塩基を用いるため基質の制限がある。

ルテニウム-コバルト系や銅アミン-塩化銀系を用いたカップリングは無水、不活性ガス雰囲気下反応を行う必要があり、酸化剤として当量以上の金属を必要とする。

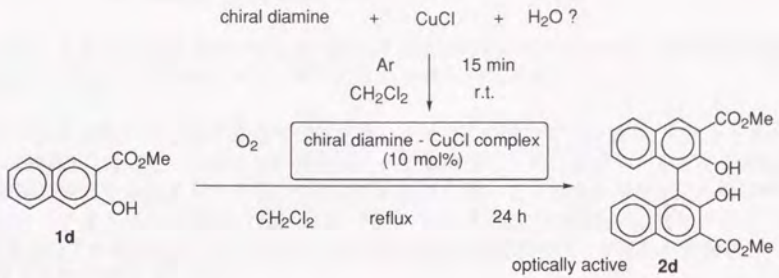
われわれが報告した$[Cu(OH)TMEDA]_2Cl_2$ を用いたカップリング法は中性条件下、非常に穏やかな反応条件で行われる。そのためより多くの基質に適用可能といえる。

また本カップリング反応は、反応後１価となった銅アミン錯体の再酸化剤として、酸素を用いている。この点で、塩化銀(I) を用いる M. Smrčina らのカップリング反応よりも汎用性が高いことが期待され、ビナフトールの優れた不斉合成法への展開が期待される。

第3節　触媒的酸化カップリングによるビナフトールの不斉合成

われわれが開発したビナフトール類新規合成法を不斉反応へ展開することは、修士までの研究[13b]で予備的におこなっていた。その実験結果を Table 3 及び Table 4 に示す。TMEDA のかわりにキラルジアミンを用いることで、不斉カップリングへ展開できると考え検討した。

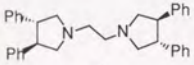
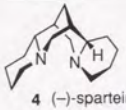
Scheme 17.



塩化メチレン中アルゴン雰囲気下、各種キラルアミンと塩化銅(I) から錯体を調製し、ナフトールを加えた後、酸素雰囲気下反応を行った(Scheme 17)。

検討の結果、キラルアミン **3** 及び **4** を用いての反応は有意な不斉誘起を示した。

Table 3. Asymmetric Coupling of 1d with Chiral Diamine-CuCl Complex[a]

amine	yield, % (*R*)-**2d**	yield, % recovered **1d**	ee, %	amine	yield, % (*S*)-**2d**	yield, % recovered **1d**	ee, %
 **3**	80	20	19	 **4** (−)-sparteine	18	82	46

[a] 10 mol% of complex was used.

次に本カップリング反応が“不斉カップリング”であるかを検討した。ラセミ体 **2d** をカップリング反応と同じ条件で処理し回収した **2d** の不斉収率を調べた(Table 4)。

Table 4. The Influence of Chiral Amine-CuCl Complex on the ee of 2d

amine	amine-CuCl equiv[a]	recovered **2d**, %	ee, %	congign.
3	0.1	100	0	-
4	1	77	3	(*S*)

[a] 0.1 equiv = 5 mol % to **2d**; 10 mol % to **1d**.

アミン **3** を用いた処理は回収した **2d** に不斉誘起は見られなかった。不斉変換は起きないことから、“不斉カップリング”による不斉誘起と判明した。

アミン **4** を用いた反応では化学収率が低いため **2d** に対して１当量の、すなわち **2d** を **1d** に換算したときの 100 mol %の錯体を用いて処理を行った。**2d** がスパルテイン銅錯体と強固な錯体を形成するため **2d** の回収率が低下した。３%の不斉誘起が見られたが、(*S*)-**2d**-スパルテイン-銅錯体と(*R*)-**2d**-スパルテイン-銅錯体では極性など物性が違うため **2d** を含むそれぞれのジアステレオマアー錯体からの回収率の差（５章第５節参照）に由来するものと考えている。

以上からアミン **4** を用いた反応もアミン **3** を用いた反応同様に、不斉はカップリング時に誘起されたといえる。このことは、触媒的不斉カップリングへの展開を行う上での確かな根拠を与える結果である。

第２章　銅-キラルジアミン錯体を触媒とするビナフトール不斉合成

第１章において様々なビナフチル化合物合成法を紹介した。その中で、我々の報告した酸素を用いた触媒的酸化カップリング反応は、反応操作の簡便性、基質の適用性や配位子の設計、反応系の設定などにおいて多くの可能性を残している。
そこで、より効率的な触媒反応として発展させるべく、本研究を開始した。

始めに、アミン **3** 及び **4** を用いた反応を再検討し改善を試みることとした。

第１節　反応系の改善のための戦略

まず不斉収率の改善について方針を考えた。

アミン **3** から調製した錯体を用いた反応は、不斉収率が低い。これはアミンの配位の自由度が高いためと考えた(Table ３)。骨格の固定したアミン **4** から調製した錯体は同じ反応条件で比較的高い不斉収率を示している。これらから不斉収率向上には骨格の固定したアミンを用いたほうが良いと判断した。

次にキラルアミンを用いたときの化学収率の低下の原因について考えた。

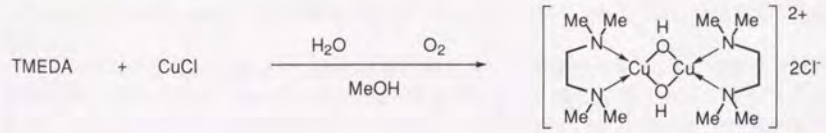
アミン **3** から調製した錯体を用いた反応では化学収率 80%にて **2d** を与えた。アミン **4** から調製した錯体を用いたときは 18%と低い化学収率にとどまった。化学収率向上のための検討として次のような点を考慮した。

1. **錯体調製条件。（酸素、水の存在）**
2. **銅アミン錯体の酸化力。**
3. **生成物もしくは基質の銅アミン錯体への配位による触媒の不活性化。**
4. **触媒錯体の不均化。**

１に関して：　錯体調製条件。（酸素、水の存在）

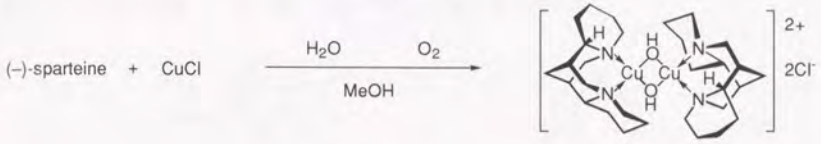
Table 1 及び Table 2 の反応で用いた触媒の構造は、TMEDA の二核錯体と考えられている（第３章参照）。G. Challa らは X 線構造解析によりその構造を決定した。[23] この２核錯体の生成には塩化銅(I) 、アミン、それらと当量の水と酸素が必要である（５章第３節）。

Scheme 18.



スパルテイン銅錯体も同様な構造と考えると、錯体調製時に塩化銅(I) とアミンと当量の水および酸素が必要である。

Scheme 19.



Assumed Structure
(–)-sparteine–CuCl complex

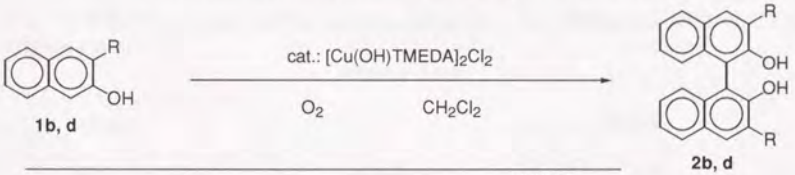
われわれはこれまで、水の役割に関しては重要視していなかった。実験操作上、微量に混入する量の水分で、部分的に錯体調製が行われ、更に反応進行とともに水が生成するため、初期の水分量が少なくても、すぐに完全な錯体調製に十分な量が補われると考えていた。

この点を改善し、反応開始前に完全に二核錯体を形成させることができれば、化学収率が改善できると考え検討した（２章第４節）。

２に関して：　銅アミン錯体の酸化力。

ナフトール誘導体のカップリング反応は基質により反応性の差がある。

Table 5.　Aerobic Oxidative Coupling of 1b and 1d



run	substrate	R	time, h	cat. (mol%)	T, °C	yield, % **2**	yield, % recovered **1**
1	**1b**	Me	1	0.5	20	92	0
2	**1d**	CO_2Me	24	5	40	71	15

塩化メチレン中 TMEDA 錯体を用い、**1b**、**1d** のカップリングを行った。**1d** は反応時間、用いた触媒量、反応温度等、より高い化学収率が期待される有利な条件で反応を行った(run 2)。しかし run 2 では原料回収があった。これに対し run 1 では反応はほぼ完結した。

ナフトールの酸化され易さが、化学収率の差となった可能性がある。**1d** は電子求引性基が置換しているため、ナフトールの電子密度が低下し、酸化を伴うカップリング反応が起こりにくくなり、反応性が低下したと考えられる。逆に **1b** は電子供与性基が置換しているため、電子密度が上昇し酸化され易くなったと考えられる。

そこで基質 **1d** を用いた反応で反応性を高めるには錯体の酸化力を上げることが効果的と考えた。この考えからアミン **3** とアミン **4** を比較し、次のような予想を立てた。アミン **4** では銅へ配位している窒素の孤立電子対の方向は常に一定と考えられ、銅への電子供与は強いと考えた。アミン **3** では配位の自由度が大きいと考えられ、そのため孤立電子対の方向は変動しやすく銅への電子供与は弱くなる考えた。

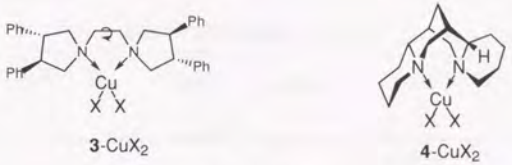


Figure 1.

これらから配位子の電子供与が強いアミン **4** の銅錯体の方が、銅の電子密度は上がり酸化力は低下すると予想した。すなわち、不斉収率向上には有利と予想したアミンの骨格の固定は反応性の面からは不利という結論になる。そこで配位子の骨格を固定しつつ銅の電子密度を低下させるためには、配位子に電子求引性基を置換させることを考えた（第２章第５節）。

３に関して：　生成物もしくは基質の銅アミン錯体への配位による触媒の不活性化。

第２節で述べたように銅アミン錯体はビナフトールと錯体を形成することが知られている。われわれの反応では不斉変換は起きていないことを確認したが、錯体形成する可能性は残っている。これは酵素の反応の生成物阻害に相当するものである。生成したビナフトールが銅アミン錯体と錯体を生成し(Scheme 20)、これが触媒反応進行の妨げになる可能性がある。

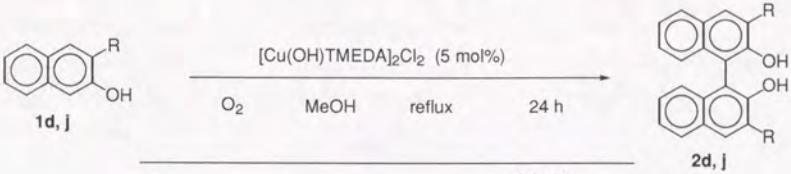
Scheme 20.

この可能性に対してはエステル部分の立体的な嵩高さの効果を検討した（第２章第４節）。

基質も同様に銅アミン錯体に強固に配位する可能性がある。その結果触媒の不活性化もあり得ると考えている。

塩化メチレン中 TMEDA 錯体を用い、**1d**, **1j** のカップリングを行った結果を示す。

Table 6. Aerobic Oxidative Coupling of 1d and 1j



run	substrate	R	yield, % **2**	yield, % recovered **1**
1	**1d**	CO_2Me	99	0
2	**1j**	OMe	20	45

1j は電子が豊富な基質と考えられ反応は速やかに完結すると考えた。しかしながら **1j** を用いた反応は進行が遅く基質の回収が見られた。また生成物と基質の量から副反応が起きていることがわかる。

副反応が起き、回収率が 100%に達しない現象は、電子の豊富な基質を用いた反応に見られる。それにも関わらず反応が遅いという事実は反応進行に関して、基質の酸化され易さ以外の他の要因があることを示唆する。

われわれは **1j** のメトキシ基の酸素が銅に配位する可能性を考えた。この配位が触媒サイクルのいずれかの段階を阻害するという考えである。

同様に Table 5 の反応性の差の説明に、触媒錯体への配位が触媒サイクルの阻害を起こしていることも考えられる。

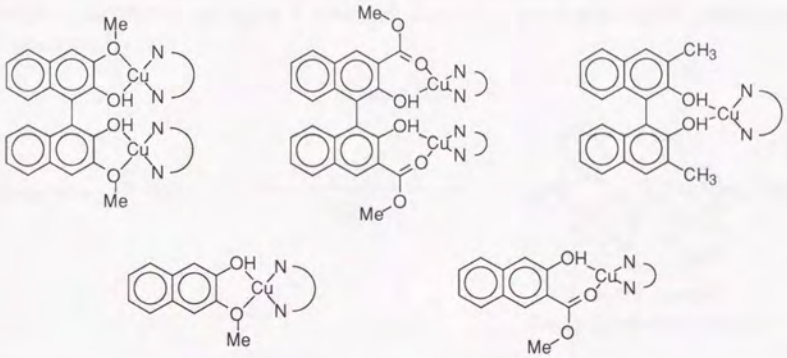


Figure 2.

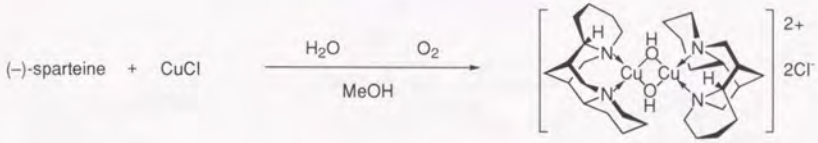
図のように配位してしまった錯体は、触媒サイクルから外れることが考えられる。反応のためには銅アミン錯体に基質が配位することが必要である。しかし配位の形式により錯体の不活性化を起こしたり、カップリング後も錯体の解離が起こらないと触媒サイクルの阻害となるだろう。これらの錯体の生成を抑えるためには、エステル置換基の検討、極性の高い溶媒、反応温度の上昇、アミンの構造を自由度が高いものにして、定まった構造をとりにくいものにする、などが考えられる。しかし不斉収率の面からは採用しにくいものもある。

４に関して：　触媒錯体の不均化。

錯体の不均化も収率低下の原因と考えた。メタノール中、塩化銅(I) と TMEDA から調製される錯体、 $[Cu(OH)TMEDA]_2Cl_2$ は二核錯体である(Scheme 18)。

同様に、塩化銅(I) とアミン **4** すなわち(–)-スパルテインから錯体を調製し緑色粉末を得た(Scheme 21)。

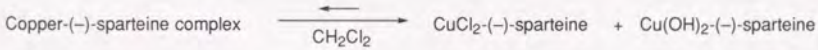
Scheme 21.



Assumed Structure
Copper-(–)-sparteine complex

このものは塩化メチレン中塩化銅(II)-スパルテイン錯体と水酸化銅(II)-スパルテイン錯体と推定される錯体に分離した(Scheme 22)。塩化銅(II)-スパルテイン錯体については元素分析と X 線構造解析によりその構造を決定した（５章第３節）。水酸化銅(II)-スパルテイン錯体は構造決定できていない。難溶性で再結晶が困難であること、加熱減圧乾燥により変質しやすいことによる。

Scheme 22.



塩化銅(II)-スパルテイン錯体と水酸化銅(II)-スパルテイン錯体は単独では触媒活性を示さない。しかし両錯体とも系内に加えると系内で調製した錯体を用いたときと同じ結果を与えた（第３章第２節）。

これらの結果から塩化メチレン中触媒活性のない錯体生成が起こることが低収率の原因と考えた。

この不均化を防ぐには銅塩の検討、溶媒の検討などが考えられる。

これらの基本方針のもと高い不斉収率、高い化学収率を実現すべく検討を行った。

まず反応系を設定し、アミンの検索を行った（第２章第３節）。

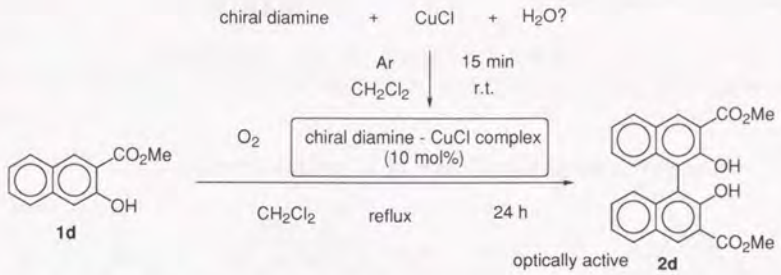
その結果比較的高い不斉誘起を示したスパルテインを中心に反応条件の再検討を行った（第２章第４節）。

次に電子的効果も含めて検討するため新規ピロロベンゾジアゼピン系ジアミンをデザインし検討した（第２章第５節）。

また、反応機構に関する考察を行った（第３章）。

第 2 節　実験の方法

Scheme 23.



修士までの検討[13]において、次のようにして反応を行ってきた(Scheme 23)。

基質 **1d** 約 0.8 mmol スケールを基準とし、触媒である銅アミン錯体を **1d** に対して 10 mol% 用いた。

塩化銅(I) は濃塩酸に溶解後、ミリ Q（通常のイオン交換水をさらにイオン交換、限外濾過したもの。比抵抗 ≈16.3 Ωcm）もしくは蒸留水を加え再沈殿させ、それぞれあらかじめ脱気、ろ取、アルゴンバブリングしたミリ Q もしくは蒸留水、エタノール、エーテルにてすばやく洗浄し、減圧乾燥、アルゴン雰囲気下保存しているものを用いた。

キラルアミンは固体のものはそのまま、液体のものについては Kugelrohr 蒸留したものを用いた。

塩化メチレンは安定剤としてメタノールを含むものを蒸留水もしくはイオン交換水で洗浄し、硫酸ナトリウムまたは硫酸マグネシウムにて乾燥後、アルゴン雰囲気下、五酸化二リンまたは水素化カルシウムから蒸留し、アルゴンをバブリングした後アルゴン雰囲気下保存したものを用いた。反応に用いた溶媒量は基質 **1d** の濃度が 40 mM となるように計算し、そのうち半量を錯体調製に用い、残りを基質 **1d** を加えるとき加えた。

基質 **1d** は市販品をそのままデシケータ中室温減圧乾燥し乾燥剤には五酸化二リンを用いた。副反応がほとんど起きないという理由から基質 **1d** を用いた。

加熱乾燥し、アルゴン雰囲気下放冷した 50 mL のナス型フラスコに、アルゴン雰囲気下塩化銅(I) 、固体のアミンを秤量し、アルゴン風船を接続した三方コックにすばやく付け替え、溶媒を加えて錯体調製を行った。液体のアミンは 10 mL のナシ型フラスコに重量で秤り取りアルゴン置換、カニューレを用い塩化銅(I) を含む 50 mL のナス型フラスコに加え錯体調製を行った。溶媒を加えた後、配位を促進する目的で、一分間超音波をかけた。

錯体調製後、秤量した **1d** をすばやく加え、溶媒を加え、酸素風船に付け替えすぐに加熱還流を行った。

われわれはこの条件を引き続き採用し、合成した各種キラルアミンを評価し、優れていたものを用いて条件検討を行うという方針をとった。

第３節　キラルアミンの検索

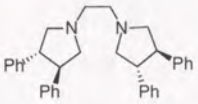
第３節　第１項　ジアミンからプロリン系化合物

第２節の反応条件に従い、TMEDA と同じエチレンジアミン骨格を持つジアミンから検討した。**3** から調製した錯体を用いた反応では化学収率 80 %、　不斉収率 19%にて (*R*)-**2d** を与えた。不斉収率の向上を期待して次のようなジアミン誘導体から錯体を調製し反応を行った。

エチレン部分の自由度を制限した **5**、**6**、５員環から６員環キレートにしてピロリジン部分が銅を両側から包み込むように期待した **7**、空間的に大きい広がりを持つ **8** 等を検討した。

Table 7.　Oxidative Coupling of 1d with Copper-Diamine Complex

run	amine	yield, %		ee, %	config.
		2d	recovered **1d**		
1	**3**	80	20	19	R
2	**5**	61	39	2	R
3	**6**	13	87	3	S
4	**7**	22	70	7	R
5	**8**	23	77	3	R



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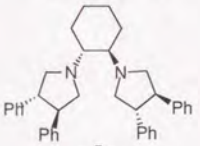

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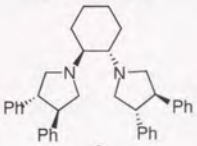

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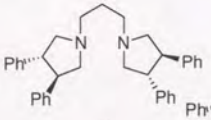

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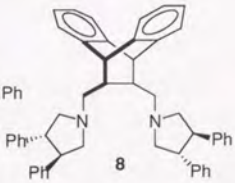


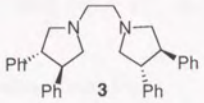
8

3 に比べ **5**、**6** とも不斉収率が低下した。シクロヘキサン環の 1,2-トランス置換基は 30 度の角度をとると予想され、**3** に比べ窒素間の距離が遠くなり、そのため配位が不安定になったからと考えられる。**7** も不斉収率が低下した。プロピレン部分の自由度が大き過ぎたためと考えられる。**8** は窒素間の距離が大きいため不斉点が離れすぎたと考えられる。

引き続き第２節の反応条件に従い、TMEDA と同じエチレンジアミン骨格を持つジアミン検討をした。**3** よりも窒素の近くに不斉点を持つ **9**、**10**、**11**、**12** を検討した。

Table 8. Oxidative Coupling of 1d with Copper-Diamine Complex

run	amine	yield, %		ee, %	config.
		2d	recovered **1d**		
1	**3**	80	20	19	R
2	**9**	0	99	-	-
3	**10**	0	99	-	-
4	**11**	0	97	-	-
5	**12**	41	53	15	S



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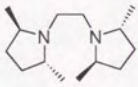

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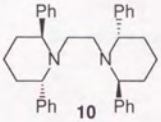

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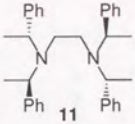

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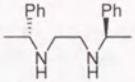


12

9、**10**、**11** を用いたときは、反応が進行しなかった。これらの錯体調製時には溶媒が緑色に着色しなかった。窒素の周囲が立体的に込み合い錯体形成出来なかったからと考えられる。**12** のように窒素上に水素が存在しても反応は進行した。

引き続き第２節の反応条件に従い、エチレンジアミン骨格のエチレン上に不斉点を持つ、ジフェニルエチレンジアミンの誘導体の検討をした。

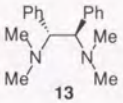
これらジフェニルエチレンジアミン系統のアミンを用いるにあたり、次のような点が重要と考えた。配位点である窒素をはさんで、フェニル基の不斉空間と、反応点である銅が反対方向へ向くため、銅の側に不斉環境を作りにくい。そこでフェニル基の不斉環境を窒素上の置換基を通して銅の側に伝えることを考えた。

13 を基本として、配位点をより嵩高くした **14**、離れたところを嵩高くした **15**、エチレン部分の回転を抑えた **16** などを検討した。

Table 9. Oxidative Coupling of 1d with Copper-Diamine Complex

run	amine	yield, %		ee, %	config.
		2d	recovered **1d**		
1	**13**	41	41	8	R
2	**14**	2[a]	60	7	S
3	**15**	37	62	7	S
4	**16**	21	79	0	-
5	**17**	0	99	-	-

[a] Reaction time: 96 h.



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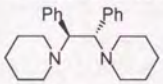

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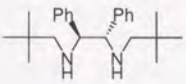

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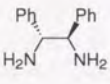


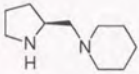
17

13 は低い不斉誘起にとどまった。メチル基では十分な不斉伝達が出来ないからと考えられる。**14** を用いたときは錯体調製時にかなりの塩化銅が溶け残った。立体的に込み合っているため、配位が遅いとためと考えている。また、ピペリジン環は、不斉炭素に結合しているフェニル基と反対側を向いているため、ピペリジン環の嵩高さが生かされなかったと考えている。**15** はフェニル基と距離的に影響を及ぼしあえる嵩高さを持つネオペンチル基を持つ。しかし、ネオペンチル基は自由度が高く、立体的に相互作用しない方向へ向くことが出来るため、低い不斉誘起にとどまったと考えられる。**16** は二座配位子として機能していないと考えられる。一級アミノ基を持つ **17** から調製した錯体は触媒活性がなかった。

第２節の反応条件に従い、配位子の骨格を固定したプロリン系統を検討した。

Table 10. Oxidative Coupling of 1d with Copper-Aminoether or Copper-Diamine Complex

run	amine	yield, %		ee, %	config.
		2d	recovered **1d**		
1	**18**	82	16	30	S
2	**19**	26	74	17	S
3	**20**	22	72	10	S
4	**21**	18	81	36	S
5	**22**	13	86	37	S



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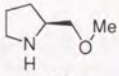

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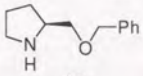

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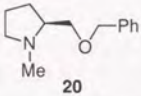

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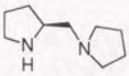


21

アミノエーテル **18** から調製した錯体も触媒として機能した。メチル基をベンジル基に変えた **19** を用いた反応では不斉収率の低下が見られた。メチル基に比べ、ベンジル基は自由度が大きく不斉環境が定まらなかったから[a] と考えてられる。窒素上にメチル基を導入したアミン **20** を用いると不斉収率が低下した。酸素の部分を窒素に変えたジアミン **21**、**22** を用いると不斉収率の向上が見られた。変更点の窒素置換基は銅に対する配位が酸素よりも強く、さらに自由度が少ない環状のため、不斉環境の固定が出来たことによるものと考えられる。

[a] メチル基が回転しても、３つの水素は等価なので、周囲に対する環境は変わらない。しかしベンジル基は２つの水素と１つのフェニル基が結合しているため、回転する角度により、周囲に対する立体的なかさ高さが変わる。

第３節　第２項　四配位型配位子

化学収率向上のための検討を行った。ナフトールが銅錯体に配位したまま２分子接近しビナフチル結合を生成するならば、適当な距離で銅錯体を導入すればカップリングに有利になると考えた。その結果化学収率の上昇が期待できる。

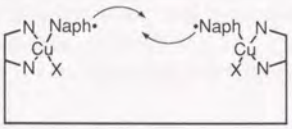
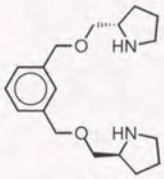


Figure 3.

反応条件は第２節の方法に従い、１分子中に、４つの配位基を持つ配位子を検討した。**23** から **27** までの配位子は銅と配位子のモル比を２対１にして用いた。パラ位にプロリノールを導入した **23**、メタ位にプロリノールを導入した **24**、**25**、オルト位にプロリノールを導入した **26**、**27** を検討した。

Table 11. Oxidative Coupling of 1d with Bidendate and Tetradendate- type Aminoether-Copper complex

run	amine	yield, % **2d**	yield, % recovered **1d**	ee, %	config.
1	**19**	26	74	17	S
2	**23**	20	70	24	S
3	**24**	45	53	12	S
4	**25**	39	55	5	S
5	**26**	39	61	18	S
6	**27**	39	55	4	S



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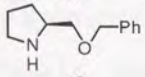

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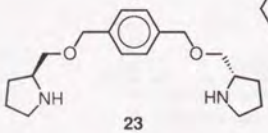

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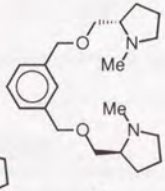

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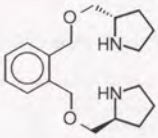

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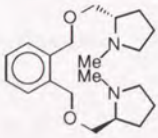


27

パラ位にプロリノールを導入した **23** を用いての反応は相当する配位子 **19** に比べ化学収率の上昇は見られなかった。メタ位にプロリノールを導入した **24**、オルト位にプロリノールを導入した **26** を用いると化学収率の上昇が見られた。適切な距離に銅錯体を導入できれば化学収率の向上が可能と考えられる。**24**、**26** のメチル体 **25**、**27** を用いると不斉収率の低下が見られた。同様な傾向が **19** とそのメチル体 **20** を用いた反応でも見られている(Table 10)。

第４節　スパルテインを用いた検討

これまでエチレンジアミン系の配位子を検討してきたが、窒素上の置換基に不斉点を有する配位子、エチレン部分に不斉点を有する配位子の、いずれも高い不斉誘起はみられなかった。

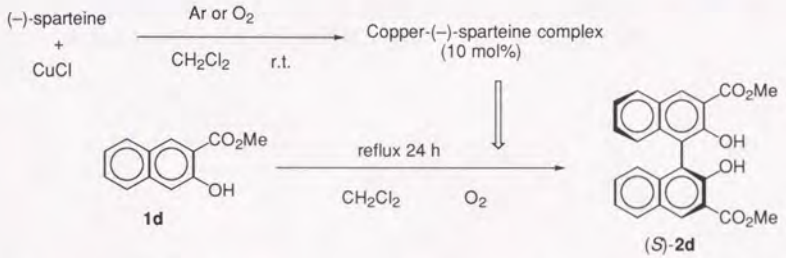
骨格の固定したプロリン系統を用いると不斉収率の上昇が見られ、更に骨格の固定したスパルテイン **4** を用いた反応が、これまでで最も高い不斉収率を示している。

しかし、スパルテイン **4** から調製した錯体を用いた反応は化学収率が低いことが欠点であった。そこで従来から用いてきた錯体調製条件を再検討することとした。

第４節　第１項　錯体調製条件の検討－酸素及び水の効果

銅スパルテイン錯体を調製するときの条件として、従来から行ってきたアルゴン雰囲気下の調製法と酸素雰囲気下の調製法を比較した。

Scheme 24.



基質 **1d** に対してそれぞれ 10 mol% の塩化銅(I) とスパルテインから錯体を調製し、基質を加え酸素雰囲気下２４時間加熱還流した（40 °C）。

Table 12.　Oxidative Coupling of 1d with Copper-Sparteine Complex

run	complex	yield, % **2d**	yield, % recovered **1d**	ee, %
1	prepared under Ar atmosphere	18	82	46
2	isolated Copper-sparteine complex	25	75	46
3	prepared under O_2 atmosphere	31	69	47

あらかじめ酸素雰囲気下、それぞれ同量の塩化銅(I) 、スパルテイン、水から調製、単離した錯体（第５章第３節）を用いた反応(run 2)の化学収率は、アルゴン雰囲気下調製した錯体を用いた反応(run 1)の化学収率より高い。さらに、酸素雰囲気下調製した錯体を用いた反応(run 3)の化学収率は run 1, run 2 より高い。それぞれの錯体調製法の不斉収率に対する影響は見られなかった。

スパルテインの塩化銅(I) への配位には酸素の存在は必要ない。塩化メチレン中アルゴン雰囲気下、塩化銅(I) はスパルテインにより溶解し無色均一溶液となる。一方、塩化

銅(I) はリガンド非存在下では酸素及び水の存在下（通常の空気中）、白色から茶色へ酸化分解する。

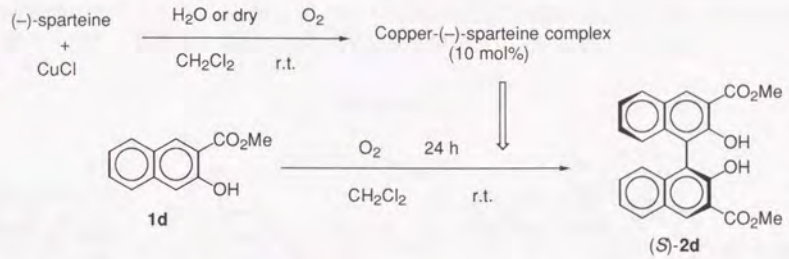
酸化分解により、どのような化学種が生成するかは不明だが、酸化分解により生成した銅(II) とスパルテインから二核錯体が生成する可能性と、塩化銅(I) とスパルテインの錯体から二核錯体が生成する可能性は、 後者の方が大きいと考えられる。酸化分解した銅塩から$[Cu(OH)TMEDA]_2Cl_2$ 二核錯体を調製することは難しいからである。これがアルゴン雰囲気下錯体調製してきた理由である。

run 1 と run 3 の比較で、酸素の存在は化学収率を向上させたことから、活性錯体の調製がより円滑に行われたといえる。上記の考察から、これは酸化分解した銅からの二核錯体の生成が有利であることではなく、スパルテインの塩化銅(I) への配位が酸化分解が起こるよりも速く行われることと関連していると考えている。この説明は酸素雰囲気下でも、アルゴン雰囲気下と同じように、塩化銅(I)-スパルテイン錯体がスムーズに生成するということを示すにすぎない。

そこで、run 1 と run 3 の条件の違いは、生成した塩化銅(I)-スパルテイン錯体が酸素により２価銅を含む二核錯体への変換される段階に現れると考えられる。run 1 では塩化銅(I) とスパルテインの錯体へナフトールを加えてすぐに加熱還流している。加熱還流条件は酸素の溶解度は非常に少ない。このため二核錯体の生成が出来ないと考えられる。run 3 では錯体調製温度は室温のため酸素の溶解は十分で塩化銅(I)-スパルテイン錯体が速やかに酸素により酸化されて二核錯体が生成するものと考えられる。

二核錯体の生成には水も必須である。この点を次に検討した。

Scheme 25.



基質 **1d** に対してそれぞれ 10 mol% の塩化銅(I) とスパルテインから酸素雰囲気下錯体を調製し、基質を加え酸素雰囲気下 24 時間室温にて撹拌した（24-25 °C）。

Table 13. Oxidative Coupling of 1d with Copper-Sparteine Complex

run	complex	H_2O (equiv[a])	yield, % **2d**	yield, % recovered **1d**	ee, %
1	isolated Copper-sparteine complex	-	7	93	53
2	prepared under O_2 atmosphere	none	23	75	52
3	prepared under O_2 atmosphere	0.1	19	80	55

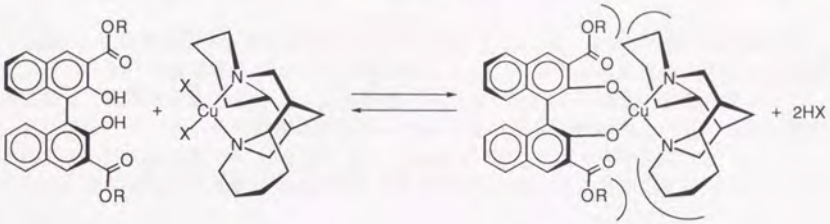
[a] equiv to **1d**

Run 2 では Table 12 の run 3 に比べて化学収率が低下し不斉収率が上昇した。反応温度を低くしたためと考えられる。run 3 は二核錯体の生成に対して酸素、水の条件を満たしている。そのため run 3 では run 2 より化学収率の向上が予想された。しかし化学収率はわずかに低下した。反応は **1d** として約 0.8 mmol スケールで行っているため、錯体を調製するのに必要な水は 1.4 μL となる。従来は量りとるときに混入した水で錯体生成が起こるのに十分だったと考えている。反応スケールが大きくなれば差が現れると考えている。しかし反応機構的に矛盾する調製法は採用できないので、これより水を加えての錯体調製をすることとした。

第４節　第２項　エステル置換基の効果

前節までで錯体調製法を改良したが、化学収率は 19 % にとどまった。この原因として生成したビナフトールがスパルテイン銅錯体と安定な錯体を形成し、触媒を不活性化する可能性を考えた(Scheme 26)。このような不活性化の機構が原因ならば、ナフトール部分のエステル置換基を嵩高くすれば不活性化を防ぐことが可能と考えた。

Scheme 26.



基質として、ヒドロキシナフトエ酸メチルエステル、エチルエステル、イソプロピルエステル、ベンジルエステル、*tert*-ブチルエステルを検討した(Scheme 27)。

錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1** に対してそれぞれ 10 mol% の塩化銅(I) 、スパルテイン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は 1 時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1** が 40 mM となるように設定し、その半量で錯体調製を行った。

Scheme 27.

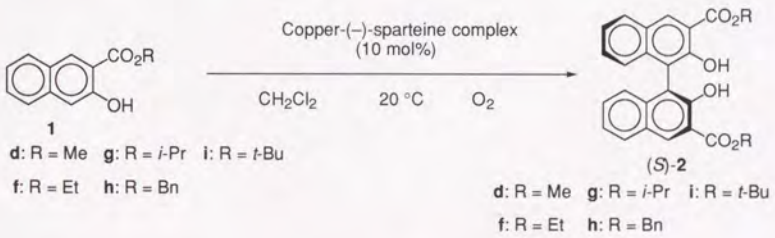


Table 14. Oxidative Coupling of 1 with Copper-(–)-Sparteine Complex

		24 h yield, %			48 h yield, %			72 h yield, %		
naphthol	R	**2**	recovered **1**	ee, %	**2**	recovered **1**	ee, %	**2**	recovered **1**	ee, %
1d	Me	19	80	55	19	79	54			
1f	Et	18	80	60	19	78	62			
1g	*i*-Pr	18	82	64	25	75	62	19	77	64
1h	Bn	18	82	67	20	80	67	23	77	64
1i	*t*-Bu	18	82	74	25	75	76	24	75	75

Table 14 に結果を示す。それぞれのエステルにつき 24、48、及び 72 時間の反応を行った。ビナフトール誘導体 2 はすべて *S* 体が得られた。エステル置換基の大きさは化学収率に対して影響を与えなかった。反応時間の延長も化学収率の向上にはならなかった。

それに対して、エステル置換基が嵩高くなるに従い不斉収率の向上が見られた。基質として *tert*-ブチルエステル **1i** を用いると 74%ee にて(*S*)-**2i** をが得られた。

これ以降の検討には基質に *tert*-ブチルエステル **1i** を用いることとした。

第４節　第３項　銅塩の効果

銅スパルテイン錯体が塩化メチレン中不均化するという現象を化学収率を低下させる原因として疑った。

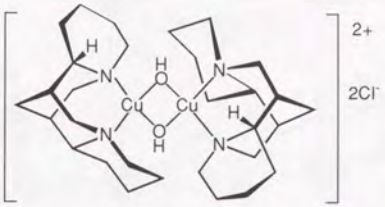
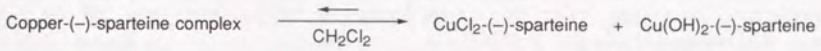


Figure 4. Assumed structure of Copper-(–)-Sparteine Complex.

二核錯体 $[Cu(OH)TMEDA]_2Cl_2$ と同様の方法で予め調製した銅スパルテイン錯体（緑色粉末）を反応に用いると（第５章第３節）、同じ錯体を反応系内で調製した場合と同じ不斉誘起を示す。

Scheme 28.



この粉末は塩化メチレン中、塩化銅(II)-スパルテイン錯体と水酸化銅(II)-スパルテイン錯体と推定しているものに分離する。塩化銅(II)-スパルテイン錯体は元素分析および、X線結晶構造解析により構造を決定した(Figure 5)。水酸化銅(II)-スパルテイン錯体と推定しているものは構造決定出来ていない。難溶性で再結晶が困難であること、加熱減圧乾燥により変質しやすいことによる。

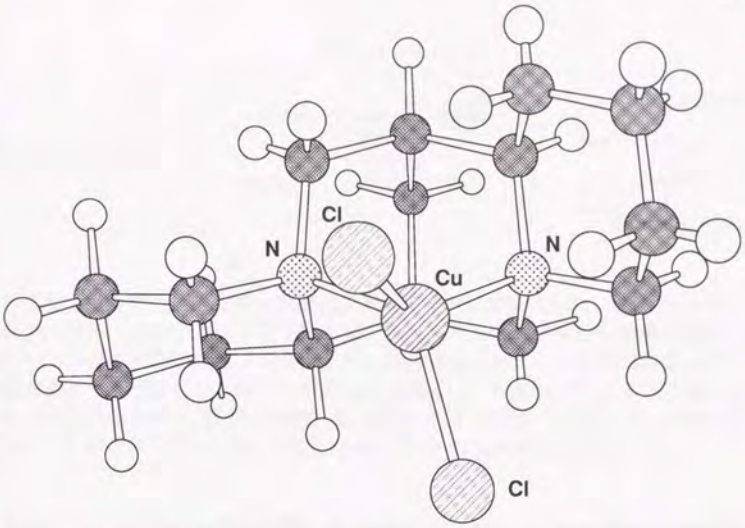
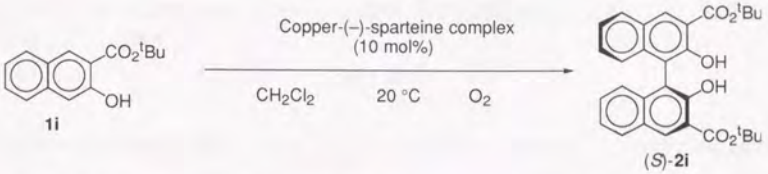


Figure 5. X-ray structure of $CuCl_2$-Sparteine Complex

塩化メチレン中、塩化銅(II)-スパルテイン錯体と水酸化銅(II)-スパルテイン錯体は単独では触媒活性を示さない。しかし両錯体を添加した反応は、系内で調製した錯体を用いたときと同じ不斉収率を示した（第３章第２節）。このように、塩化メチレン中では活性錯体と不活性錯体との間に平衡が存在すると考えられることから、触媒活性のない錯体生成が起こることが低収率の原因と考えた。

Scheme 28 に示した好ましくない平衡を動かすには、銅塩の陰イオン部分を大きくすれば良いと考えた。推定される二核錯体(Figure 4)に比べ、塩化銅(II)-スパルテイン錯体の場合は架橋部のヒドロキソ配位子が存在しないので、陰イオンとスパルテインが直接相互作用すると考えられる。従って、陰イオン部分を大きくすれば、対陰イオンが銅の二つの配座を塞いだ塩化銅(II)-スパルテイン錯体の構造(Figure 5)をとりにくくなり、活性な錯体の割合が増えると考えた。

Scheme 29.



錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の銅(I) のハロゲン化物塩、スパルテイン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は 1 時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。塩化銅(I) 臭化銅(I) ヨウ化銅(I) を検討した。Table 15 に結果を示す。それぞれの銅(I) 塩につき 24、48、及び 72 時間の反応を行った。

Table 15. Oxidative Coupling of 1i with Copper-(–)-Sparteine Complex

	24 h yield, %			48 h yield, %			72 h yield, %		
CuX	**2i**	recovered **1i**	ee, %	**2i**	recovered **1i**	ee, %	**2i**	recovered **1i**	ee, %
CuCl	18	82	74	25	75	76	24	75	75
CuBr	31	66	70	31	67	70	39	61	69
CuI	20	80	72	29	71	65	23	77	69

臭化銅(I)を用いた時は収率の上昇が見られた。臭化銅(I) を用いた時は錯体調製時から溶液が茶色になり、またヨウ化銅(I) を用いたときは錯体調製時から溶液が赤紫色になった。

これらの着色は Br^-、I^- が酸素により酸化されたためと考えた。Br_2、I_2 等による副反応が起こりうるこれらの条件は、適当ではないと判断し、引き続き塩化銅を用いることとした。

第４節　第４項　溶媒効果

スパルテイン及び水から錯体を調製、単離し、得られた緑色粉末は、塩化メチレン中触媒活性がない塩化銅(II)-スパルテイン錯体、及び水酸化銅(II)-スパルテイン錯体と推定されるものに分離する。

Scheme 30.

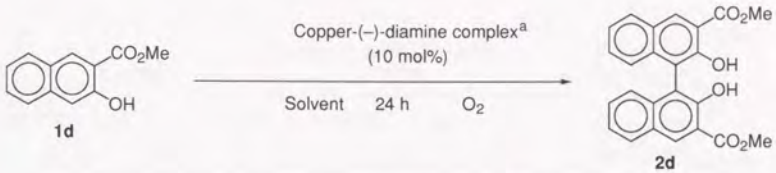
これらの結果から Scheme 30 に示す平衡が存在すると考えた。この平衡から、系内で調製した錯体を用いた反応中にも同じような平衡が起こり触媒の活性を低下させることが予想できる。そこで、反応溶媒を変えることで、平衡を動かすことができ、活性のある錯体の割合を増加できれば、化学収率の上昇につながると考えた。

また低化学収率の原因が生成物もしくは基質の銅アミン錯体への安定な配位が原因とも考えられる。このような配位が原因で、錯体が触媒サイクルから外れるとすると、極性の高い溶媒を用いることで化学収率が向上することが予想される。

われわれは修士の検討[13b]において溶媒等の検討を行っている。その結果を下記に示す(Table 16)。

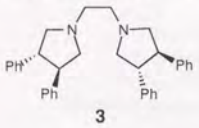
基質 **1d** に対してそれぞれ 10 mol% の銅(I) ハロゲン化物塩、及びジアミンからアルゴン雰囲気下、錯体を調製した。錯体調製時間は 15 分とした。錯体調製後ナフトール及び溶媒を加え酸素雰囲気下撹拌した。

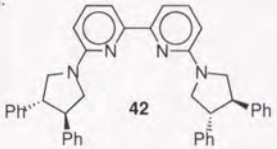
Table 16. Oxidative Coupling of 1d in Various Solvents



run	amine	solvent	CuX	T °C	yield, % 2d	yield, % recovered 1d	ee, %	config.
1	**3**	CH_2Cl_2	CuCl	40	80	20	19	R
2	**3**	CH_2Cl_2	CuI	40	9	88	18	R
3	**3**	CH_2Cl_2	CuI	40	93[b]	7	19	-
4	**3**	CH_3OH	CuI	65	99[c]	0	2	R
5	**3**	CH_3OH	CuI	r.t.	18	82	6	R
6	**3**	CH_3CN	CuI	81	91	3	3	S
7	**3**	acetone	CuI	56	60	33	2	R
8	**42**	THF	CuI	66	17[d]	83	0	-

[a] Prepared under Ar atmosphere and anhydrous condition. [b] Reaction time: 132 h.
[c] Reaction time: 19 h. [d] Reaction time: 72 h.





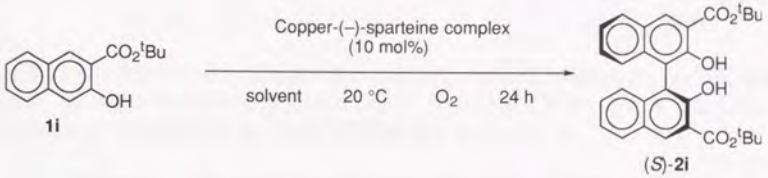
塩化銅(I) から調製した錯体に比べ、ヨウ化銅(I) から調製した錯体は活性が低い。しかし反応時間を延長すると化学収率は上昇する(run 1-3)。溶媒としてメタノールを用いると高い化学収率で **1d** を与えるが不斉誘起はほとんど起こらない。反応温度が高い方が化学収率が高い。反応温度を低くしても不斉誘起はほとんど起こらない(run 4-5)。溶媒としてアセトニトリルを用いると高い化学収率で **1d** を与えるが不斉誘起はほとんど起こらない(run 6)。溶媒としてアセトン、THF を用いても反応は進行する(run 7-8)。

極性の高い溶媒を用いると化学収率が向上するが不斉収率は低下する傾向がある。

これらの結果から不斉反応には塩化メチレンを用いてきた。しかしここでは化学収率の向上を優先し、メタノール等の溶媒を検討した。

錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の塩化銅(I) 、スパルテイン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は 1 時間とした。錯体調製後ナフトール及び溶媒を加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。

Scheme 31.



化学収率向上が期待できるアルコール系溶媒や酸素の溶解度の大きい含フッ素系溶媒などを検討した。

Table 17. Oxidative Coupling of 1i with Copper-(–)-Sparteine Complex in Various Solvents

run	solvent	yield, % **2i**	yield, % recovered **1i**	ee, %
1	CH_2Cl_2	18	82	74
2	CH_3OH	9	64	58
3	CF_3CH_2OH	5	95	50
4	perfluorohexanes (PFH)	0	97	-
5	CH_2Cl_2 + PFH (1 / 3)[a]	37	63	73

[a] Biphasic reaction.

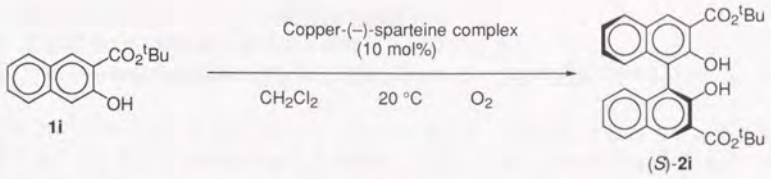
溶媒としてメタノールを用いると化学収率は低下し、副反応が起きた(run 2)。ペルフルオロヘキサンを溶媒として用いたときには錯体、ナフトールとも溶解せず反応は進行しなかった。塩化メチレンとの混合溶媒を検討したところ両溶媒が混合せず 2 相系の反応になった。しかし化学収率の向上が見られた(run 5)。

Run 5 を更に検討した結果、錯体、ナフトールとも全て塩化メチレン相に溶解していることが判明した。これは通常の反応に比べて 4 倍の濃度で反応を行っているのに等しいと考えた。よって本反応の化学収率が濃度によって影響を受けることが示唆された。そこで基質の濃度の検討を行うこととした。

第４節　第５項　濃度効果

溶媒効果の検討において示唆された化学収率と濃度の関係を検討した。

Scheme 32.



基質 **1i** の濃度がそれぞれ設定した値となるように溶媒量を調節した。run 1 と run 4 では設定した溶媒の半量で錯体調製をおこない、残りは基質を加えるときに加えた。 それ以外の反応では錯体調製時に設定した溶媒量をすべて用いた。

Table 18.　The Effect of Concentration on the Chemical Yields

run	**1i** concentration	solvent	time, h	yield, % **2i**	yield, % recovered **1i**	ee, %
1	40 mM	CH_2Cl_2	24	18	82	74
2	80 mM	CH_2Cl_2	24	24	75	72
3	160 mM	CH_2Cl_2	24	34	66	72
4	practically 160 mM	CH_2Cl_2 + PFH (1 / 3)[a]	24	37	63	73
5	320 mM	CH_2Cl_2	24	47	52	72
6	640 mM	CH_2Cl_2	24	65	35	74
7	640 mM	CH_2Cl_2	48	77	23	74
8	640 mM	CH_2Cl_2	72	78	19	75
9	960 mM	CH_2Cl_2	24	69	31	71
10	960 mM	CH_2Cl_2	48	76	23	73
11	1280 mM	CH_2Cl_2	24	73	27	68
12	1280 mM	CH_2Cl_2	48	84	16	68

[a] Biphasic reaction.

これまで行ってきた不斉反応の基質濃度、40 mM（**1i** 195 mg に対して塩化メチレン 40 mL）から溶媒を減らし、濃度を上げていくと、化学収率の向上が見られ、640 mM（**1i** 195 mg に対して塩化メチレン 1.25 mL）において化学収率 65％にて **2i** が得られた(run 1-6)。反応時間を延長すると化学収率の向上が見られた(run 6-8)。基質濃度 960 mmol 以上の反応では不斉収率の低下が見られた(run 9,11)。反応時間を延長すると収率の上昇が見られた(run 9-12)。

以上の結果を基にして、これ以降の実験は嵩高いエステル置換基を持つ基質を用いてアミンの検索を行い、さらに化学収率向上のため濃度の検討を行い反応条件を最適化するという方針を立てた。

第５節　ピロロベンゾジアゼピン系ジアミンを用いた検討

スパルテインを超える配位子として新たな光学活性アミン **28** をデザインした。このピロロベンゾジアゼピン骨格を持つアミン **28** は次のような特徴を持つ。

1　電子供与力が弱いアニリン型窒素を持つ。
2　芳香環部分の置換基により電子的効果を期待できる。
3　プロリン部分の誘導体化ができ、逆配置のアミンも合成可能である。

CPK 分子モデル等による予想から、立体的な要因で **28** は銅に Figure 6 のように配位すると考えた。左の芳香環部分は手前側が上に上がりプロリン由来の五員環は図の奥側が上にもち上がっている少しねじれた構造をとると予想した。

縮合した環形を持つため銅への配位により配座の固定が起こり置換基の効果が明確に現れてくると期待した。

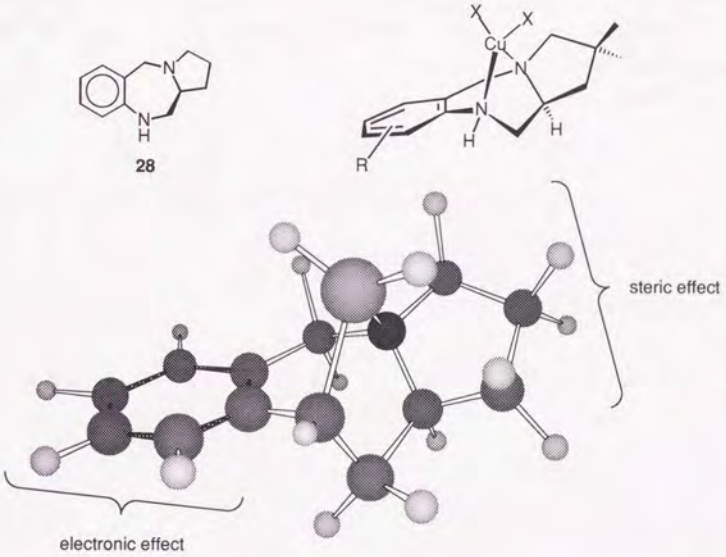


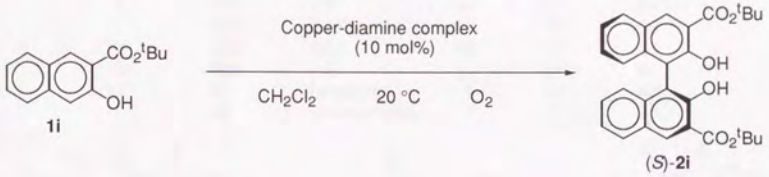
Figure 6. A possible coordination mode of metal-pyrrolobenzodiazepine type diamine (28) complex.

第５節　第１項　電子的効果についての検討

アミン側に電子求引性の置換基を持たせれば、銅の電子密度が低下し、銅の酸化力が強くなると予想した。その結果が化学収率の向上となって表れることを期待した。

錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の塩化銅(I)、ジアミン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は１時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。

Scheme 33.

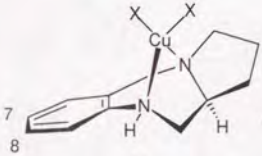


アニリン型の窒素を１個持つアミン **28** を基本とし、窒素のパラ位である７位に置換基をつけたアミン **29**、メタ位である８位に置換基をつけた **30**、脂肪族アミン型の窒素を２個持つアミン **31**、**33** などを検討した。

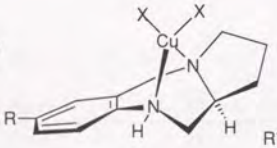
Table にはそれぞれのアミンから推定される錯体構造を示してある。

Table 19. Oxidative Coupling of 1i with Copper-Diamine Complex

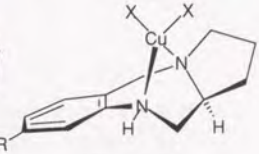
run	amine	substituent	yield, % **2i**	yield, % recovered **1i**	ee, %
1	**28**	none	55	45	53
2	**29a**	7-N(Me)$_2$	4	84	0
3	**29b**	7-I	12	88	56
4	**29c**	7-Br	48	52	55
5	**29d**	7-Cl	55	45	57
6	**29e**	7-F	46	54	53
7	**29f**	7-NO$_2$	17	83	66
8	**30a**	8-Cl	42	58	61
9	**30b**	8-F	31	69	60
10	**31**	hexahydro	7	90	60
11	**33**	without moiety	7	93	20



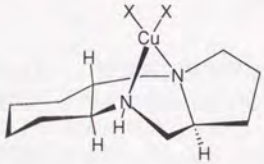
28



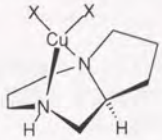
29 **a**: R=N(Me)$_2$
b: R=I
c: R=Br
d: R=Cl
e: R=F
f: R=NO$_2$



30 **a**: R=Cl
b: R=F



31



33

アミン **28** から調製した錯体を用いた反応では化学収率 55%、53% ee にて(*S*)-**2i** を与えた。化学収率的に最も反応性が優れているといえる(run 1)。ヨウ素からフッ素まで電子求引性を変化させたが化学収率との相関は見られなかった(run 3-6)。ジメチルアミノ基を持つアミン、ニトロ基を持つアミンとも化学収率が低下した(run 2, 7)。メタ位に電子求引性基を持つアミンを用いても化学収率の向上は見られなかった(run 8, 9)。脂肪族アミンを用いると化学収率が低下した(run 10, 11)。

化学収率が低い原因として、**29a** はアミンの電子密度が高いため、酸素により自動酸化されアミンが分解したからであると考えられる。他の誘導体のアミンと違い全く不斉誘起が見られないことから **29a** の場合にはジメチルアミノ基が配位子として働いた可能性や分解したアミンが配位子として働いた可能性がある。**29f** は電子求引性が非常に強い。このため銅への配位が弱くなり錯体が不安定になったと考えられる。また、もう

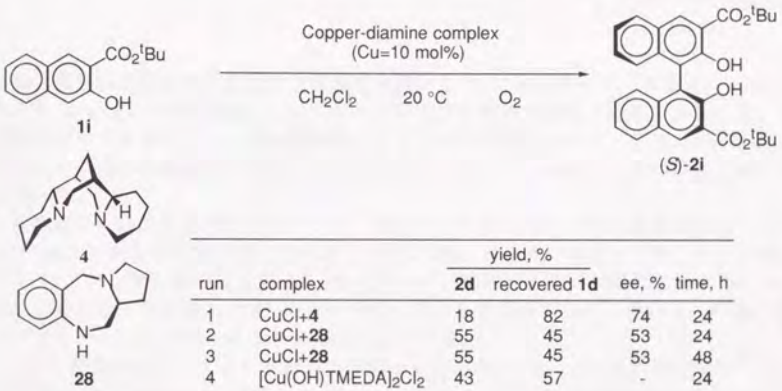
一つの可能性として、ナフトールの酸化後電子を受け取り１価に還元された銅アミン錯体が、ニトロ基の電子求引効果により安定化され、酸素により酸化されにくくなり、触媒の再生が遅くなったことが考えられる。

脂肪族ジアミン **31**、**33** を用いると化学収率の低下が見られたことは銅への電子供与性が大きく銅の酸化力が低下したことによると考えられる。

結果的に **28** が最も良い収率を与えたがこの結果はアニリン型の窒素を持つため電子供与が適切になったためと考えている。

他のタイプのアミンとの比較として、銅として錯体 10 mol% 用いての検討結果を示す。

Table 20. Oxidative Coupling of 1i with Copper-Diamine Complex



run	complex	yield, % 2d	yield, % recovered 1d	ee, %	time, h
1	CuCl+**4**	18	82	74	24
2	CuCl+**28**	55	45	53	24
3	CuCl+**28**	55	45	53	48
4	$[Cu(OH)TMEDA]_2Cl_2$	43	57	-	24

Run 1-3 の錯体調製温度並びに反応温度は、恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の塩化銅(I) 、ジアミン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は１時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。Run 4 も溶媒量を基質 **1i** が 40 mM となるように設定した。

28 を用いた反応は 24 時間での収率は TMEDA 錯体よりも優れていることがわかる。

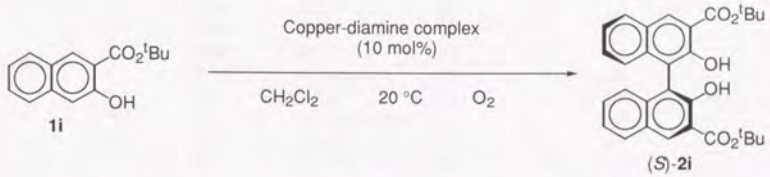
しかし **28** を用いた反応もスパルテインを用いた反応と同様に、反応時間の延長が化学収率の向上につながらなかった(run 3)。

24 時間と 48 時間の反応で収率が全く変わらないことから 24 時間より早い段階で反応が止まっている可能性がある。

第5節　第2項　不斉収率に対する立体的効果－芳香環部分

アミン **28** は種々の構造変換が可能である。それにより不斉収率の向上が期待できる。芳香環部分の変換の不斉収率への影響を検討した。

Scheme 34.



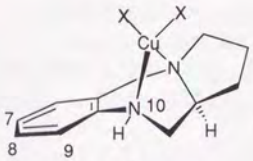
錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の塩化銅(I) 、ジアミン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は 1 時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。

置換基のないアミン **28** を基本とし、窒素のパラ位である 7 位に置換基を導入したアミン **29**。メタ位である 8 位に置換基をつけた **30**。ベンゼン環をシクロヘキサン環に変えた **31**。ベンゼン環を取り去った **33**。ベンゼン環をナフタレン環に変えた **34**。9、10 位をプロピレンで架橋した **35** などを検討した。不斉収率を念頭に置いて、Table 19 のデータを含めて表にまとめたのが Table 21 である。

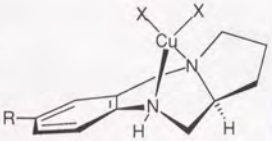
7 位に置換基が存在すると不斉収率の向上が見られる(run 1-5)。置換基が大きいほど効果がある(ee: 7-NO_2 > 7-I > 7-Br > 7-Cl > 7-F ≈ none)。8 位に置換基が存在すると不斉収率の向上が見られる(run 6, 7)。7 位と 8 位では 8 位の方が小さい置換基でも効果がある(run 4, 6 vs run 5, 7)。9 位に置換基が存在すると不斉収率の向上が見られる(run 9)。ベンゼン環をシクロヘキサン環に変えると不斉収率の向上が見られる(run 8)。ベンゼン環を除くと不斉収率は低下する(run 10)。ベンゼン環を 7、8 位に縮合させても不斉収率は変化しない(run 11)。9、10 位をプロピレンで架橋すると不斉収率は低下する(run 12)。

Table 21. Oxidative Coupling of 1i with Copper-Diamine Complex

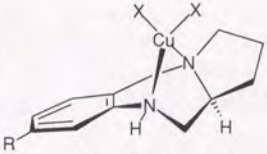
run	amine	substituent	ee, %	yield, %	
				2i	recovered **1i**
1	**28**	none	53	55	45
2	**29f**	7-NO_2	66	17	83
3	**29b**	7-I	56	12	88
4	**29d**	7-Cl	57	55	45
5	**29e**	7-F	53	46	54
6	**30a**	8-Cl	61	42	58
7	**30b**	8-F	60	31	69
8	**31**	hexahydro	60	7	90
9	**32**	9-Me	60	33	67
10	**33**	without moiety	20	7	93
11	**34**	naphto	55	35	69
12	**35**	9,10-$(CH_2)_3$	20	9	65



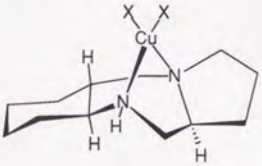
28



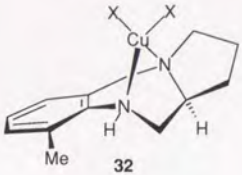
29 **f**: R=NO_2
b: R=I
d: R=Cl
e: R=F



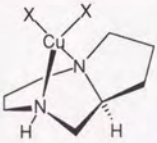
30 **a**: R=Cl
b: R=F



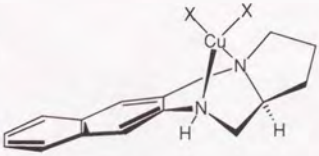
31



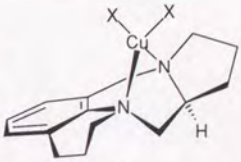
32



33



34



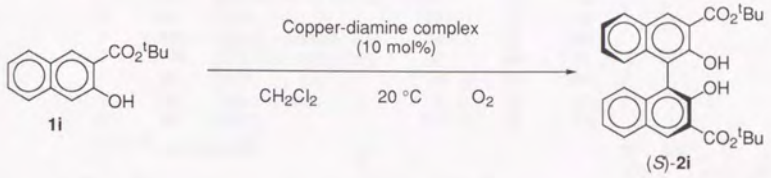
35

ベンゼン環上に置換基をつけると不斉収率が上昇する傾向にある。7 位よりも 8 位、9 位の側（手前側）に置換基がある方が効果的である。**34** で不斉収率の変化が見られないことから、図に示した方向で手前側上が立体的にふさがれている方が良いといえる。

第５節　第３項　不斉収率に対する立体的効果－プロリン環由来部分

プロリン環由来部分の変換の不斉収率への影響を検討した。

Scheme 35.



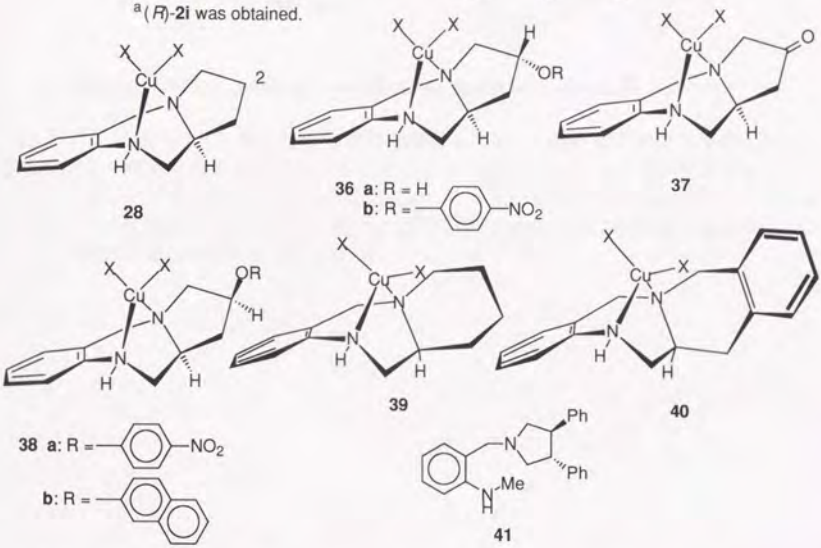
錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。基質 **1i** に対してそれぞれ 10 mol% の塩化銅(I) 、ジアミン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は１時間とした。錯体調製後ナフトール及び塩化メチレンを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1i** が 40 mM となるように設定し、その半量で錯体調製を行った。

(*2S*)-ヒドロキシプロリン誘導体 **36**、2-オキソ体 **37**、(*2R*)-ヒドロキシプロリン誘導体 **38**、ピペコリン酸誘導体 **39**、テトラヒドロイソキノリンカルボン酸誘導体などを検討した。

Table 22. Oxidative Coupling of 1i with Copper-Diamine Complex

run	amine	substituent	ee, %	yield, %	
				2i	recovered **1i**
1	**28**	none	53	55	45
2	**36a**	(2*S*)-2-OH	53	16	84
3	**36b**	(2*S*)-2-*p*-nitrophenoxy	41	42	58
4	**37**	2-oxo	29	15	83
5	**38a**	(2*R*)-2-*p*-nitrophenoxy	78	38	62
6	**38b**	(2*R*)-2-(2-naphtyloxy)	74	24	76
7	**39**	homo	4[a]	20	80
8	**40**	homo +benzo	0	45	55
9	**41**	seco	12[a]	52	48

[a] (*R*)-**2i** was obtained.



2位に *S* 配置で置換基を導入したアミンを用いた反応では不斉収率の向上は見られなかった(run 2, 3)。2-オキソ体を用いると不斉収率は低下した(run 4)。2位に *R* 配置で置換基を導入したアミンを用いると不斉収率は上昇した(run 5, 6)。プロリン由来五員環を六員環に変えた誘導体を用いると不斉誘起はみられなかった(run 7, 8)。

銅が配位すると予想した面と反対側へ置換基を導入したアミンは不斉収率の向上につながらない。逆に銅が配位すると予想した面と同じ側へ置換基を導入したアミンについては不斉収率の大幅な向上がみられた。**37** は銅の側へ立ち上がっている水素がないため大幅な不斉収率の低下が見られたと考えられる。

以上の結果から、プロリン由来五員環の変換においては、銅が配位すると予想した面と同じ側へ置換基を導入すれば不斉収率の向上が期待できる。この考えから **39** とこれを更にかさ高くした **40** を検討した。しかしこれらのアミンは不斉誘起を示さなかった。この理由は次のように考えられる。

分子モデルによる考察であるが、**28** においては立体的要因から銅の配位の方向は図に

示した方向と予想した。プロリン由来窒素に関して反対側から銅が配位すると環にひずみがかかり非常に不利である。しかし **39** に関しては六員環がひずみを解消するため反対側からの配位が可能である(Figure 7)。**40** も同様に反対側からの配位が可能と考えられる。このため不斉環境の固定が起こらずに不斉誘起が見られなかったと考えられる。

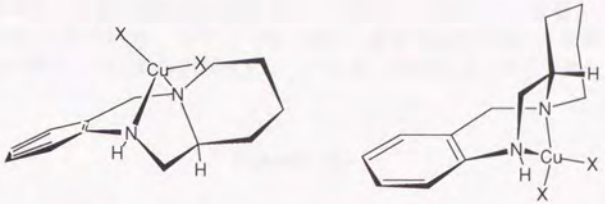


Figure 7. Two possible coordination mode of copper-38 complex.

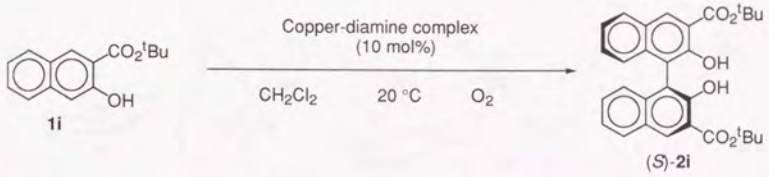
41 のアミンはプロリン環上に直接炭素が置換しており、銅が配位すると予想した面と同じ側がより嵩高くなることも考えられた。しかし他のピロロベンゾジアゼピンジアミンと全く違った不斉誘起を示した。環が開裂しているため配位の自由度が高く、アミン **3** に近い不斉誘起能を持つと考えられる。化学収率に関しては比較的良い値を示した。アニリン型窒素を持つためと考えている。

第5節　第4項　濃度効果

スパルテインを用いた検討において、本カップリング反応の化学収率が濃度によって影響を受けることが示されたため、ピロロベンゾジアゼピン系ジアミンを用いて基質の濃度の検討を行うこととした。

錯体調製温度並びに反応温度は恒温槽を用いて20℃に調節した。基質**1i**に対してそれぞれ10 mol% の塩化銅(I) 、ジアミン及び水から酸素雰囲気下錯体を調製した。錯体調製時間は1時間とした。錯体調製後ナフトール及び溶媒を加え酸素雰囲気下撹拌した。

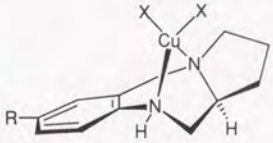
Scheme 36.



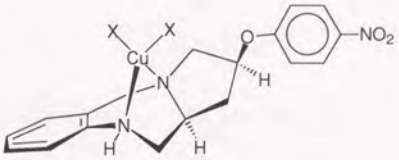
基質**1i**がそれぞれ設定した濃度となるように溶媒量を調節した。基質濃度40 mM以下の反応では、設定した溶媒量の半量で錯体調製を行った。基質濃度640 mM以上の反応では、設定した溶媒量をすべて用い、錯体調製を行った。

Table 23. Oxidative Coupling of 1i with Copper-Diamine Complex

run	amine	**1i** concentration	yield, % **2i**	yield, % recovered **1i**	ee, %
1	**28**	20 mM	41	59	51
2	**28**	40 mM	55	45	53
3	**28**	640 mM	45	55	62
4	**28**	1280 mM	40	60	62
5	**29d**	40 mM	55	45	57
6	**29d**	640 mM	47	53	61
7	**38a**	40 mM	38	62	78
8	**38a**	640 mM	11	88	77



28: R=H
29d: R=Cl



38a

通常の不斉反応の濃度である 40 mM に比べ、基質濃度を上げた反応では期待された化学収率の向上は見られず、かえって化学収率の低下が見られた。基質濃度 40 mM において 50%から 60%程度の不斉収率を示すアミンを用いて基質濃度を上げて反応を行うと、不斉収率が上昇した。70%後半の不斉誘起を示したアミンを用いて高濃度の反応を行ったが、不斉収率の上昇は見られなかった。

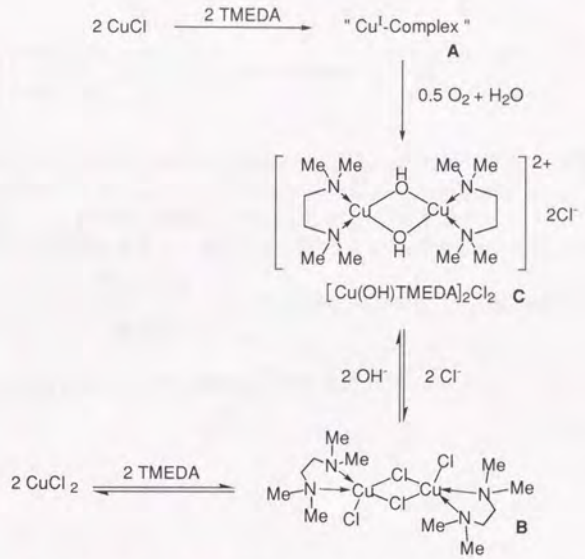
これらの結果は、スパルテインを用いた検討とは全く逆の結果である。スパルテインとの大きな違いは配位子としての配位力と考えられる。すなわち、スパルテインは配位力が強く高濃度でもスパルテインの銅錯体は維持されるのに対して、ピロロベンゾジアゼピン系ジアミンの銅錯体は高濃度では基質や生成物により銅が解離されてしまうと考えられる。

第３章　反応機構に関する考察

第１節　背景、錯体構造、反応機構について

本不斉反応の原点である TMEDA 二核錯体は合成的には末端アセチレンのカップリングに用いられてきた。[24] また、フェノールの重合、ジフェノキノンへの酸化の触媒としても知られている。[5-7] G.Challa らは錯体調製条件と、末端アセチレンのカップリンおよびフェノールの重合の触媒活性の関係を研究し次のような結論を得ている。

Scheme 37.

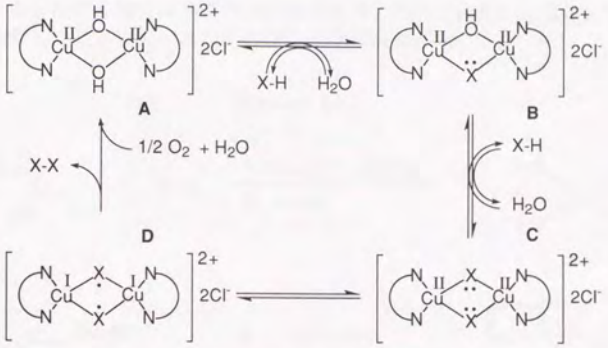


塩化銅(I) と TMEDA から酸素雰囲気下調製される錯体は、X線結晶構造解析により構造が確認されている **C** である。**C** は触媒活性を有する。この **C** は **A** を経て生成すると推定されている。

一方、塩化銅(II) と TMEDA から調製される錯体は **B** である。**B** には反応活性、触媒活性がない。**B** に銅に対して１当量の水酸化ナトリウムを加えると、触媒活性が現れ、その活性は塩化銅(I) と TMEDA から酸素雰囲気下調製された錯体と等しい。

これらの結果から触媒活性にヒドロキソ架橋部が触媒活性に必須であるとの結論を得、次のような反応機構を提示している。

Scheme 38.

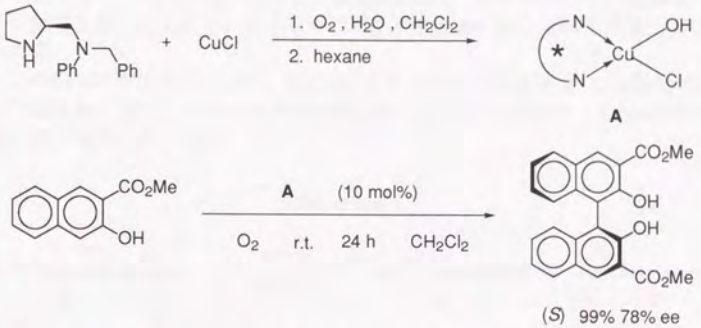


1　二核錯体 **A** の１つのヒドロキソ架橋部が基質Ｘ－Ｈと交換し **B** を生成する。この時基質の水素（プロトン）とヒドロキソ架橋部から水が生成する。
2　同様に残りのヒドロキソ架橋部が基質と交換し **C** を生成する。
3　２価の銅は架橋部の基質から電子を受け取り１価に還元され、基質上には酸化的にラジカルが生成し **D** となる。
4　このラジカル同士がカップリングし生成物Ｘ－Ｘを生じ、１価の銅アミン錯体は再び酸素と水により二核錯体になる。

酸化による二核錯体 **A** の再生の機構は不明である。

M.Nakajima らは酸素雰囲気下ジアミンと塩化銅(I) からキラル錯体を調製して、ナフトールの触媒的不斉カップリングをおこなった。[22] 非常に高い化学収率と高い不斉収率を実現している。基質にメチルエステルを用いた反応で最も高い不斉誘起を示す。*tert*-ブチルエステルを用いた場合は不斉収率が低下する。系内で調製した錯体を用いるより、あらかじめ調製した錯体を用いる反応のほうが化学収率が高い。

Scheme 39.



著者らはその錯体構造を **A** と推定している。ヒドロキソ配位子を持つ構造を仮定しており、反応の結果酸素は水に還元されると考えている。しかしカップリング時の反応機構は１つの銅に対して２つのナフトールが配位した構造を推定している(Figure 8)。[25] 触媒サイクルの完結に関しては不明である。

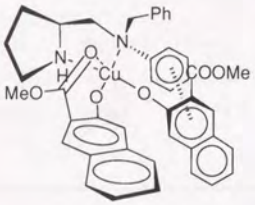


Figure 8.

第2節　実験的に得られた知見

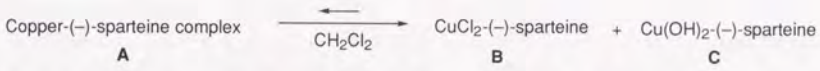
二核錯体 $[Cu(OH)TMEDA]_2Cl_2$ はメタノール中、室温、酸素雰囲気下、塩化銅(I)、TMEDA 及び水から調製され暗紫色結晶として得られる。[12]

同様に我々は塩化銅(I) とスパルテインから錯体を得ている。$[Cu(OH)TMEDA]_2Cl_2$ は調製時に固体として沈殿するが、銅スパルテイン錯体は緑色ゲル状物質となる。このためエーテルを加え固体とし、ろ取、乾燥し緑色粉末 **A** を得た。この粉末を二核錯体と仮定して第2章で用いてきた。

この粉末 **A** を用いての反応は、系内で、酸素雰囲気下、水の存在のもと調製した銅スパルテイン錯体を用いた反応と、同じ不斉収率を示す(Table 13)。そのため活性種は同一と考えられる。

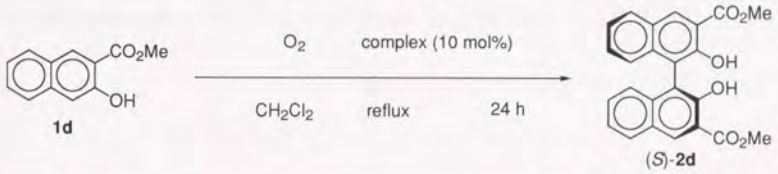
また、この粉末は塩化メチレン中、塩化銅(II)-スパルテイン錯体 **B** と水酸化銅(II)-スパルテイン錯体 **C** と推定しているものに分離することをすでに述べた(Scheme 40)（第2章第4節、第5章第3節　参照）。

Scheme 40.



これらの錯体 **A**、**B**、**C** を用いて検討を行った。それぞれの錯体について予想される構造から分子量を計算し、銅として 10 mol% 用いて **1d** の酸化的カップリング反応を行った。

Table 24.　Oxidative Coupling of 1d with Copper-Diamine Complex



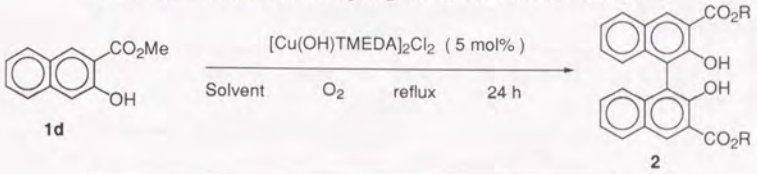
run	complex	yield, % 2d	yield, % recovered 1d	ee, %
1	Copper-(−)-sparteine complex crude	25	75	46
2	$CuCl_2$-(−)-sparteine	0	100	-
3	$Cu(OH)_2$-(−)-sparteine	3	97	16
4	$CuCl_2$-(−)-sparteine + $Cu(OH)_2$-(−)-sparteine	25	73	46

銅スパルテイン錯体 **A** を用いた反応では化学収率 25%にて **2d** を与えた(run 1)。錯体 **B** 及び **C** は触媒活性を示さなかった(run 2, 3)。しかし **B** と **C** を同時に用いると活性が回復する(run 4)。

この結果はヒドロキソ架橋部を持つ錯体が活性な錯体であるという、G. Challa らの予想を支持する。また run 4 の実験で活性の回復が見られることから Scheme 40 で示した平衡により不均化とは逆の過程が起こっていることが示唆される。

基質がフェノール性酸素以外で銅に配位する可能性は次の実験によって示唆される。**1d** のカップリングを各種アルコール系溶媒中行った。

Table 25. Oxidative Coupling of 1d in Various Solvents



run	solvent	product	R	yield, %	
				2	recovered **1d**
1	MeOH	**2d**	Me	99	0
2	EtOH	**2f**	Et	99	0
3	*i*-PrOH	**2g**	*i*-Pr	99	0
4	*t*-BuOH	**2d**	Me	99	0

エタノールを溶媒として用いるとエチルエステル **2f** が得られた。イソプロピルアルコールを溶媒として用いるとイソプロピルエステル **2g** が得られた。しかし、 *tert*-ブチルアルコールを溶媒として用いたときには、エステル交換は起こらなかった。

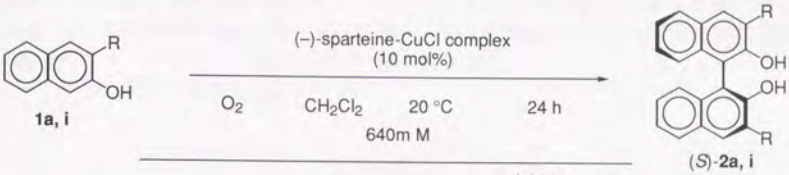
エタノールを溶媒として用いた反応において、反応開始から 12 時間の時点でカップリングしていないナフトールをＮＭＲにより調べると、すべてエチルエステルとなっていることが判明した。触媒なしでエタノール中メチルエステル **1d** を加熱環流してもエステル交換は起こらなかった。

これらの結果から銅がルイス酸として働き基質のカルボニル基を活性化してエステル交換を起こしたと考えられる。

その配位構造は第３章第３節にて考察をおこなっている。

不斉誘起に関してはつぎのような実験をした。

Table 26. Oxidative Coupling of 1a and 1i with Copper-Sparteine Complex



run	substrate	R	ee, %	yield, %	
				2	recovered **1**
1	**1a**	H	9	49	-
2	**1i**	$CO_2{}^tBu$	75	78	19

基質 1 に対してそれぞれ 10 mol% の塩化銅(I) 、スパルテイン及び水から酸素雰囲気下錯体を調製し、ナフトールを加え酸素雰囲気下撹拌した。用いた溶媒量は基質 **1** が 640 mmol となるようにした。錯体調製温度並びに反応温度は恒温槽を用いて 20 ℃ に調節した。

基質 **1a** を用いた反応では不斉誘起がほとんど見られなかった。基質 **1i** に対して最適化した条件のため **2a** の化学収率も低下している。

不斉誘起に対してカルボニル部分の配位が必要と考えている。

この考えを証明するには **1i** と同じ立体的かさ高さを持つが配位しない置換基を持つナフトールを用いて反応を行う必要がある。

以上をまとめると以下のようである。

1. 銅スパルテイン錯体は塩化メチレン中、錯体間の平衡により不均化し、反応活性のない錯体を生成する。
2. ナフタレンの 3 位にカルボニル基を持つ基質に関してはカルボニル酸素の銅への配位が示唆される。
3. 不斉誘起にはナフタレンの 3 位のカルボニル基が必要である。

第３節　反応機構の推定

この章で示した立体モデルはすべてCPKモデル等による推定である。

TMEDA 二核錯体を用いた 2-ナフトールのカップリング反応を、第３章第１節の G.Challa らの反応機構(Scheme 38)をもとに推定した。Scheme 38 の **D** の結合生成の段階は(Figure 9)の **A** と **B** の２つの配位形式が考えられる。

（ラジカル生成部位は点で示してある）

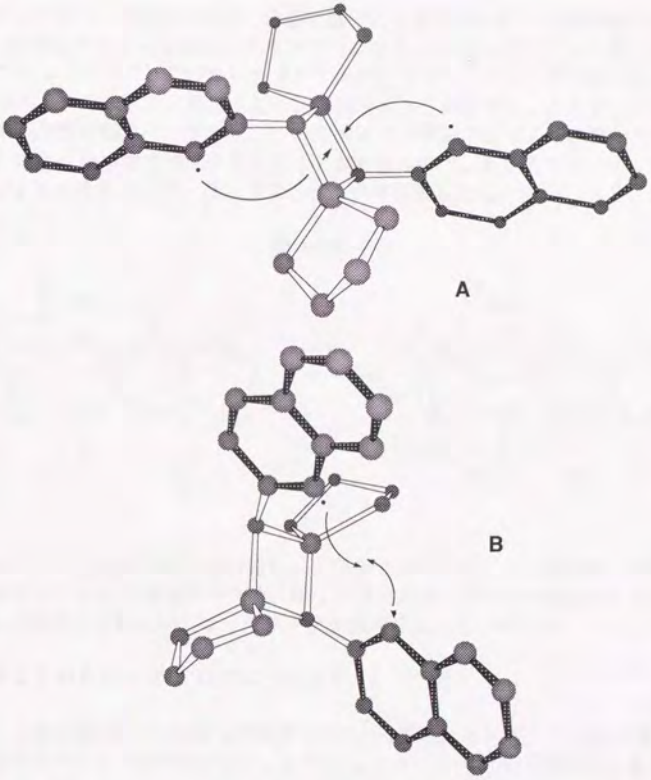


Figure 9. Possible Mechanism for Oxidative Coupling of 2-Naphthol with TMEDA Complex

１価の銅は正四面体四配位の構造を仮定し、２価の銅は平面四配位と仮定した。

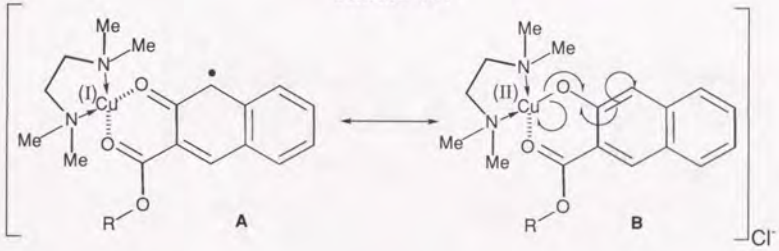
A は２つのナフトールが向きを反対にして対称に配位したものである。この配位形式では生成したラジカルの距離が遠く反応しにくいと考えられる。

B は２つのナフトールが向きを同じにして配位したものである。この配位形式では生成したラジカルの距離が近くなる。

TMEDA 錯体を用いてのカップリングで配位性の置換基をフェノール性水酸基以外に持たない基質の場合はこの二核錯体構造が保たれたままの **B** の機構によりカップリングが進行するものと考えられる。

銅に対するキレート配位が可能な、２個の配位性の置換基を持つ基質の場合は Scheme 41 のような基質がキレート配位したモノマーの状態が中間に存在すると考えられる。Table 25 でカップリングしていないナフトールがすべてエステル交換を起こしているという結果から、カルボニルが配位した中間体(**A** ↔ **B**）が存在し、カルボニルが活性化されエステル交換が起きると考えた。この中間体は２価銅が図のように電子を受け取った **A** ↔ **B** のような極限構造式を考えることができるので、配位したナフタレン基質の１位がラジカル的性質を帯び、カップリング反応が可能になると考えられる。

Scheme 41.



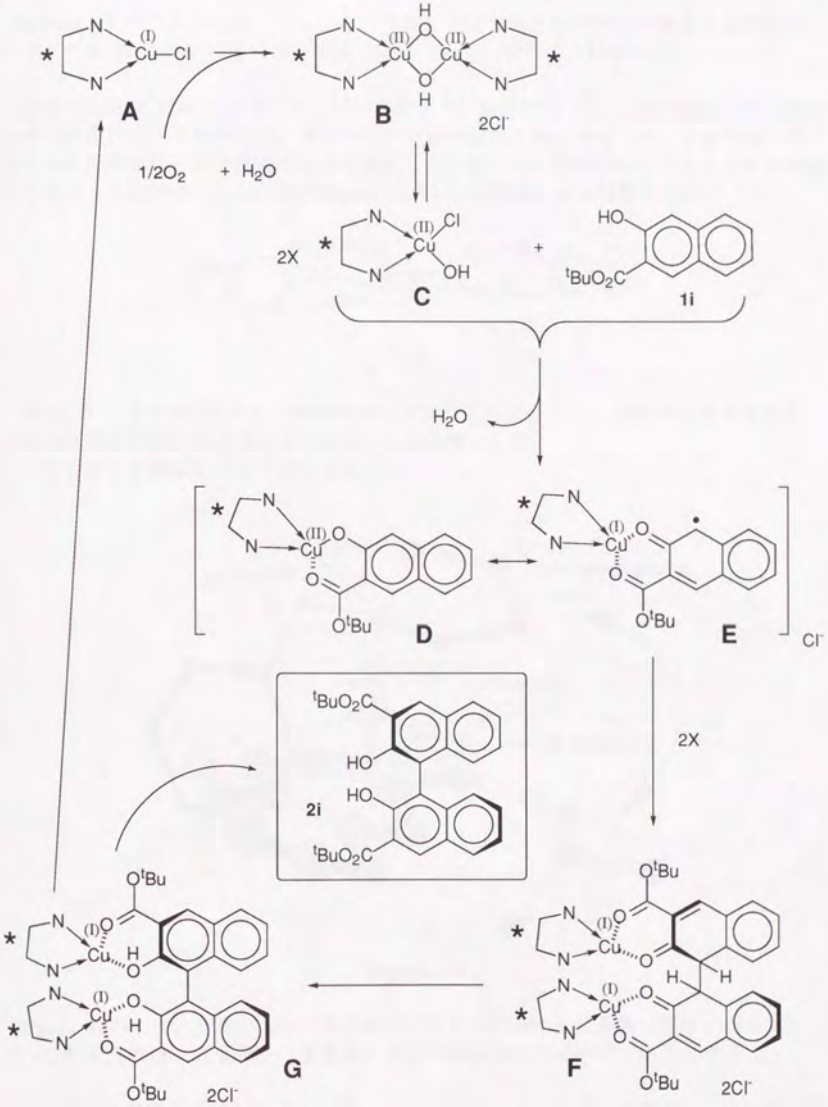
スパルテインを用いた不斉反応の場合、ナフトールの配位した二核錯体の構造(Figure 9, **A**, **B**)をとることが立体障害のために難しいといえる。そこで Scheme 41 のラジカル種 **A** ↔ **B** が溶液中で出会い、カップリング生成物が生じると考えた。

これらをまとめると Scheme 42 のようになる。

ジアミンと塩化銅(I) から生成した錯体 **A**（Cu^{I})は酸素と水により二核錯体 **B**（Cu^{II})になる。**B** はモノマー**C** との平衡にあり、**C** に対してナフトール **1i** が配位し、**D** と水が生成する。**D**（Cu^{II})は **E**（Cu^{I})との共鳴状態にあり、ナフタレンの１位がラジカル的性質を帯びる。このような中間体同士が **F**（Cu^{I})がを生成する。**F** がエノール化し、**G** になり、**A** と **2i** を生成する。

不斉の誘起は **F** が生成するときに決まると考えられる。ナフタレン環同士がＳ体に近い状態で接近し結合を生成しこの方向を保ったままエノール化するのであろう。

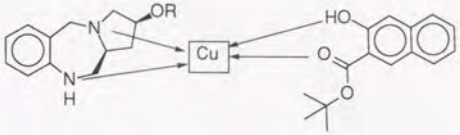
Scheme 42.



第4節　不斉の誘起について

Scheme 42 中の **F** の生成、すなわち、生成したラジカルから結合が生成する段階の、ナフトール-銅-アミン錯体の接近する方向について、次のように考えた。

はじめに銅-ピロロベンゾジアゼピン系ジアミン錯体にナフトールが配位した3成分錯体の構造について考察した。カップリング時の銅は1価と考えられ、1価の銅に多く見られる正四面体の配位構造をとると仮定した。銅アミン錯体に対してフェノール酸素とカルボニル酸素のどちらが図中(Figure 10, 11)の左を向くかが問題となる。



次に、ナフトール-銅-アミン錯体中のラジカル生成部分どうしが結合生成するとき、立体的反発ができるだけ少なくなる接近方向を推定した。
（ラジカル生成部位は点で示してある）

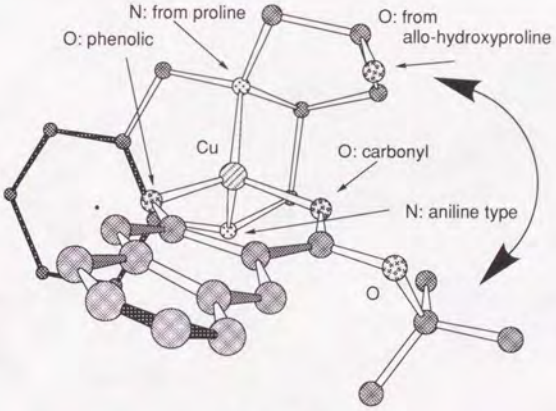


Figure 10.

Figure 10 のように嵩高い *tert*-ブチル基がプロリン由来の五員環側（図中、右方向）へ向いた配位方向は、五員環上の置換基との立体的反発のため不利であると考えた。

そのため立体反発を避けるように Figure 11（次ページ）のような嵩高い *tert*-ブチル基が芳香環側（図中、左方向）へ向く配位形式が有利と考えた。またアミンはややねじれた構造をとっているため、芳香環側は図中の上側が奥に向かっていると予想した。そのためエステル部分は図中の左上方を向くと考えた。

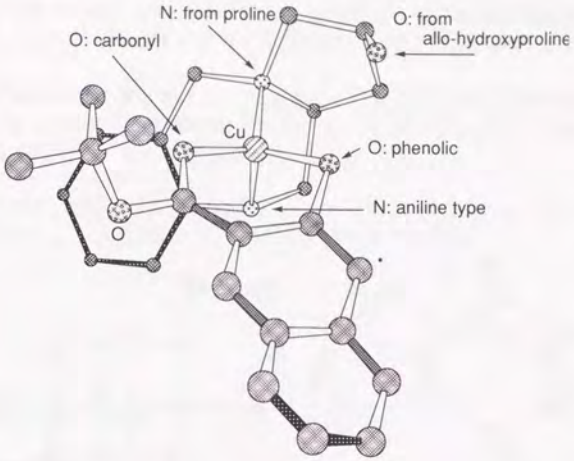


Figure 11.

このような配位構造の錯体が2分子接近しうる方向を Figure 12 に示した。

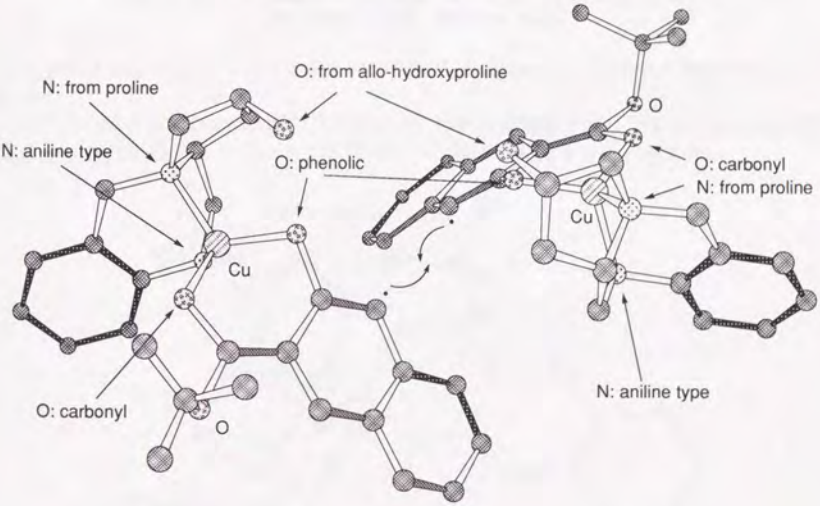


Figure 12. Possible Mechanism for Asymmetric Coupling: PBD-Type-Diamine–Cu–1i Complex

Scheme 42 中の **F** の生成、すなわち、生成したラジカルから結合が生成する段階の、ナフトール-銅-スパルテイン錯体の接近する方向について、同様に次のように考えた。

カップリング時の銅を１価と考え、１価の銅に多く見られる正四面体の配位構造をとると仮定した。銅スパルテイン錯体に対してナフトール **1i** のフェノール酸素とカルボニル酸素のどちらが図中の下を向くかを考えた。

スパルテインは C_2 対称ではなく、Figure 13 で示したように図中 **A** の右上が立体的に前面に突き出ている。（塩化銅(II)-スパルテイン錯体からの推定）

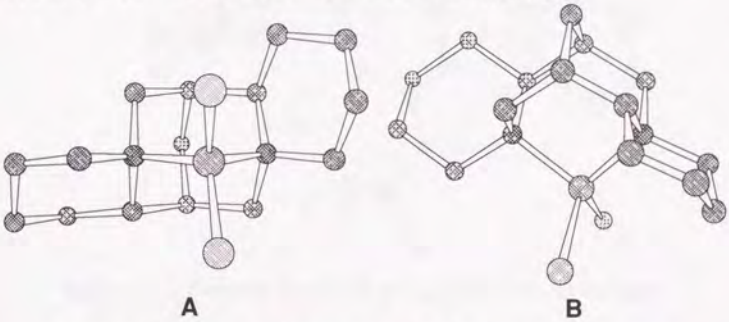


Figure 13. Possible Structures of CuX_2–Sparteine Complex
A: Front View B: Top View

Figure 13 の **A** のスパルテイン右上の立体障害は Figure 14 では図中の奥側に示されている。

エステル部分と、図中の奥側のスパルテインの立体障害部分が反発する Figure 14 の構造よりも Figure 15 のようなエステル部分を下に向けた構造をとると考えた。

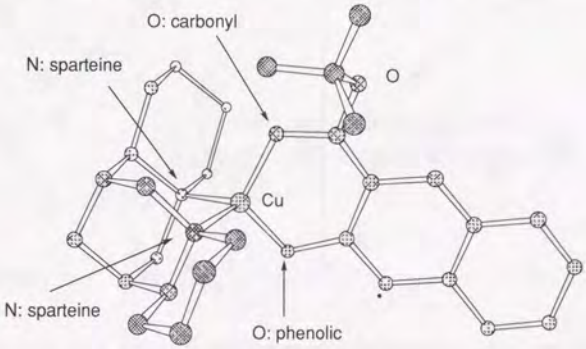


Figure 14. Possible Structure of Sparteine–Cu–1i Complex

Figure 13 の **A** のスパルテイン右上の立体障害は Figure 15 では図中の右上に示されている。

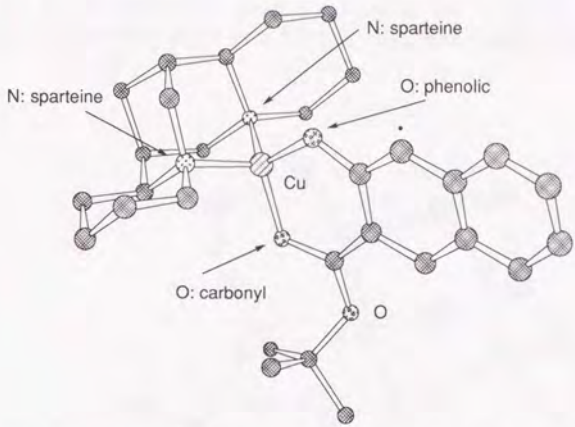


Figure 15. Possible Structure of Sparteine–Cu–1i Complex

有利と考えた構造をラジカルが生成する炭素と反対側から眺めると、 Figure 16 のようになる。スパルテインは図中ではナフタレン環の下側に突き出ているのがわかる。そのためこの配位構造の錯体がもう1分子接近する方向は太矢印で示した図中の右上方向が考えられる。

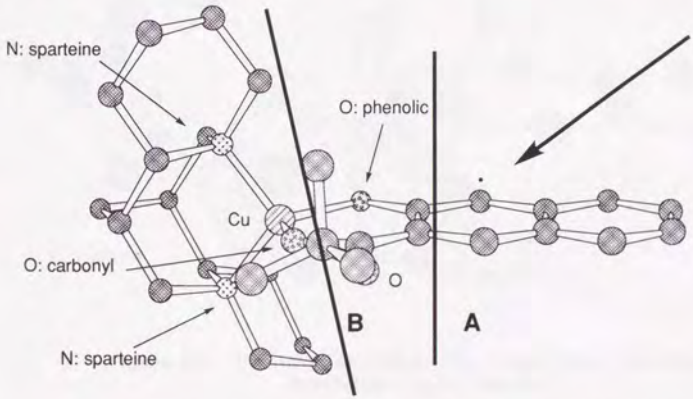


Figure 16. Possible Structure of Sparteine–Cu–1i Complex

Figure 13 の **A** のスパルテイン右上の立体障害は Figure 16 では図中の下側に示されている。

この配位構造と錯体接近方向を組み合わせると Figure 17 のようになる。
Figure 16 で示した錯体の紙面奥側、右上方向から、同じ構造の錯体が接近する様子を示した。

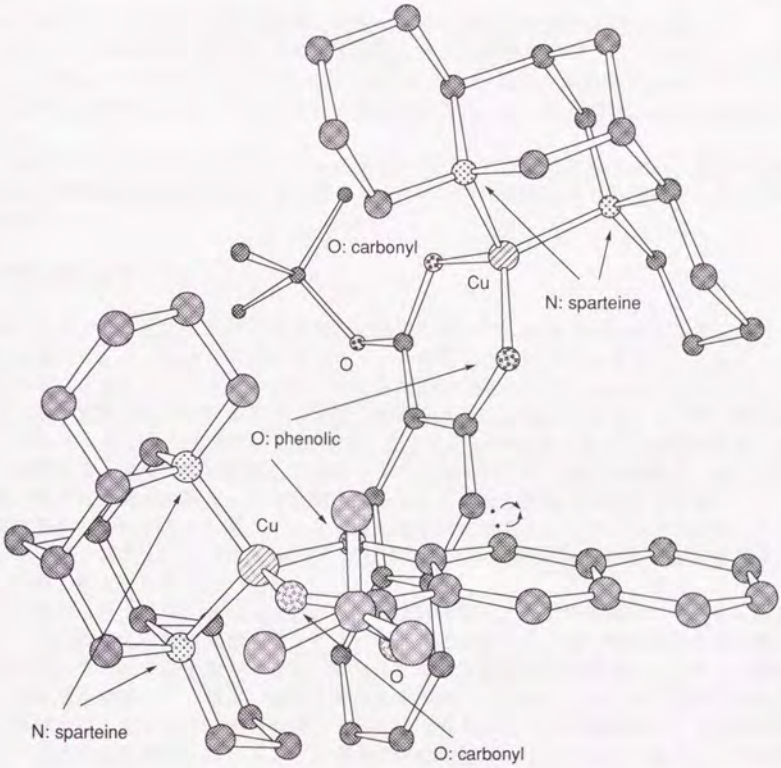


Figure 17. Possible Mechanism for Asymmetric Coupling: Sparteine–Cu–1i Complex

以上の考察により、(1) S 配置のビナフトール誘導体が生成すること、(2) 高い不斉収率の実現のために 3 位のエステル置換基が必須であること、(3) エステル部分が嵩高い程不斉収率が向上すること、を合理的に説明することが可能である。

第４章　本論のポイントと将来の発展への道

本研究で得られた知見をまとめると以下のようになる

TMEDA 錯体を用いる 2-ナフトールの酸化的カップリングが不斉反応へ展開可能なことが示された。 しかし、TMEDA の代わりに不斉配位子を用いると化学収率が低下し反応が完結しない。

配位の自由度が高いアミンより、ドナー原子の固定したアミンのほうが不斉誘起能は高い。

２つの銅アミン錯体を適当な距離で配置すると化学収率の向上が見られる。

スパルテインを用いての反応では基質濃度上昇が化学収率の向上につながる。スパルテインを用いての反応ではナフトール３位のエステル部分の置換基が大きくなるほど不斉収率が上昇する。ナフトール３位に置換基が存在しないと不斉誘起はほとんど見られない。

ピロロベンゾジアゼピン系ジアミンも本カップリング反応に有効である。触媒の活性は高いが触媒活性の失活が速やかに起こる。適切な化学変換により不斉収率の向上が可能である。

今後の指針について

本カップリング反応においては TMEDA 錯体を用いたときは化学収率が非常に高く合成的に有用である。しかし不斉カップリングへ展開した時はスパルテインやピロロベンゾジアゼピン系のジアミンいずれにおいても反応が完結しないという結果になった。

これまで重要視してきた銅アミン錯体の酸化力は反応が進行するかしないかに関係し、キラルアミンを用いたときに反応が途中で止まるという事実は何らかの阻害があることを示唆する。基質が銅に配位して触媒サイクルから外れてしまう可能性や、生じた生成物が銅アミン錯体に配位して生成物阻害をしている可能性などが考えられる。

現在最も可能性があると考えているのは生成物阻害である。これは配座の固定したアミンを中心に検討してきたため銅アミンビナフトール錯体が生成すると安定な錯体になるためと考えている。

この点から考えれば、M. Nakajima らの例は縮合型のアミンではないため、ある程度配位に自由度が生じ触媒回転をスムーズにしていると考えられる。配位の自由度が増した分不斉収率の低下が予想されるが、彼らはアミンに置換した芳香環とナフタレン環との相互作用を期待して、事実、高い不斉誘起を実現している。しかし彼らの反応ではエステル部分を大きくしても不斉収率の上昇は見られない。これは縮合型のアミンではないため基質の立体障害を避けるような錯体の構造変化が起きるのためであろう。我々のアミンは縮合した環系を持つため配位形式の変化が起こらず置換基の効果が明確に現れるといえる。

ピロロベンゾジアゼピン系ジアミンを誘導体化するにあたり立体障害による反応の規制だけでは化学収率の低下を招く。基質に積極的に相互作用して配向を制御する方法が考えられる。

また２分子のジアミンを適当な距離に配置しカップリングをスムーズに進行させる方法も考えられる。

酸化状態により配位構造が違う金属への配位子の設計を見直す必要がある。

本研究をおこなってきた結果から、ドナー原子の固定が、配位子のデザインとして、有利な点だけではないと考えている。酸化還元触媒として働く中心金属の１つである銅は１価と２価で配位形式が違うことが多い。１価の銅は正四面体四配位構造が多く見られ、２価の銅は平面四配位構造が多く見られる。キラルアミンの骨格を完全に固定したときそれぞれの酸化状態に対する配位の強さが違い錯体が不安定となることが考えられる。

酸化還元触媒として働く金属としてはオレフィンのジヒドロキシル化反応のオスミウムやエポキシ化のマンガンがあげられる。しかしこれらの反応は cis-vicinal の関係に新結合が形成されるので、基質と錯体が接触する方向により選択性が決まる。言い方を変えれば、点の不斉の誘起を面の選択に置き換えているため、試薬の反応の方向を結合を生成する瞬間だけ規制しておけばよいといえる。

酸化数変化に伴う配位構造変化は、基質との反応のときに直接は関係ない触媒再生段階で行われることがほとんどであろう。

銅を用いた本カップリング反応においては、ナフトールの１位がラジカル的性質を持つためには、銅が１価に近い状態になる必要がある。ラジカルカップリングして炭素炭素結合が生成するとき、銅は２価と１価のどちらの配位形式なのかが問題である。

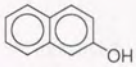
酸素を使う酸化反応においてアミン系の化合物を配位子として使うことは、常にアミンの酸化という問題がつきまとう。TMEDA 錯体はなぜ高い活性を示すのかという点をもう一度考え直す必要がある。一つの考え方として銅への配位がしっかりしていれば酸化はされにくいという考えが挙げられる。これにはスパルテインのように、元々の構造を配位しやすく設計するという考えと、酸化状態により配位構造が違う金属の場合に、ある程度のしなやかさを持つ配位子を設計するという考え方がありうる。不斉誘起と配位子のしなやかさを両立するには立体障害による制御だけでなく芳香環同士のスタッキングやキレーションなどによる制御が有効となるだろう。

反応機構の解明に対しては、電子密度の低下したナフトールを用いて銅-アミン-ナフトール錯体の X 線結晶構造解析を行うことができれば、貴重な構造的情報が得られるであろう。それをもとに配位子の設計に役立てることができるだろう。

また中間体で生じていると考えているラジカルを、ナフトール以外でトラップする事ができれば新たな結合生成反応として展開することが可能になると考えている。

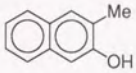
第５章　実験に用いた化合物及び取り扱いについて

第１節　基質の入手、合成



1a

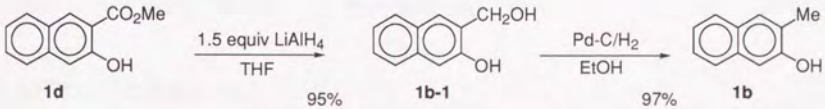
市販品をエタノールまたはトルエンより再結晶した。



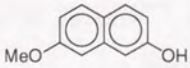
1b

以下のように合成した。

Scheme 43.

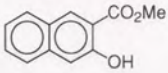


1d　　**1b-1**　　**1b**



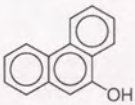
1c

市販品（Aldrich）をそのまま用いた。



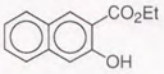
1d

市販品（東京化成）をそのまま用いた。



1e

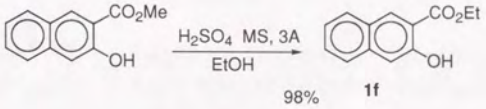
市販品（Aldrich）をシリカゲルカラムクロマト（ヘキサン/エーテル=10/1）を用い精製後、アルゴン雰囲気下エタノールから再結晶した。

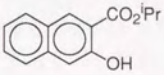


1f

以下のように合成した。

Scheme 44.

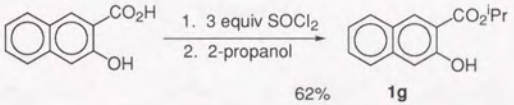


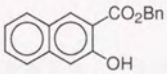


1g

以下のように合成した。

Scheme 45.

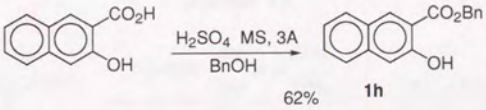


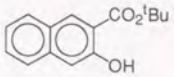


1h

以下のように合成した。

Scheme 46.

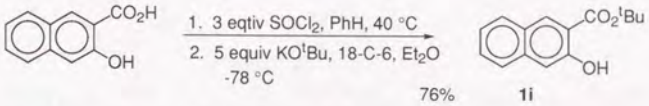




1i

以下のように合成した。

Scheme 47.

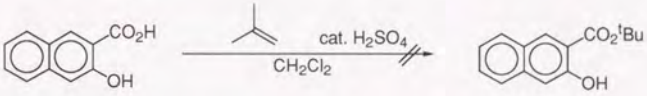


酸塩化物を合成するとき温度を上げると、副生成物が生じる。

THF に溶解した酸塩化物を *tert*-ブチルアルコール中に滴下しても **1i** はほとんど生成しなかった。LiOtBu の THF 溶液中に滴下しても化学収率は低かった。KOtBu, 18-Crown-6 の Et_2O 溶液に滴下すると化学収率が向上した。-78 ℃ にて 5 時間かけて酸塩化物の THF 溶液を滴下すると最も良い結果が得られた。滴下を速く行うと収率は低下する。

tert-ブチルエステル合成の定法であるイソブチレンを用いた反応は進行しなかった。触媒として BF_3OEt_2 溶媒として Et_2O なども検討したが **1i** は得られなかった。

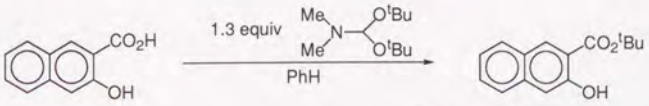
Scheme 48.



1i

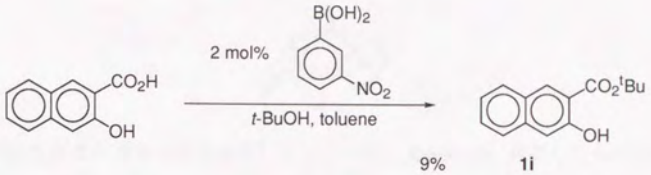
ジメチルホルムアミドのジ *tert*-ブチルアセタール(Aldrich)は *tert*-ブチルエステル合成に用いられる。[26] この方法を適用した。副生成物は見られず分液操作のみでかなり純粋な **1i** を得ることができる。文献では酸に対してアセタールを 4 当量用いている。試薬が高価なため当量を減らして用いたことが収率が低くとどまった原因とも考えられる。

Scheme 49.

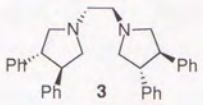


電子求引性アリールホウ酸誘導体はアミド結合生成の優れた触媒である。[27] エステル化については活性はやや低いが、検討を行った。副生成物は見られず分液操作のみでかなり純粋な **1i** を得ることができる。しかし化学収率は低くとどまった。

Scheme 50.

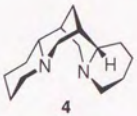


第2節　キラルアミンの入手、合成



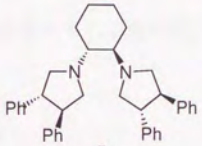
3

中島らにより当教室で既に合成されたものを用いた。[28]



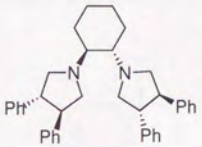
4

市販品の硫酸塩水和物を（和光純薬）をフリー化し Kugelrohr 蒸留したものを用いた。



5

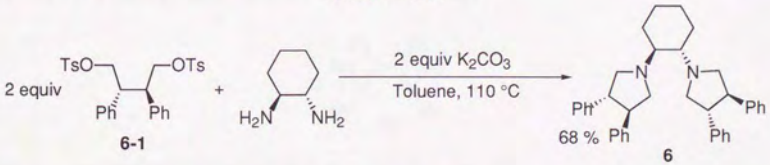
窪田らにより当教室で既に合成されたものを用いた。[29]



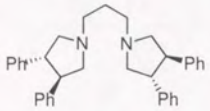
6

以下のように合成した。

Scheme 51.

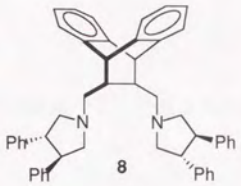


ジトシレートは当教室で既に合成されたものを用いた。[28] ジアミンは市販品（Aldrich）を用いた。

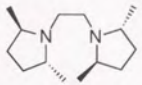


7

中島らにより当教室で既に合成されたものを用いた。[28)]

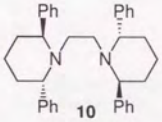


8

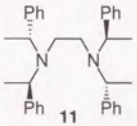


9

窪田らにより当教室で既に合成されたものを用いた。[29)]

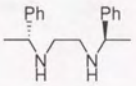


10



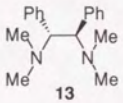
11

熊本らにより当教室で既に合成されたものを用いた。[30)]



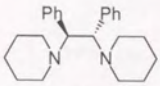
12

石井らにより当教室で既に合成されたものを用いた。[31)]



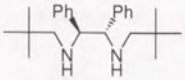
13

青木らにより当教室で既に合成されたものを用いた。[32)]



14

松井らにより当教室で既に合成されたものを用いた。[33]



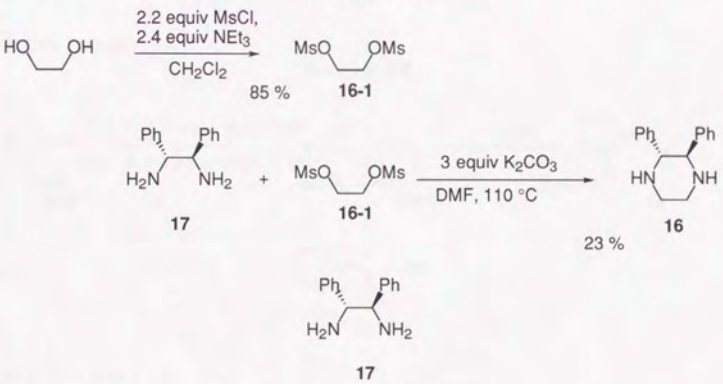
15

石井らにより当教室で既に合成されたものを用いた。[31]

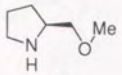
16

以下のように合成した。

Scheme 52.



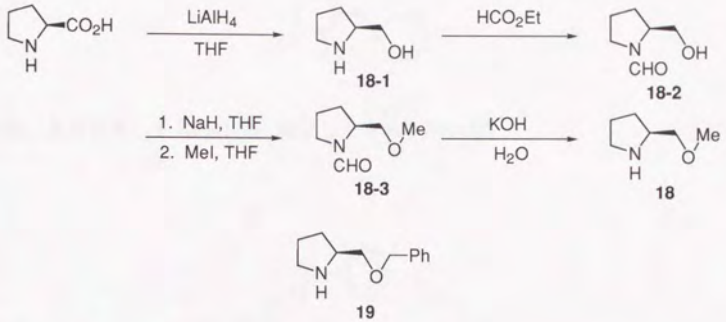
文献[49]に従い既に合成されたものを用いた。



18

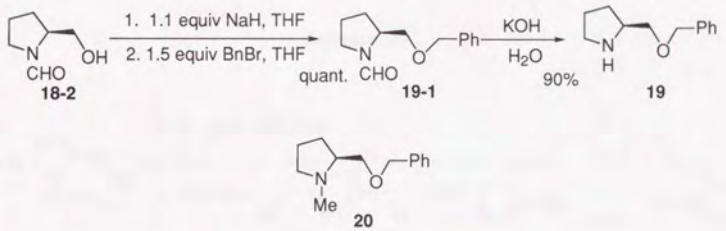
文献[34]に従い以下のように合成した。

Scheme 53.



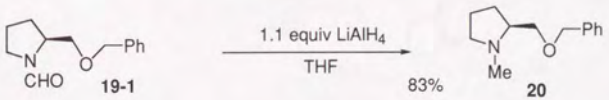
以下のように合成した。

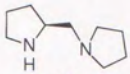
Scheme 54.



以下のように合成した。

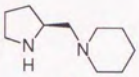
Scheme 55.





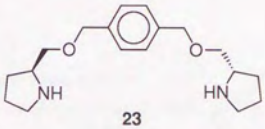
21

市販品（東京化成）を Kugelrohr 蒸留したものを用いた。



22

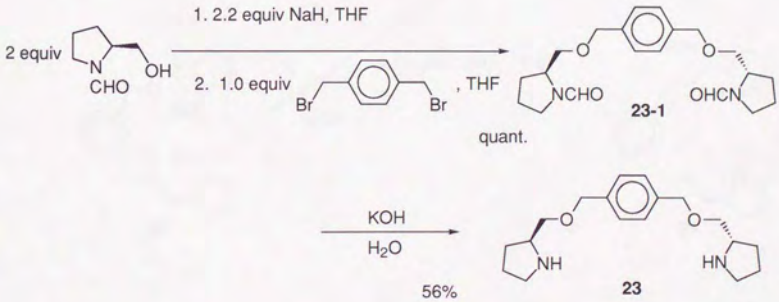
市販品（東京化成）を Kugelrohr 蒸留したものを用いた。

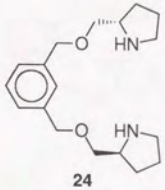


23

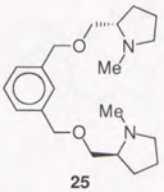
以下のように合成した。

Scheme 56.





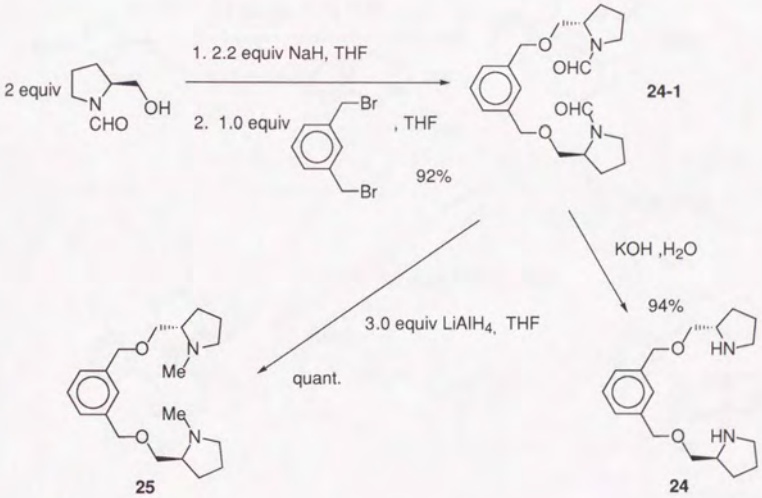
24

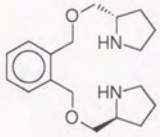


25

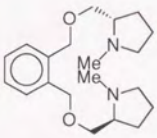
以下のように合成した。

Scheme 57.





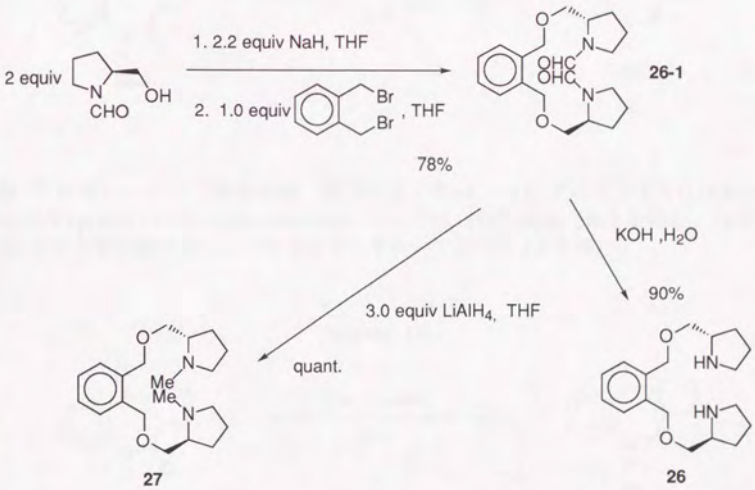
26

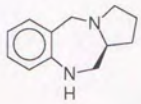


27

以下のように合成した。

Scheme 58.

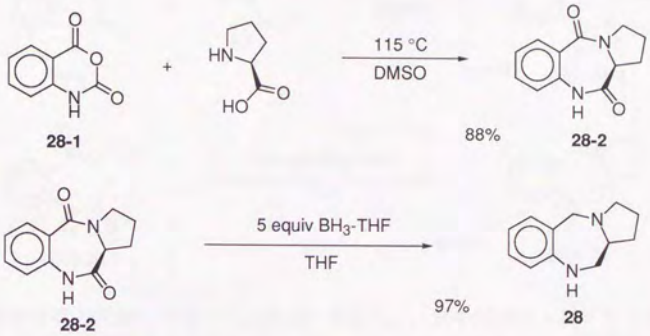




28

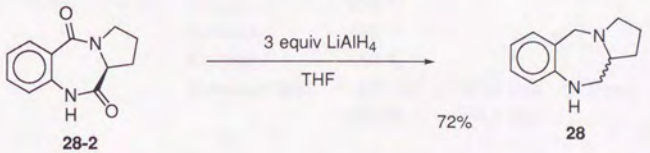
以下のように合成した。

Scheme 59.



文献 [35] に従い、イサト酸無水物（東京化成）**28-1** と(*S*)-プロリンより(11a*S*) 2,3-Dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*, 11a*H*)dione **28-2** を得た。**28-2** は Aldrich より入手可能である。これをボランを用いて還元し **28** を得た。

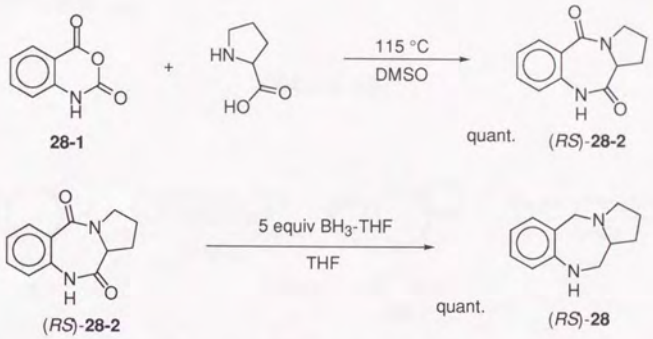
Scheme 60.



$LiAlH_4$ を用いて **28-3** を還元すると部分的にラセミ化した **28** が得られる。再結晶品の比較において、$LiAlH_4$ 還元で得た **28** の旋光度はボラン還元で得た **28** の旋光度に比べ６％ほど低い。

ボラン還元で得た **28** の光学純度は次のようにして調べた。

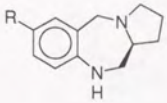
Scheme 61.



光学活性体合成と同様の方法にて(*RS*)-**28** を合成し、光学活性キャピラリーカラムを用いた GC により分離条件を検討した。ボラン還元で得た **28** の再結晶品は単一のピークのみであった。

分離条件

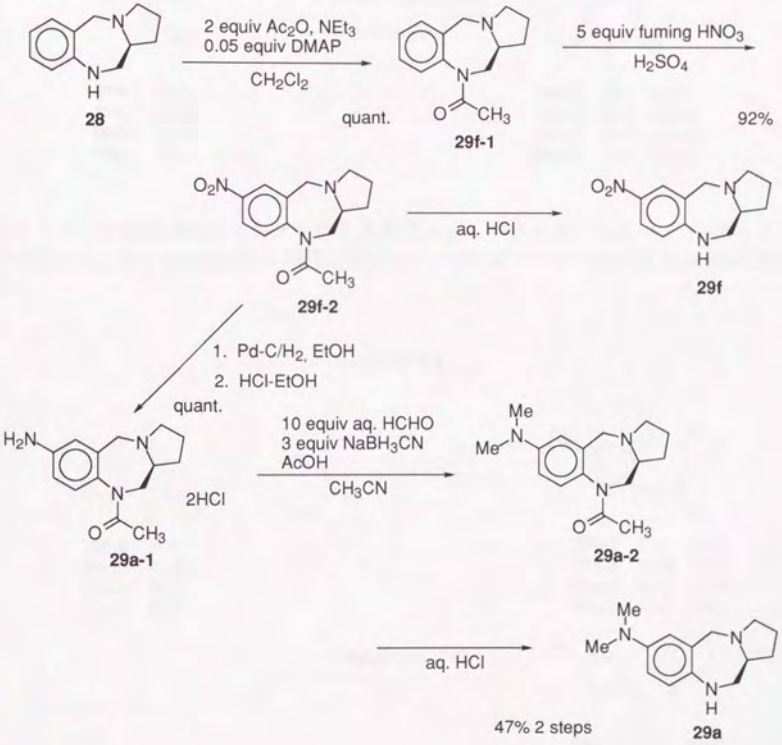
Column	CP Cyclodextrin β-236 M			
Carrier Gas	N_2, 50 ml/min			
Temp.	Injector	150 ℃		
	Detector	150 ℃		
	Column	150 ℃		
	Retention time	(*RS*)-28	63.8 min	64.9 min
		(*S*)-28	64.1 min	

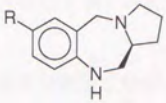


29a R=N(Me)$_2$
29f R=NO$_2$

以下のように合成した。

Scheme 62.

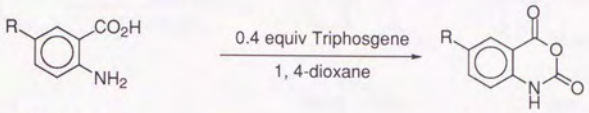




29b R=I
29c R=Br
29d R=Cl
29e R=F

以下のように合成した。

Scheme 63.

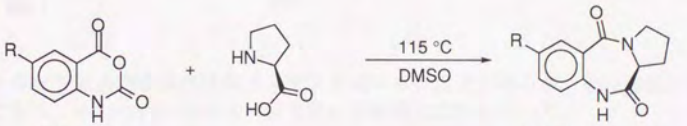


29b-1 R=I
29c-1 R=Br
29d-1 R=Cl
29e-1 R=F

29b-2 R=I 97%
29c-2 R=Br quant.
29d-2 R=Cl Aldrich
29e-2 R=F quant.

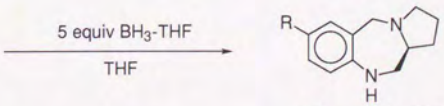
アントラニル酸誘導体をホスゲンの３量体であるトリホスゲンを用いて N-カルボキシ無水物とし、以下 Scheme 59 と同様に合成した。**29d-2** については市販品(Aldrich)を用いた。

Scheme 64.



29b-2 R=I
29c-2 R=Br
29d-2 R=Cl
29e-2 R=F

29b-3 R=I 84%
29c-3 R=Br 83%
29d-3 R=Cl quant.
29e-3 R=F 77%

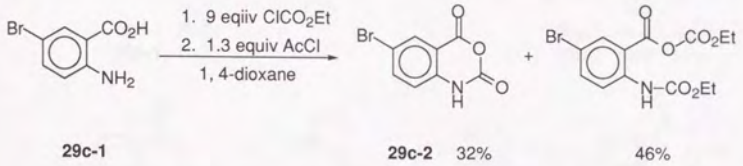


29b R=I 99%
29c R=Br 96%
29d R=Cl quant.
29e R=F 93%

N-カルボキシ無水物（イサト酸無水物）合成法はいくつか報告されている。[36] それらの検討も行った。

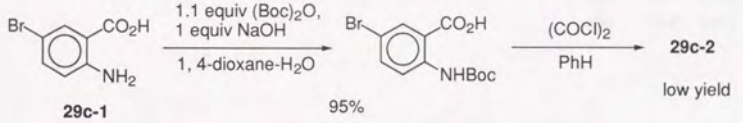
クロルギ酸エチルを用いた反応は副生成物が生じた。

Scheme 65.

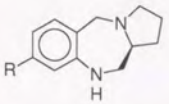


オキザリルクロライドを用いる反応は収率が低く、**29c-1** の回収をみた。

Scheme 66.



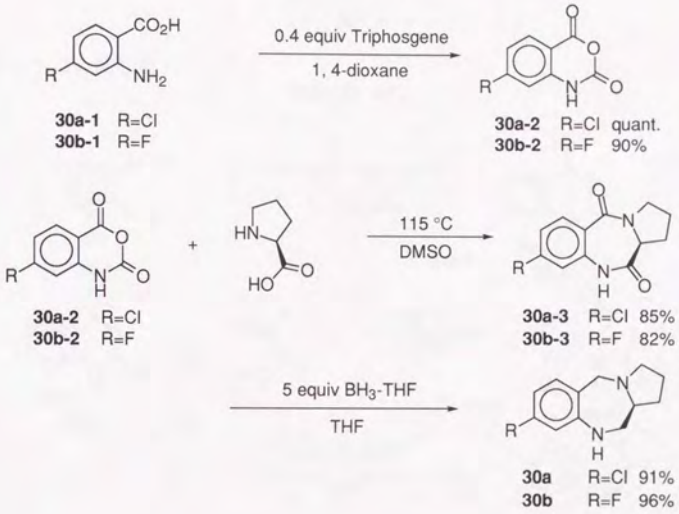
N-カルボキシ無水物合成法にはホスゲンを用いる合成法があるが、その毒性のため使用困難である。そのためトリホスゲンを用いる新規合成法を用いた。



30a R=Cl
30b R=F

以下のように合成した。

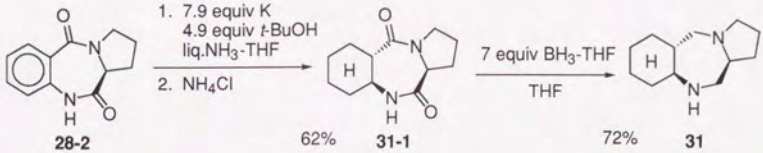
Scheme 67.



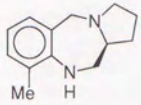
31

以下のように合成した。

Scheme 68.



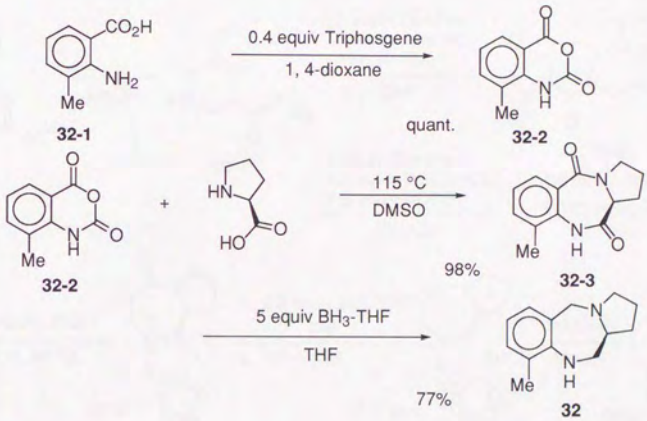
文献[37]に従い **31-1** を合成した後、ボランを用いて還元し **31** を得た。

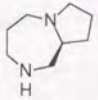


32

以下のように合成した。

Scheme 69.

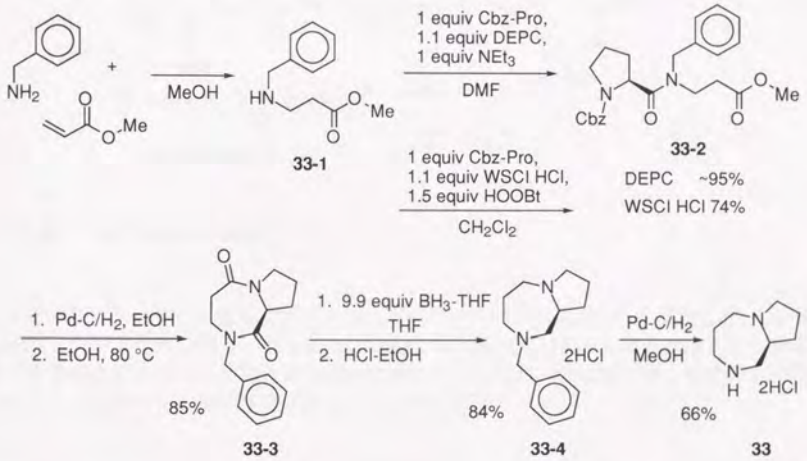




33

以下のように合成した。

Scheme 70 .



(DEPC: diethylphosphorocyanidate, WSCI HCl: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochrolide, HOOBt: 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one)

文献[48]に従いベンジルアミンとアクリル酸メチルとのマイケル付加反応を用いて**33-1**を得た。

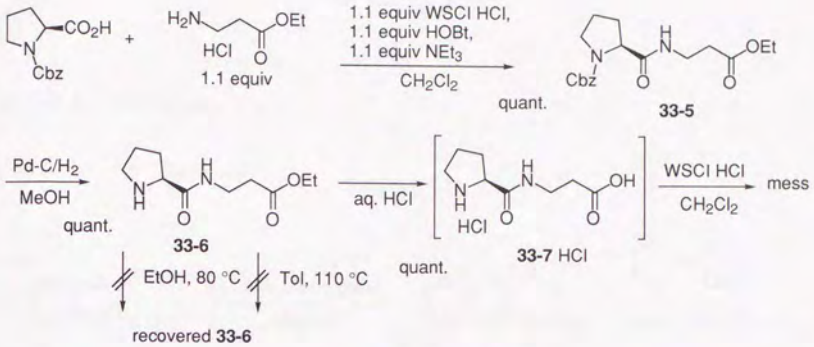
これにCbz-プロリンを縮合させ**33-2**を得た。 DEPC法は収率の点で優れているが、リンを含むと思われる不純物との分離が非常に困難であった（シリカゲルカラムクロマトで分離不可能）。次の段階にPd-C を用いた接触還元を予定していたのでリン由来不純物を除きたかった。そこでWSCI・HCl（水溶性カルボジイミド）を用いて反応を行った。収率は低下したが純粋な**33-2**を得ることができた。幸運なことに不純物を含む**33-2**でも問題なく脱Cbz反応は進行した。

引き続きアミンとエステルの分子内環化反応をおこなった。この反応にはアミド上のベンジル基は必須である。 DEPC法由来の不純物は**33-3**と分離可能であった。

33-4の脱ベンジル反応はあらかじめ塩酸塩にしておくことで常圧にて進行し**33**を得ることができた。

33 の合成にあたり他のルートも検討した。

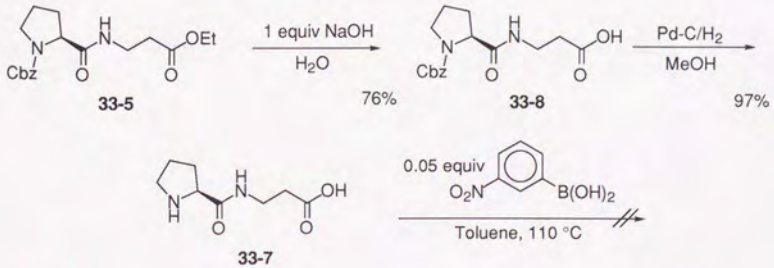
Scheme 71.



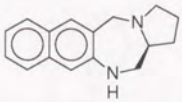
(HOBt: 1-hydroxybenzotriazole)

アミノ酸エステルの 2 量体であるジケトピペラジンの合成条件 [38] を検討した。**33-6** を加熱したが環化体は得られなかった。Scheme 70 で環化体 **33-3** を得るにはアミド窒素上に置換基必要といえる。縮合剤を用いた試みも行ったが、分液操作後、有機物の回収はほとんどなかった。環化体は生成していないと考えている。

Scheme 72.



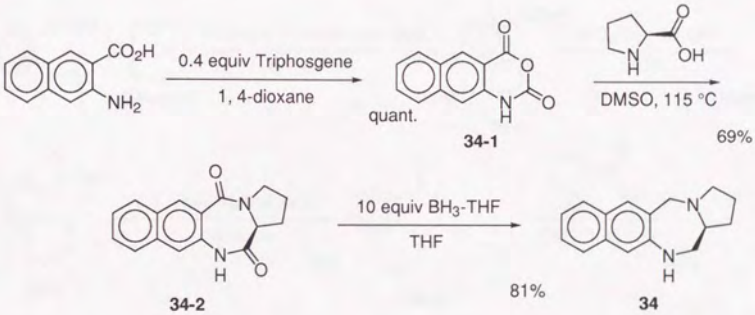
アミド結合生成の触媒として報告 [27] されている電子求引性アリールホウ酸誘導体を用いた環化反応を検討した。7 員環の生成も報告されているが、**33-7** は環化しなかった。



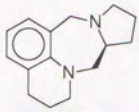
34

以下のように合成した。

Scheme 73.



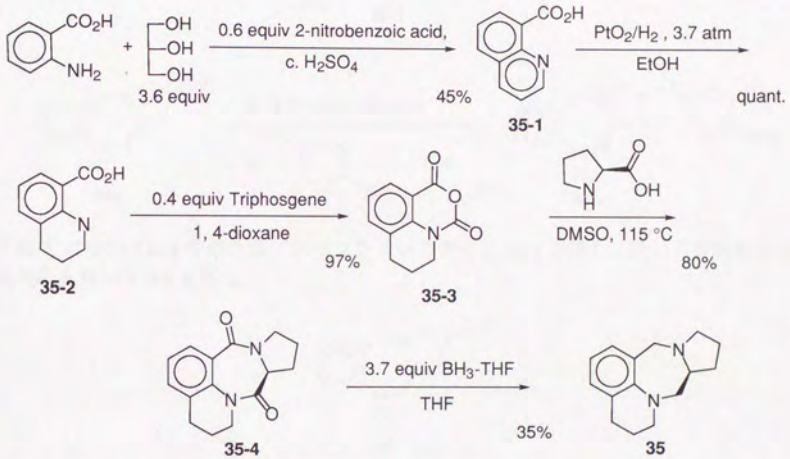
34-1 の合成法にはクロルギ酸エチルを用いる方法が報告[39]されているが、トリホスゲンを用いた方法が収率が良い。



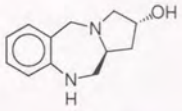
35

以下のように合成した。

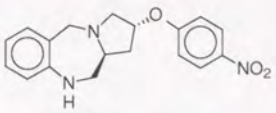
Scheme 74.



文献[40] に従い **35-2** を得たのち、これまでと同様の反応にて **35** を得た。



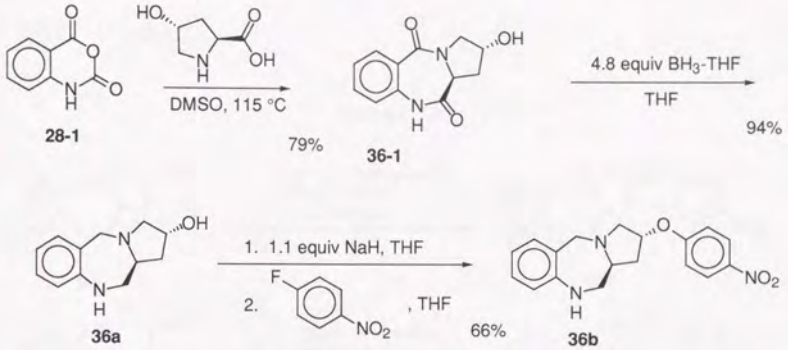
36a



36b

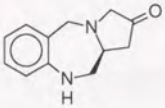
以下のように合成した。

Scheme 75.



28-1 **36-1** **36a** **36b**

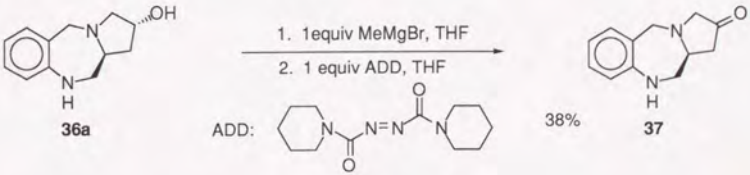
文献[35]に従い **36-1** を得た後、ボランを用いて還元し **36a** を得た。続いて芳香族求核置換反応を用いて **36** を得た。



37

以下のように合成した。

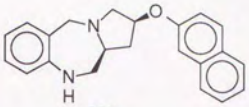
Scheme 76.



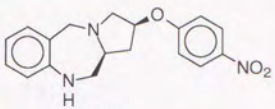
36a **37**

アミノ基を保護しない状態での酸化反応を検討した。ADD を用いる方法[44]を採用した。TPAP (Tetrapropylammonium perruthenate) を用いる酸化反応[45]は低収率にとどまった。基質のルテニウムへの配位が触媒回転を阻害したと考えている。

２級窒素を保護するルートをとれば収率が改善できると考えている。



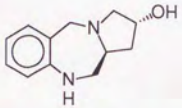
38b



38a

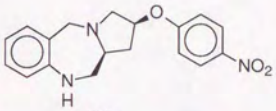
以下のように合成した。

Scheme 77.

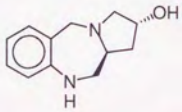


36a

1.1 equiv 4-nitrophenol,
1.5 equiv DEAD,
1.5 equiv PPh_3
THF
30%

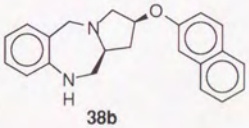


38a



36a

1.1 equiv 2-naphthol,
1.5 equiv DEAD,
1.5 equiv PPh_3
THF
35%

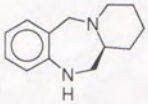


38b

化学収率は３０％台にとどまった。

ヒドラジン体の生成が見られた。アルコールの酸性度が小さいためと立体障害が考えられる。

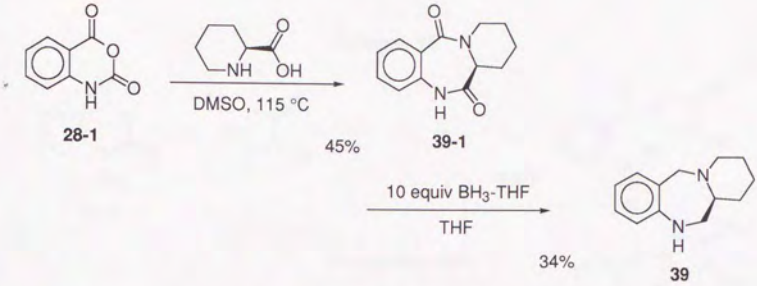
TMAD-PBu_3 系[46]を用いれば収率の改善が可能と考えている。



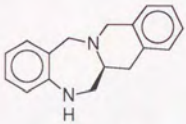
39

以下のように合成した。

Scheme 78.



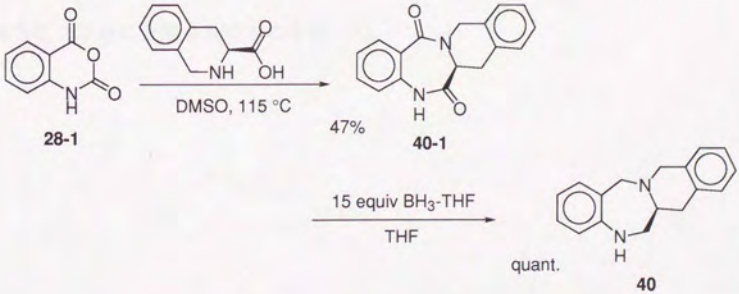
28-1 **39-1** **39**



40

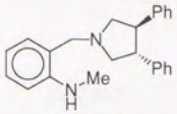
以下のように合成した。

Scheme 79.



28-1 **40-1** **40**

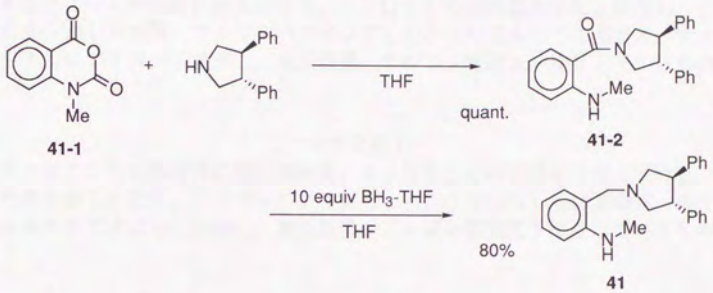
(*S*)-テトラヒドロイソキノリン-３-カルボン酸は市販品(Aldrich)を用いた。



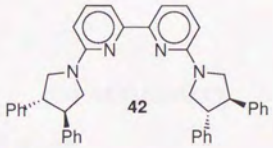
41

以下のように合成した。

Scheme 80.



41-1　**41-2**　**41**



42

光森らにより既に合成されたものを用いた。[47]

第３節　錯体の調製

第１項　銅塩の精製

塩化銅(I)

濃塩酸に溶解後、ミリＱ（通常のイオン交換水をさらにイオン交換、限外濾過したもの。比抵抗 ≈16.3 Ωcm ）もしくは蒸留水を加え再沈殿させ、ろ取し、それぞれあらかじめ脱気、アルゴンバブリングしたミリＱもしくは蒸留水、エタノール、エーテルにてすばやく洗浄し、減圧乾燥、アルゴン雰囲気下保存しているものを用いた。

臭化銅(I)

飽和臭化カリウム水溶液に加温溶解後、ミリＱもしくは蒸留水を加え放冷し、ろ取、それぞれあらかじめ脱気、アルゴンバブリングした、ミリＱもしくは蒸留水、エタノール、エーテルにてすばやく洗浄し、減圧乾燥、アルゴン雰囲気下保存しているものを用いた。

ヨウ化銅(I)

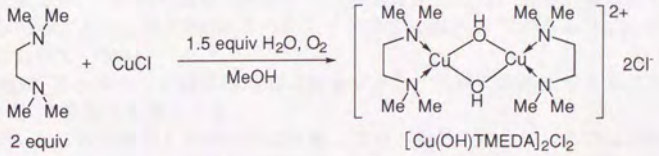
飽和ヨウ化カリウム水溶液に加温溶解後、ミリＱもしくは蒸留水を加え放冷し、ろ取、それぞれあらかじめ脱気、アルゴンバブリングした、ミリＱもしくは蒸留水、エタノール、エーテルにてすばやく洗浄し、減圧乾燥、アルゴン雰囲気下保存しているものを用いた。

第２項　錯体の調製

$[Cu(OH)TMEDA]_2Cl_2$

文献に従い、以下のように合成した。

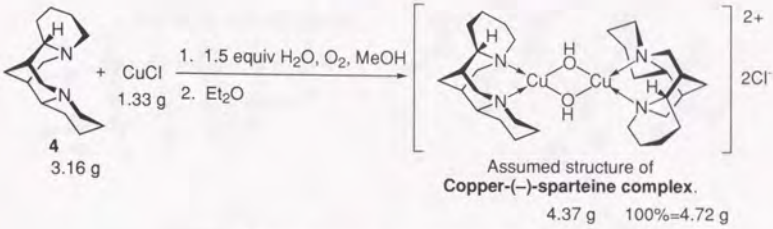
Scheme 81.

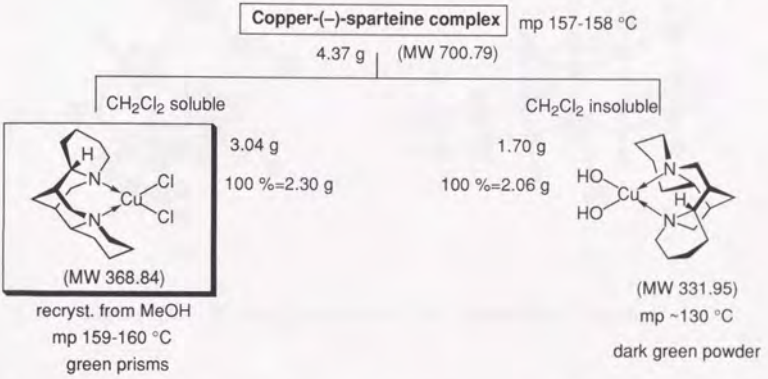


Copper-(−)-sparteine complex

以下のように合成した。

Scheme 82.





メタノール中酸素雰囲気下錯体を調製、銅スパルテイン錯体は緑色ゲル状物質となった。このためエーテルを加え固体とし、ろ取、乾燥し緑色粉末を得た。この粉末を２核錯体と仮定して実験に用いた。

この粉末を塩化メチレンに可溶成分と不溶成分に分離し、塩化メチレン可溶成分はメタノールから再結晶した。

塩化メチレン可溶成分から再結晶して得られた結晶は塩化銅(II)-スパルテイン錯体であった。元素分析、 X 線結晶構造解析により構造を確定した。構造が確定しているのはこの錯体だけである。塩化銅(II)-スパルテイン錯体は報告例[49]があるが、X 線結晶構造解析は行われていない。

水酸化銅(II) スパルテイン錯体の構造は推定である。溶媒に難溶性であること、減圧乾燥（60 °C) で黒変する事による。

塩化メチレンに可溶成分と不溶成分に分離した時、重量が増えているのは溶媒が含まれているためと考えている。重量比が計算値と合わないのは２核錯体と仮定しているものが均質でないことを示すものと考えている。

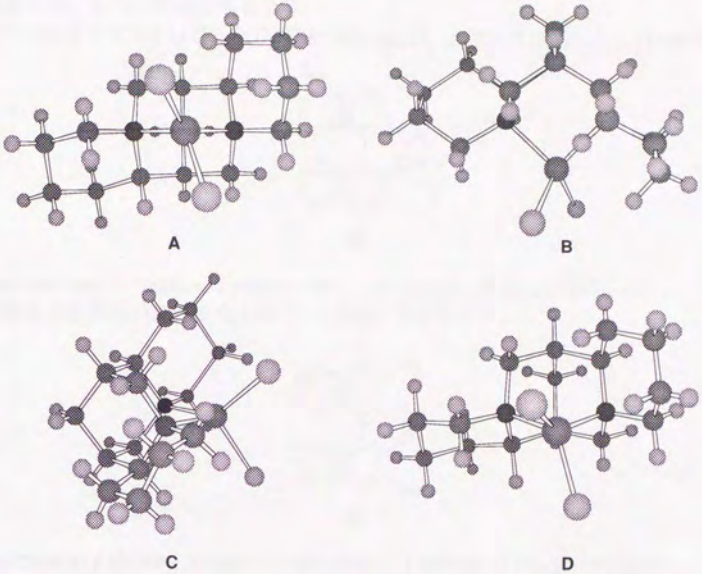
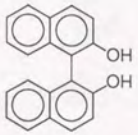


Figure 18. X-ray structure of $CuCl_2$-Sparteine Complex

第4節　反応生成物について

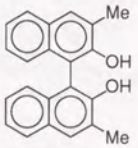
すべての反応生成物の不斉収率は光学活性カラムを用いた HPLC により決定した。用いた溶出溶媒、カラム保持時間を示す。

2a から **2e** までは 0.5 mol% の$[Cu(OH)TMEDA]_2Cl_2$ を用いて合成した。(Table 1 参照)



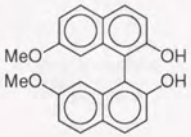
2a

Waters Opti-Pak TA　hexane:2-propanol=9:1　1.5 ml/min　16 min(*R*) 20 min(*S*)
絶対配置は生成物の旋光度を文献[41]と比較して決定した。



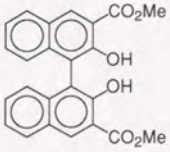
2b

Daicel CHIRALPAK AD　hexane:2-propanol=9:1　1 ml/min　8 min(*R*) 10 min(*S*)
絶対配置は生成物の旋光度を文献[42]と比較して決定した。



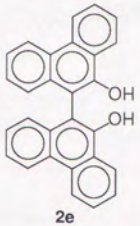
2c

Daicel CHIRALPAK AD　hexane:2-propanol=9:1　1.5 ml/min　29 min(*S*) 36 min(*R*)
絶対配置は生成物の旋光度を文献[43]と比較して決定した。



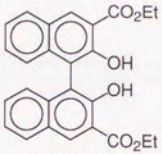
2d

Daicel CHIRALPAK AD　hexane:2-propanol=9:1　1 ml/min　12 min(*S*) 18 min(*R*)
絶対配置は生成物の旋光度を文献[42]と比較して決定した。



2e

Waters Opti-Pak TA　ethanol 0.3 ml/min　21 min 27 min

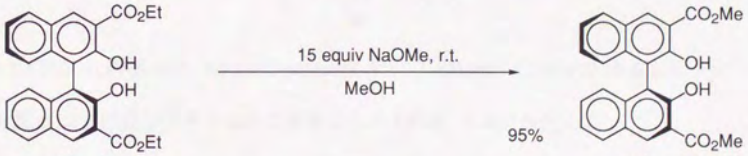


2f

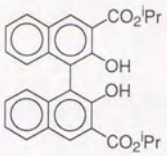
Daicel CHIRALPAK AD　hexane:2-propanol=9:1　1 ml/min　7 min(*S*) 10 min(*R*)

絶対配置は文献既知である **2d** に誘導した後 HPLC により決定した。

Scheme 83.



2f　64% ee　　**2d**　64% ee

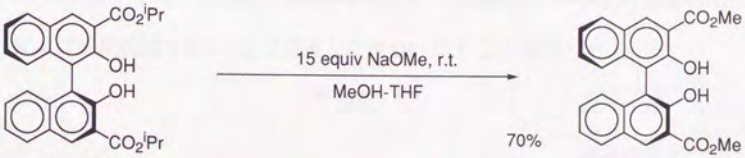


2g

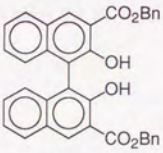
SUMICHIRAL OA-2000 hexane:2-propanol=20:1 0.5 ml/min 17 min(*R*) 19 min(*S*)
Daicel CHIRALPAK AD hexane:2-propanol=100:1 0.3 ml/min 26 min(*S*) 32 min(*R*)

絶対配置は文献既知である **2d** に誘導した後 HPLC により決定した。

Scheme 84.



2g 64% ee **2d** 64% ee

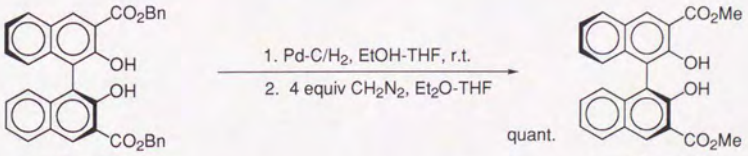


2h

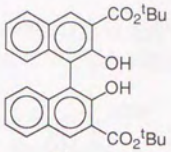
Daicel CHIRALPAK AD hexane:2-propanol=9:1 1 ml/min 12 min(*S*) 16 min(*R*)

絶対配置は文献既知である **2d** に誘導した後 HPLC により決定した。

Scheme 85.



2h 66% ee **2d** 66% ee

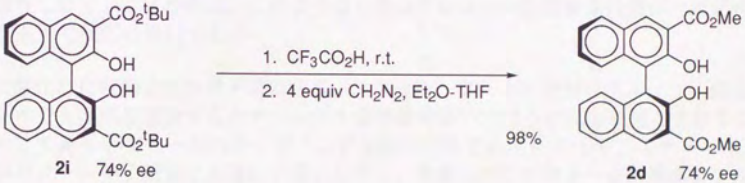


2i

SUMICHIRAL OA-3300 hexane:1,2-dichroloethane:2-propanol=180:20:1 0.5 ml/min
16 min(*S*) 19 min(*R*)
Daicel CHIRALPAK AD hexane:2-propanol=200:1 0.5 ml/min 14 min(*S*) 20 min(*R*)

絶対配置は文献既知である **2d** に誘導した後 HPLC により決定した。

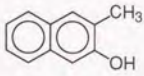
Scheme 86.



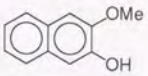
第５節　ビナフトール合成及び後処理全般について

ラセミ体ビナフトール合成について

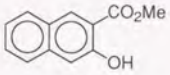
TMEDA 錯体を用いたビナフトール合成反応は有用であり、様々なナフトール誘導体に適用可能である。合成的な面に関していくつかの知見を得たので以下に述べる。



A



B



C

A は電子供与性置換基を持つグループ。酸化に不安定であり塩化メチレン中反応を行う。空気下で反応は進行する。副生成物が多いときは反応温度を下げる。9-phenanthrol はこのグループである。

B は電子供与性置換基があるが、銅に対してキレートする可能性が考えられる置換基を持つグループ。酸化に不安定であり塩化メチレン中反応を行うことが望ましいが、反応が進行しにくいことがある。このようなときはアルコール系溶媒中低温にて反応を行う。空気下で反応は進行する。

C は酸化に比較的安定な電子求引性基（エステル、アミド）を持つグループ。塩化メチレン中でも反応は進行するがアルコール系溶媒を用いたほうが反応は早く完結する。例に示してあるナフトールのカップリング反応はそれぞれメタノール、エタノール、2－プロパノール中、問題なく進行する。しかし、生成したビナフトールは溶媒のアルコールがエステル交換したものが得られるので注意が必要である。このグループのカップリング反応は加熱したほうが反応は早くなる。しかし加熱環流状態（溶媒が沸騰している状態）では酸素の溶媒への溶解がほとんどなくなり反応進行の妨げとなる。反応温度は溶媒が沸騰する直前の温度が良い。このことを注意すれば空気下で反応は進行する。メタノール中の反応であれば、酸素雰囲気下加熱環流するよりも、空気下 50 ℃にて反応をおこなったほうが反応時間は短い。

クロスカップリングを行うときは、より酸化に不安定な基質に条件を合わせる。電子豊富な基質 **A** と電子不足の基質 **C** のカップリングは優先的にクロスカップリング体が生成する。

使用可能な溶媒には塩化メチレン、ジクロロエタン、アセトニトリル、アセトン（加熱すると溶媒どうしのアルドール体が得られる）、アルコール系溶媒、テトラヒドロフラン、水（2-ナフトールと TMEDA 錯体の反応は懸濁状態で進行する）などがあげられる。

TMEDA 錯体を用いたビナフトール誘導体合成法は大量合成にも適用できる。Table 1. は小スケールで反応をおこなったため、反応液を直接減圧濃縮し、シリカゲルカラムクロマトグラフィーにより精製した。大量合成時には分液操作による後処理が便利である。1 例として 0.05 N EDTA - 2 Na（エチレンジアミン４酢酸２ナトリウム）, sat. $NaHCO_3$,

飽和食塩水による洗浄が勧められる。銅を有機相から水相へキレート抽出し,TMEDA も水相へ移行する。酸による後処理も可能だが、*tert*-ブチルエステルなど酸に弱い官能基を持つときはこの後処理法は有用である。

不斉反応について

不斉収率を正確に評価するために次のような注意点がある。

1. ビナフトール-銅-キラルアミン錯体を直接カラムクロマトグラフィーで生成するときは生成物と原料の回収率に注意する必要がある。
2. 光学活性ビナフトールをカラムクロマトグラフィーで生成するとき回収率に注意する必要がある。

1.に関して

ラセミ体ビナフトール **2d** と銅スパルテイン錯体を塩化メチレン中撹拌後、減圧濃縮し、残査をシリカゲルカラムクロマトグラフィーにより精製すると光学活性ビナフトールが溶出する。初めに *S* 体、遅れて *R* 体が溶出する。カラム上で銅スパルテイン錯体によるラセミ体ビナフトールの分割が起きていると考えている。

そのためスパルテインを用いた不斉反応の後処理には、酸による銅スパルテイン錯体の分解が必要である。

塩化メチレン中の銅スパルテイン錯体の緑色を目安に錯体の分解を判断すると、2 N 塩酸での洗浄では銅スパルテイン錯体は完全には分解しないといえる。1 N 硫酸での洗浄では速やかに緑色の消失が見られることから錯体は分解すると考えている。 0.05 N EDTA -2Na（エチレンジアミン四酢酸二ナトリウム）は硫酸より錯体の分解能力は低いがスパルテイン以外のアミンに対しては効果的である。

2.に関して

不斉反応後、分液操作をして銅アミン錯体を除いた後、残差をシリカゲルカラムクロマトグラフィーにより精製すると溶出するフラクションにより不斉収率に差がある。この現象をビナフトール誘導体 **2d** と **2i** で確認した。**2d**、**2i** ともに初めに溶出するフラクションの不斉収率が高い。不斉反応ではすべての生成物を集めた後 HPLC で決定している。

スパルテインを用いた不斉反応のうち Table 3、12、13 には硫酸を用いての後処理を行っていない。原料回収と生成物をあわせて定量的に回収されていることを確認した。すなわち、*R* 体か *S* 体どちらかのビナフトールが銅スパルテイン錯体にとらえられないことを確認した。

スパルテインを用いた不斉反応のうち Table 3、12、13 以外には硫酸を用いての後処理を行った。ただし基質として *tert*-ブチルエステル **1i** を用いた不斉反応の後処理には 0.05 N EDTA -2Na を用いた。

Table 19 以降のスパルテイン以外のアミンを用いた不斉反応の後処理には 0.05 N EDTA -2Na を用いた。

Table 19 以前のスパルテイン以外のアミンを用いた不斉反応の後処理には分液操作を行っていない。原料回収と生成物をあわせて定量的に回収されていることを確認した。

Experimental Section

General Procedures

^{1}H NMR and ^{13}C NMR spectra ware measured with a JEOL JNM-EX-270 (270 MHz ^{1}H, 67.8 MHz ^{13}C) spectrometer in the solvent indicated. 1H chemical shift are reported in δ ppm with tetramethylsilane (TMS) as internal standard. ^{13}C chemical shift are reported relative to the central peak of $CDCl_3$ (77 ppm). The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, qd = quartet-of-doublets, s = singlet, t = triplet

Infrared spectra were measured with a JASCO IR Report-100 Infrared spectrometer.

Mass spectra were measured with a JEOL JMS-DX-300 Mass Spectrometer and high resolution mass spectra were measured with a JEOL JMS-SX-102 Mass Spectrometer.

Optical rotations were measured with a JASCO DIP-370 Digital Polarimeter.

High performance liquid chromatography (HPLC) was performed with a JASCO PU-986 Intelligent Prep. Pump equipped with a JASCO UV-970 Intelligent UV/VIS Spectrophotometer. Detection was done at 254 nm. The chiral columns used were Daicel CHIRALPAK AD, Waters Opti-pak TA, Sumika Chemical Analysis SUMICHIRAL OA-3300, OA-2000.

Gas chromatography (GC) was performed with a HITACHI 263-50 Gas Chromatograph.

Melting point were measured on a Bühi 510 melting point apparatus and are not corrected.

Silica gel column chromatography was performed on BW-200 (Fuji Davison) or Silica Gel 60 (Merck), aluminum gel column chromatography was performed on aluminum oxide 90 (Merck).

The solvents were dried before use by distillation from standard drying agents.

Tables

Table 1. Aerobic Oxidative Coupling of 2-Naphthol Derivatives

2a $[Cu(OH)TMEDA]_2Cl_2$ (8.0 mg, 17.3 μmol) was added to the solution of **1a** (496.7 mg, 3.45 mmol) in CH_2Cl_2 (34.4 mL), and the mixture was stirred at 0 ℃ for 20 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 10:1) to afford 471.5 mg (96 %) of **2a**.

2b $[Cu(OH)TMEDA]_2Cl_2$ (2.0 mg, 4.31 μmol) was added to the solution of **1b** (136.2 mg, 861 μmol) in CH_2Cl_2 (8.6 mL), and the mixture was stirred at for 1 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 10:1) to afford 129.7 mg (96 %) of **2b**.

2c $[Cu(OH)TMEDA]_2Cl_2$ (1.0 mg, 2.15 μmol) was added to the solution of **1c** (75.0 mg, 431 μmol) in CH_2Cl_2 (4.3 mL), and the mixture was stirred at room temperature for 2 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 70.8 mg (95 %) of **2c**.

2d $[Cu(OH)TMEDA]_2Cl_2$ (10.0 mg, 21.5 μmol) was added to the solution of **1d** (870.9 mg, 4.31 mmol) in MeOH (43 mL), and the mixture was stirred at 53 ℃ for 90 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-Et_2O, 5:1) to afford 870 mg (99 %) of **2d**.

2e $[Cu(OH)TMEDA]_2Cl_2$ (10.0 mg, 21.5 μmol) was added to the solution of **1e** (83.6 mg, 431 μmol) in CH_2Cl_2 (4.3 mL), and the mixture was stirred for 1.5 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 64.3 mg (77 %) of **2e**.

Table 2. Aerobic Oxidative Coupling of 2-Naphthol Derivatives in Solid State

2a A mixture of $[Cu(OH)TMEDA]_2Cl_2$ (45 mg, 96.9 μmol) and **1a** (558.3 mg, 3.88 mmol) was finely powdered, and heated at 70 ℃ for 24 h under Air. The residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 508.1 mg (92 %) of **2a**.

2b A mixture of $[Cu(OH)TMEDA]_2Cl_2$ (45 mg, 96.9 μmol) and **1b** (613.2 mg, 3.88 mmol) was finely powdered, and heated at 70 ℃ for 24 h under Air. The residue was chromatographed on silicagel column (hexanes-AcOEt, 9:1) to afford 522.0 mg (86 %) of **2b**.

2c A mixture of $[Cu(OH)TMEDA]_2Cl_2$ (2.5 mg, 5.38 μmol) and **1c** (75.0 mg, 431 μmol) was finely powdered, and heated at 70 ℃ for 24 h under Air. The residue was chromatographed on silicagel column (Et_2O-hexanes, 9:1) to afford 47.0 mg (63 %) of **2c** and 27.7 mg (37 %) of **1c**.

2d A mixture of $[Cu(OH)TMEDA]_2Cl_2$ (45.0 mg, 96.9 μmol) and **1d** (783.7 mg, 3.88 μmol) was finely powdered, and heated at 70 ℃ for 24 h under Air. The residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 736.5 mg (93 %) of **2d** and 57.8 mg (7 %) of **1d**.

Table 3. Asymmetric Coupling of 1d with Chiral Diamine-CuCl Complex

Amine 3 To a mixture of CuCl (4.7 mg, 47.4 μmol) and **3** (26.5 mg, 56.06 μmol) was added CH_2Cl_2 (6.0 mL) at room temperature under argon. The CuCl was dissolved, and the

solution became pale blue. After the solution was stirred for 15 min, **1d** (96.0 mg, 475 μmol) in CH_2Cl_2 (6.0 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 20.6 mg (20%) of **1d** and 81.0 mg (80 %) of (*R*)-**2d** in 19% ee.

Amine 4 To a mixture of CuCl (4.4 mg, 44.5 μmol) and **4** (10.4 mg, 56.06 μmol) was added CH_2Cl_2 (5.6 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale yellow-green. After the solution was stirred for 15 min, **1d** (89.9 mg, 446 μmol) in CH_2Cl_2 (5.6 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 73.7 mg (82%) of **1d** and 16.1 mg (18 %) of (*S*)-**2d** in 46% ee.

Table 4. The Effect of Chiral Amine-CuCl Complex on the ee of 2d

Amine 3 To a mixture of CuCl (4.7 mg, 47.4 μmol) and **3** (26.5 mg, 56.06 μmol) was added CH_2Cl_2 (5.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, racemic **2d** (79.7 mg, 198 μmol) in CH_2Cl_2 (4.8 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-AcOEt, 9:1) to afford 80.0 mg (100%) of **2d** in 0% ee.

Amine 4 To a mixture of CuCl (70.9 mg, 716 μmol) and **4** (167.9 mg, 716.2 μmol) was added CH_2Cl_2 (8 mL) at room temperature under argon. The CuCl was dissolved, and the solution became green. After the solution was stirred for 15 min, racemic **2d** (82.5 mg, 410 μmol) in CH_2Cl_2 (9.9 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The mixture was diluted with CH_2Cl_2 (10 mL), and successively washed with aqueous 2N HCl (14 mL × 2) and brine (20 mL × 2). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-AcOEt, 9:1) to afford 111.7 mg (77%) of (*S*)-**2d** in 3% ee.

Table 5. Aerobic Oxidative Coupling of 1b and 1d

run 1 $[Cu(OH)TMEDA]_2Cl_2$ (2.0 mg, 4.31 μmol) was added to the solution of **1b** (136.2 mg, 861 μmol) in CH_2Cl_2 (8.6 mL), and the mixture was stirred at for 1 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 10:1) to afford 129.7 mg (96 %) of **2b**.

run 2 $[Cu(OH)TMEDA]_2Cl_2$ (7.6 mg, 1.64 μmol) was added to the solution of **1d** (66.2 mg, 327 μmol) in CH_2Cl_2 (3.3 mL), and the mixture was stirred at for 1 h under Air. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 3:1) to afford 46.8 mg (71 %) of **2d** and 9.9 mg (15%) of **id**.

Table 6. Aerobic Oxidative Coupling of 1d and 1j

run 1 $[Cu(OH)TMEDA]_2Cl_2$ (7.4 mg, 15.9 μmol) was added to the solution of **1d** (68.9 mg, 319 mmol) in MeOH (8.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 3:1) to afford 69.1 mg (99 %) of **2d**.

run 2 $[Cu(OH)TMEDA]_2Cl_2$ (19.5 mg, 42.0 μmol) was added to the solution of **1j** (146.3 mg, 319 mmol) in MeOH (21.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 4:1) to afford 65.7 mg (45 %) of **1j** and 28.5 mg (20 %) **2j**.

Table 7. Oxidative Coupling of 1d with Copper-Diamine Complex

run 1 To a mixture of CuCl (4.7 mg, 47.4 μmol) and **3** (26.5 mg, 56.06 μmol) was added CH_2Cl_2 (6.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (96.0 mg, 475 μmol) in CH_2Cl_2 (6.0 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 20.6 mg (20%) of **1d** and 81.0 mg (80 %) of (*R*)-**2d** in 19% ee.

run 2 To a mixture of CuCl (6.7 mg, 67.7 μmol) and **5** (35.7 mg, 67.7 μmol) was added CH_2Cl_2 (8.5 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (136.9 mg, 676.8 μmol) in CH_2Cl_2 (8.5 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 55.7 mg (39%) of **1d** and 87.6 mg (61 %) of (*R*)-**2d** in 2% ee.

run 3 To a mixture of CuCl (8.5 mg, 85.7 μmol) and **6** (45.2 mg, 85.7 μmol) was added CH_2Cl_2 (11.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (173.6 mg, 858.7 μmol) in CH_2Cl_2 (11.0 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 166.5 mg (87%) of **1d** and 23.8 mg (13 %) of (*S*)-**2d** in 3% ee.

run 4 To a mixture of CuCl (2.1 mg, 21.2 μmol) and **7** (10.4 mg, 21.4 μmol) was added CH_2Cl_2 (2.7 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale yellow. After the solution was stirred for 15 min, **1d** (42.9 mg, 212.4 μmol) in CH_2Cl_2 (2.7 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 30.0 mg (70%) of **1d** and 9.2 mg (22 %) of (*R*)-**2d** in 7% ee.

run 5 To a mixture of CuCl (8.0 mg, 80.8 μmol) and **8** (54.7 mg, 80.8 μmol) was added CH_2Cl_2 (10.1 mL) at room temperature under argon. The solution became pale yellow but CuCl was still remained. After the solution was stirred for 15 min, **1d** (163.4 mg, 800.2 μmol) in CH_2Cl_2 (10.1 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 138.4 mg (77%) of **1d** and 40.0 mg (13 %) of (*R*)-**2d** in 3% ee.

Table 8. Oxidative Coupling of 1d with Copper-Diamine Complex

run 1 To a mixture of CuCl (4.7 mg, 47.4 μmol) and **3** (26.5 mg, 56.06 μmol) was added CH_2Cl_2 (6.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (96.0 mg, 475 μmol) in CH_2Cl_2 (6.0 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown

solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 20.6 mg (20%) of **1d** and 81.0 mg (80 %) of (*R*)-**2d** in 19% ee.

run 2 To a mixture of CuCl (5.2 mg, 53.23 μmol) and **9** (12.1 mg, 53.92 μmol) was added CH_2Cl_2 (6.6 mL) at room temperature under argon. The CuCl was not dissolved, and the CH_2Cl_2 phase was colorless. After the solution was stirred for 15 min, **1d** (106.2 mg, 525.3 μmol) in CH_2Cl_2 (6.6 mL) was added. The atmosphere was changed from argon to oxygen. The pale yellow solution containing solid was stirred under reflux for 120 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 106 mg (99%).

run 3 To a mixture of CuCl (6.8 mg, 68.7 μmol) and **10** (31.1 mg, 68.7 μmol) was added CH_2Cl_2 (8.6 mL) at room temperature under argon. The CuCl was not dissolved, and the CH_2Cl_2 phase was colorless. After the solution was stirred for 15 min, **1d** (138.9 mg, 687 μmol) in CH_2Cl_2 (8.6 mL) was added. The atmosphere was changed from argon to oxygen. The pale yellow solution containing solid was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 141.0. mg (99%) of **1d**.

run 4 To a mixture of CuCl (7.2 mg, 72.7 μmol) and **11** (34.6 mg, 72.7 μmol) was added CH_2Cl_2 (9.1. mL) at room temperature under argon. The CuCl was not dissolved, and the CH_2Cl_2 phase was colorless. After the solution was stirred for 15 min, **1d** (147.1 mg, 727 μmol) in CH_2Cl_2 (9.1 mL) was added. The atmosphere was changed from argon to oxygen. The pale yellow solution containing solid was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 142.7. mg (97%) of **1d**.

run 4 To a mixture of CuCl (6.0 mg, 60.6 μmol) and **12** (16.3 mg, 60.6 μmol) was added CH_2Cl_2 (7.6 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (122.6 mg, 606 μmol) in CH_2Cl_2 (7.6 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 65.1 mg (53%) of **1d** and 50.0 mg (41 %) of (*S*)-**2d** in 15 ee.

Table 9. Oxidative Coupling of 1d with Copper-Diamine Complex

run 1 To a mixture of CuCl (2.6 mg, 26.7 μmol) and **13** (7.1 mg, 26.5 μmol) was added CH_2Cl_2 (3.3 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (96.0 mg, 475 μmol) in CH_2Cl_2 (3.3 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 29.3 mg (55%) of **1d** and 21.4 mg (41 %) of (*S*)-**2d** in 8% ee.

run 2 To a mixture of CuCl (2.4 mg, 24.2 μmol) and **14** (8.8 mg, 25.3 μmol) was added CH_2Cl_2 (3.1 mL) at room temperature under argon. After the solution was stirred for 15 min, **1d** (49.0 mg, 253 μmol) in CH_2Cl_2 (3.1 mL) was added. The atmosphere was changed from argon to oxygen. The pale yellow solution was stirred under reflux for 96 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 29.3 mg (60%) of **1d** and 0.9 mg (2 %) of (*S*)-**2d** in 7% ee.

run 3 To a mixture of CuCl (6.3 mg, 63.6 μmol) and **15** (22.4 mg, 63.6 μmol) was added CH_2Cl_2 (8.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (128.7 mg, 637 μmol) in CH_2Cl_2 (8.0 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 80.1 mg (62%) of **1d** and 47.8 mg (37 %) of (*S*)-**2d** in 7 ee.

run 4 To a mixture of CuCl (2.9 mg, 29.3 μmol) and **16** (7.0 mg, 29.3 μmol) was added CH_2Cl_2 (3.7 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (59.2 mg, 293 μmol) in CH_2Cl_2 (3.7 mL) was added. The atmosphere was changed from argon to oxygen. The pale yellow solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 46.8 mg (79%) of **1d** and 12.4 mg (21 %) of (*S*)-**2d** in 7 ee.

run 5 To a mixture of CuCl (3.4 mg, 34.4 μmol) and **17** (7.3 mg, 34.4 μmol) was added CH_2Cl_2 (4.3 mL) at room temperature under argon. The solution became purple suspension. After the solution was stirred for 15 min, **1d** (69.5 mg, 344 μmol) in CH_2Cl_2 (4.3 mL) was added. The atmosphere was changed from argon to oxygen. The purple suspension was stirred under reflux for 96 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 69.5 mg (99%) of **1d**.

Table 10. Oxidative Coupling of 1d with Copper-Aminoether or Copper-Diamine Complex

run 1 To a mixture of CuCl (3.1 mg, 31.3 μmol) and **18** (3.6 mg, 31.3 μmol) was added CH_2Cl_2 (3.9 mL) at room temperature under argon. The CuCl was dissolved, and the solution became yellow-green. After the solution was stirred for 15 min, **1d** (63.3 mg, 313 μmol) in CH_2Cl_2 (3.9 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 9.2 mg (15%) of **1d** and 51.4 mg (82 %) of (*S*)-**2d** in 30% ee.

run 2 To a mixture of CuCl (5.7 mg, 57.6 μmol) and **19** (11.1 mg, 58.0 μmol) was added CH_2Cl_2 (7.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (116.4 mg, 576 μmol) in CH_2Cl_2 (7.0 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 86.2 mg (1745%) of **1d** and 30.0 mg (26 %) of (*S*)-**2d** in 17% ee.

run 3 To a mixture of CuCl (3.0 mg, 30.3 μmol) and **20** (6.2 mg, 30.3 μmol) was added CH_2Cl_2 (3.9 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale yellow. After the solution was stirred for 15 min, **1d** (61.3 mg, 303 μmol) in CH_2Cl_2 (3.9 mL) was added. The atmosphere was changed from argon to oxygen. The light yellow solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 44.1 mg (72%) of **1d** and 13.3 mg (22 %) of (*S*)-**2d** in 10% ee.

run 4 To a mixture of CuCl (9.8 mg, 99.0 μmol) and **21** (15.3 mg, 99.0 μmol) was added CH_2Cl_2 (12.4 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (200.2 mg, 990 μmol) in

CH_2Cl_2 (12.4 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 163.0 mg (81%) of **1d** and 36.3 mg (18 %) of (*S*)-**2d** in 36% ee.

run 5 To a mixture of CuCl (10.0 mg, 101.0 μmol) and **22** (15.6 mg, 101.0 μmol) was added CH_2Cl_2 (12.8 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (204.3 mg, 1.01 mmol) in CH_2Cl_2 (12.8 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 175.2 mg (86%) of **1d** and 25.5 mg (13 %) of (*S*)-**2d** in 37% ee.

Table 11. Oxidative Coupling of 1d with Bidendate and Tetradendate- type Aminoether-Copper Complex

run 1 To a mixture of CuCl (5.7 mg, 57.6 μmol) and **19** (11.1 mg, 58.0 μmol) was added CH_2Cl_2 (7.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (116.4 mg, 576 μmol) in CH_2Cl_2 (7.0 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 86.2 mg (74%) of **1d** and 30.0 mg (26 %) of (*S*)-**2d** in 17% ee.

run 2 To a mixture of CuCl (5.5 mg, 55.6 μmol) and **23** (8.5 mg, 27.8 μmol) was added CH_2Cl_2 (7.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became yellow-green. After the solution was stirred for 15 min, **1d** (112.4 mg, 556 μmol) in CH_2Cl_2 (7.0 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 78.2 mg (70%) of **1d** and 22.4 mg (20 %) of (*S*)-**2d** in 24% ee.

run 3 To a mixture of CuCl (3.3 mg, 38.34 μmol) and **24** (5.1 mg, 16.7 μmol) was added CH_2Cl_2 (4.2 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (67.4 mg, 333 μmol) in CH_2Cl_2 (4.2 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 35.8 mg (53%) of **1d** and 30.0 mg (82 %) of (*S*)-**2d** in 12% ee.

run 4 To a mixture of CuCl (11.8 mg, 119.2 μmol) and **25** (19.8 mg, 59.6 μmol) was added CH_2Cl_2 (14.5 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (241.0 mg, 1.19 mmol) in CH_2Cl_2 (14.5 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 133.9 mg (55%) of **1d** and 94.4 mg (39 %) of (*S*)-**2d** in 30% ee.

run 5 To a mixture of CuCl (6.6 mg, 66.7 μmol) and **26** (10.1 mg, 33.4 μmol) was added CH_2Cl_2 (8.4 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (134.8 mg, 667 μmol) in CH_2Cl_2 (8.4 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 83.5 mg (61%) of **1d** and 52.1 mg (39 %) of (*S*)-**2d** in 18% ee.

run 6 To a mixture of CuCl (7.9 mg, 79.8 μmol) and **27** (13.3 mg, 39.9 μmol) was added CH_2Cl_2 (10 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale green. After the solution was stirred for 15 min, **1d** (161.4 mg, 798 μmol) in CH_2Cl_2 (10 mL) was added. The atmosphere was changed from argon to oxygen. The light brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 88.8 mg (55%) of **1d** and 62.8 mg (39 %) of (*S*)-**2d** in 4% ee.

Table 12. Oxidative Coupling of 1d with Copper-Sparteine Complex

run 1 To a mixture of CuCl (4.4 mg, 44.5 μmol) and **4** (10.4 mg, 56.06 μmol) was added CH_2Cl_2 (5.6 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale yellow-green. After the solution was stirred for 15 min, **1d** (89.9 mg, 446 μmol) in CH_2Cl_2 (5.6 mL) was added. The atmosphere was changed from argon to oxygen. The brown solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 73.7 mg (82%) of **1d** and 16.1 mg (18 %) of (*S*)-**2d** in 46% ee.

run 2 To a Copper-sparteine complex (17.0 mg, 24.3 μmol) was added CH_2Cl_2 (6.1 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (98.1 mg, 485 μmol) in CH_2Cl_2 (6.1 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 75.5 mg (75%) of **1d** and 25.5 mg (25 %) of (*S*)-**2d** in 46% ee.

run 3 To a mixture of CuCl (17.1 mg, 173.2 μmol) and **4** (40.6 mg, 173.2 μmol) was added CH_2Cl_2 (21.7 mL) at room temperature under oxygen. The CuCl was dissolved, and the solution became dark green. After the solution was stirred for 15 min, **1d** (350.3 mg, 1.732 mmol) in CH_2Cl_2 (21.7 mL) was added. The dark brown solution was stirred under reflux for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (43 mL × 1), saturated $NaHCO_3$ (40 mL × 2) and brine (40 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 246.3 mg (69%) of **1d** and 109.8 mg (31 %) of (*S*)-**2d** in 46% ee.

Table 13. Oxidative Coupling of 1d with Copper-Sparteine Complex

run 1 To a Copper-sparteine complex (24.7 mg, 70.49 μmol) was added CH_2Cl_2 (8.8 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (142.5 mg, 705 μmol) in CH_2Cl_2 (8.8 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 132.5 mg (93%) of **1d** and 10.0 mg (7 %) of (*S*)-**2d** in 53% ee.

run 2 To a mixture of CuCl (19.0 mg, 191.6 μmol) and **4** (11.9 mg, 191.6 μmol) was added CH_2Cl_2 (24.0 mL) at room temperature under oxygen. The CuCl was dissolved, and the solution became dark green. After the solution was stirred for 15 min, **1d** (387.4 mg, 1.916 mmol) in CH_2Cl_2 (24.0 mL) was added. The dark brown solution was stirred at room temperature for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over

anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 288.9 mg (75%) of **1d** and 87.4 mg (23 %) of (*S*)-**2d** in 52% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1d** (161.8 mg, 800 μmol) in CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 130.0 mg (80%) of **1d** and 30.1 mg (19 %) of (*S*)-**2d** in 55% ee.

Table 14. Oxidative Coupling of 1 with Copper-(–)-Sparteine Complex

1d 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1d** (161.8 mg, 800 μmol) in CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 130.0 mg (80%) of **1d** and 30.1 mg (19 %) of (*S*)-**2d** in 55% ee.

1f 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1f** (173.0 mg, 800 μmol) in CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 137.2 mg (79%) of **1f** and 30.2 mg (18 %) of (*S*)-**2f** in 60% ee.

1g 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1g** (184.2 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 40:1) to afford 158.1 mg (82%) of **1g** and 35.1 mg (18 %) of (*S*)-**2g** in 64% ee.

1h 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1h** (222.6 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The

mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 50:1) to afford 183.9 mg (82%) of **1h** and 40.1 mg (18 %) of (*S*)-**2h** in 64% ee.

1i 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 74% ee.

1d 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1d** (161.8 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 20:1) to afford 128.4 mg (79%) of **1d** and 31.1 mg (19 %) of (*S*)-**2d** in 54% ee.

1f 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1f** (173.0 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 20:1) to afford 135.1 mg (78%) of **1f** and 32.9 mg (19 %) of (*S*)-**2f** in 62% ee.

1g 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1g** (184.2 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 40:1) to afford 139.1 mg (75%) of **1g** and 44.5 mg (18 %) of (*S*)-**2g** in 62% ee.

1h 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the

solution became green. After the solution was stirred for 1 h, **1h** (222.6 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 50:1) to afford 176.9 mg (80%) of **1h** and 45.3 mg (20 %) of (*S*)-**2h** in 67% ee.

1i 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 146.9 mg (75%) of **1i** and 49.4 mg (25 %) of (*S*)-**2i** in 74% ee.

1g 72 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1g** (184.2 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 40:1) to afford 141.0 mg (77%) of **1g** and 35.0 mg (19 %) of (*S*)-**2g** in 60% ee.

1h 72 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1h** (222.6 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 1N H_2SO_4 (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 50:1) to afford 170.4 mg (77%) of **1h** and 51.2 mg (23 %) of (*S*)-**2h** in 64% ee.

1i 72 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 147.1 mg (75%) of **1i** and 46.0 mg (24 %) of (*S*)-**2i** in 75% ee.

Table 15. Oxidative Coupling of 1i with Copper-(–)-Sparteine Complex

CuCl 24 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 74% ee.

CuBr 24 h To a mixture of CuBr (11.5 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 128.2 mg (66%) of **1i** and 60.9 mg (31 %) of (*S*)-**2i** in 70% ee.

CuI 24 h To a mixture of CuI (15.2 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became dark red-brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 158.7 mg (80%) of **1i** and 40.5 mg (20 %) of (*S*)-**2i** in 72% ee.

CuCl 48 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 146.9 mg (75%) of **1i** and 49.4 mg (25 %) of (*S*)-**2i** in 74% ee.

CuBr 48 h To a mixture of CuBr (11.5 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous

$MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 131.6 mg (67%) of **1i** and 59.3 mg (31 %) of (*S*)-**2i** in 70% ee.

CuI 48 h To a mixture of CuI (15.2 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became dark red-brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 147.5 mg (71%) of **1i** and 59.4 mg (29 %) of (*S*)-**2i** in 65% ee.

CuCl 72 h To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 147.1 mg (75%) of **1i** and 46.0 mg (24 %) of (*S*)-**2i** in 75% ee.

CuBr 72 h To a mixture of CuBr (11.5 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 133.0 mg (67%) of **1i** and 65.9 mg (33 %) of (*S*)-**2i** in 71% ee.

CuI 72 h To a mixture of CuI (15.2 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became dark red-brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 153.0 mg (77%) of **1i** and 45.8 mg (23 %) of (*S*)-**2i** in 69% ee.

Table 16. Oxidative Coupling of 1d with Copper-Diamine Complex

run 1 To a mixture of CuCl (4.7 mg, 47.4 μmol) and **3** (26.5 mg, 56.06 μmol) was added CH_2Cl_2 (6.0 mL) at room temperature under argon. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (96.0 mg, 475 μmol) in CH_2Cl_2 (6.0 mL) was added. The atmosphere was changed from argon to oxygen. The reddish brown

solution was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 9:1) to afford 20.6 mg (20%) of **1d** and 81.0 mg (80 %) of (*R*)-**2d** in 19% ee.

run 2 To a mixture of CuI (4.1 mg, 21.5 μmol) and **3** (10.3 mg, 21.79 μmol) was added CH_2Cl_2 (2.8 mL) at room temperature under argon. The CuI was dissolved, and the solution became pale pink suspension. After the solution was stirred for 15 min, **1d** (45.5 mg, 225 μmol) in CH_2Cl_2 (2.8 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-accept, 3:1) to afford 40.2 mg (88%) of **1d** and 4.1 mg (9 %) of (*R*)-**2d** in 18% ee.

run 3 To a mixture of CuI (5.6 mg, 29.4 μmol) and **3** (14.8 mg, 31.3 μmol) was added CH_2Cl_2 (3.7 mL) at room temperature under argon. The CuI was dissolved, and the solution became pale pink suspension. After the solution was stirred for 15 min, **1d** (59.5 mg, 294 μmol) in CH_2Cl_2 (3.7 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred under reflux for 132 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 5:1) to afford 4.5 mg (7%) of **1d** and 55.1 mg (93 %) of (*R*)-**2d** in 19% ee.

run 4 To a mixture of CuI (4.1 mg, 21.5 μmol) and **3** (10.2 mg, 21.5 μmol) was added CH_2Cl_2 (3.5 mL) at room temperature under argon. The CuI was dissolved, and the solution became pale pink suspension. After the solution was stirred under reflux for 1 h, **1d** (45.3 mg, 215 μmol) in CH_2Cl_2 (3.5 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred under reflux for 19 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 3:1) to afford 46.0 mg (99 %) of (*R*)-**2d** in 2% ee.

run 5 To a mixture of CuI (3.0 mg, 15.8 μmol) and **3** (9.2 mg, 19.5 μmol) was added CH_2Cl_2 (2.5 mL) at room temperature under argon. The CuI was dissolved, and the solution became pale blue suspension. After the solution was stirred for 15 min, **1d** (31.9 mg, 158 μmol) in CH_2Cl_2 (2.5 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 5:1) to afford 30 mg (82%) of **1d** and 6.6 mg (18 %) of (*R*)-**2d** in 6% ee.

run 6 To a mixture of CuI (3.3 mg, 17.3 μmol) and **3** (9.2 mg, 19.5 μmol) was added CH_2Cl_2 (2.5 mL) at room temperature under argon. After the solution was stirred for 15 min, **1d** (35.1 mg, 173 μmol) in CH_2Cl_2 (2.5 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 5:1) to afford 0.9 mg (3%) of (*R*)-**2d** in 3% ee.

run 7 To a mixture of CuI (5.0 mg, 50.5 μmol) and **3** (25.5 mg, 53.9 μmol) was added CH_2Cl_2 (6.3 mL) at room temperature under argon. The CuI was dissolved, and the solution became pale blue. After the solution was stirred for 15 min, **1d** (102.1 mg, 505 μmol) in CH_2Cl_2 (6.3 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 4:1) to afford 33.4 mg (33 %) of **1d** and 60.6 mg (60 %) of (*R*)-**2d** in 2% ee.

run 8 To a mixture of CuI (4.1 mg, 21.5 μmol) and **41** (12.9 mg, 21.5 μmol) was added CH_2Cl_2 (3.5 mL) at room temperature under argon. The CuI was partially dissolved, and the

solution became pale yellow. After the solution was stirred under reflux for 3 h, **1d** (43.5 mg, 215 μmol) in CH_2Cl_2 (3.5 mL) was added. The atmosphere was changed from argon to oxygen. The suspension was stirred under reflux for 72 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silicagel column (hexanes-AcOEt, 4:1) to afford 40.1 mg (83 %) of **1d** and 8.0 mg (17 %) of (*R*)-**2d** in 0% ee.

Table 17. Oxidative Coupling of 1i with Copper-(–)-Sparteine Complex in Various Solvents

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added 2,2,2-trifluoroethanol (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became pale blue. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 187.5 mg (95%) of **1i** and 9.2 mg (5 %) of (*S*)-**2i** in 50% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added MeOH (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 124.6 mg (64%) of **1i** and 19.3 mg (9 %) of (*S*)-**2i** in 58% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 74% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, the CH_2Cl_2 was evaporated under reduced pressure. To the residue **1i** (195.4 mg, 800 μmol) and perfuluorohexanes (20.0 mL) was added. The mixture was stirred at 20 ℃ for 24 h., and successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 64% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (5.0 mL) and perfuluorohexanes (10,0 mL) at 20 ℃ under oxygen. The two solvent separated. The CuCl was dissolved, and the upper layer became green, and the lower layer became colorless. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and perfluorohexanes (5.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h.

The mixture was diluted with CH_2Cl_2 (20 mL), and successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 123.5 mg (63%) of **1i** and 73.3 mg (37 %) of (*S*)-**2i** in 73% ee.

Table 18. The Influence of Concentration on the Chemical Yields

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 74% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 146.1 mg (75%) of **1i** and 46.4 mg (24 %) of (*S*)-**2i** in 72% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 130.4 mg (66%) of **1i** and 65.1 mg (34 %) of (*S*)-**2i** in 72% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (5.0 mL) and perfuluorohexanes (10,0 mL) at 20 ℃ under oxygen. The two solvent separated. The CuCl was dissolved, and the upper layer became green, and the lower layer became colorless. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and perfluorohexanes (5.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL), and successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 123.5 mg (63%) of **1i** and 73.3 mg (37 %) of (*S*)-**2i** in 73% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (2.5 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced

pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 101.4 mg (52%) of **1i** and 91.5 mg (47 %) of (*S*)-**2i** in 72% ee.

run 6 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (1.25 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 70.4 mg (35%) of **1i** and 127.8 mg (65 %) of (*S*)-**2i** in 74% ee.

run 7 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (1.25 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 48 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 46.3 mg (23%) of **1i** and 149.2 mg (77 %) of (*S*)-**2i** in 74% ee.

run 8 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (1.25 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 72 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 37.7 mg (19%) of **1i** and 151.6 mg (78 %) of (*S*)-**2i** in 75% ee.

run 9 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (0.94 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 62.6 mg (31%) of **1i** and 135.9 mg (69 %) of (*S*)-**2i** in 71% ee.

run 10 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (0.94 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 48 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 44.5 mg (23%) of **1i** and 147.1 mg (76 %) of (*S*)-**2i** in 73% ee.

run 11 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (0.625 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively

washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 54.1 mg (27%) of **1i** and 145.3 mg (73 %) of (*S*)-**2i** in 68% ee.

run 12 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (0.625 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 48 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 32.6 mg (16%) of **1i** and 167.5 mg (84 %) of (*S*)-**2i** in 68% ee.

Table 19. Oxidative Coupling of 1i with Copper-Diamine Complex

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29a** (18.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became brown. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 164.2 mg (84%) of **1i** and 7.0 mg (4 %) of (*S*)-**2i** in 0% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29b** (25.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 171.0 mg (88%) of **1i** and 23.6 mg (12 %) of (*S*)-**2i** in 56% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29c** (21.4 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column

(hexanes-Et_2O, 100:1) to afford 104.0 mg (52%) of **1i** and 95.7 mg (48 %) of (*S*)-**2i** in 55% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29d** (17.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 93.6 mg (45%) of **1i** and 93.6 mg (55 %) of (*S*)-**2i** in 57% ee.

run 6 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29e** (16.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 106.5 mg (54%) of **1i** and 46.4 mg (46 %) of (*S*)-**2i** in 53% ee.

run 7 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29f** (18.7 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 173.0 mg (83%) of **1i** and 34.5 mg (17 %) of (*S*)-**2i** in 66% ee.

run 8 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **30a** (17.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 116.6 mg (58%) of **1i** and 83.2 mg (42 %) of (*S*)-**2i** in 61% ee.

run 9 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **30b** (16.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 136.0 mg (69%) of **1i** and 61.6 mg (31 %) of (*S*)-**2i** in 61% ee.

run 10 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **31** (15.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2

(10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 176.3 mg (90%) of **1i** and 13.9 mg (7 %) of (*S*)-**2i** in 60% ee.

run 11 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **33** (11.2 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 181.3 mg (93%) of **1i** and 12.4 mg (7 %) of (*S*)-**2i** in 20% ee.

Table 20. Oxidative Coupling of 1i with Copper-Diamine Complex

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **4** (18.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 162.7 mg (82%) of **1i** and 36 mg (18 %) of (*S*)-**2i** in 74% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 48 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 4 $[Cu(OH)TMEDA]_2Cl_2$ (18.6 mg, 40 μmol) was added to the solution of **1i** (195.4 mg, 800 μmol) in CH_2Cl_2 (20 mL). The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was 43 on silicagel column (hexanes-Et_2O, 100:1) to afford 111.6 mg (57%) of **1i** and 83.6 mg (55 %) of (*S*)-**2i** in

53% ee.

Table 21. Oxidative Coupling of 1i with Copper-Diamine Complex

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29f** (18.7 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 173.0 mg (83%) of **1i** and 34.5 mg (17 %) of (*S*)-**2i** in 66% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29b** (25.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 171.0 mg (88%) of **1i** and 23.6 mg (12 %) of (*S*)-**2i** in 56% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29d** (17.8 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 93.6 mg (45%) of **1i** and 93.6 mg (55 %) of (*S*)-**2i** in 57% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **29e** (16.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 106.5 mg (54%) of **1i** and 46.4 mg (46 %) of (*S*)-**2i** in 53% ee.

run 6 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **30a** (17.8 mg, 80 μmol)

was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 116.6 mg (58%) of **1i** and 83.2 mg (42 %) of (*S*)-**2i** in 61% ee.

run 7 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **30b** (16.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 136.0 mg (69%) of **1i** and 61.6 mg (31 %) of (*S*)-**2i** in 61% ee.

run 8 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **31** (15.5 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 176.3 mg (90%) of **1i** and 13.9 mg (7 %) of (*S*)-**2i** in 60% ee.

run 9 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **32** (16.2 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 141.0 mg (67%) of **1i** and 69.3 mg (33 %) of (*S*)-**2i** in 60% ee.

run 10 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **33** (11.2 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 181.3 mg (93%) of **1i** and 12.4 mg (7 %) of (*S*)-**2i** in 20% ee.

run 11 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **34** (19.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL

× 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 133.3 mg (65%) of **1i** and 70.8 mg (35 %) of (*S*)-**2i** in 55% ee.

run 12 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **35** (18.3 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 174.8 mg (90%) of **1i** and 17.8 mg (9 %) of (*S*)-**2i** in 20% ee.

Table 22. Oxidative Coupling of 1i with Copper-Diamine Complex

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **36a** (16.3 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 164.4 mg (84%) of **1i** and 30.9 mg (16 %) of (*S*)-**2i** in 53% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **36b** (26.0 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 121.7 mg (58%) of **1i** and 89.6 mg (42 %) of (*S*)-**2i** in 41% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **37** (16.2 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 2 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 161.7 mg (83%) of **1i** and 29.4 mg (15 %) of (*S*)-**2i** in 29% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **38a** (26.0 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) under oxygen. The mixture was sonicated at 0 ℃ for 3 h to give a green suspension. After the suspension was stirred for 15 min at 20 ℃, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark green suspension was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 125.0 mg (62%) of **1i** and 75.0 mg (38 %) of (*S*)-**2i** in 78% ee.

run 6 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **38b** (26.4 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 2 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 154.1 mg (76%) of **1i** and 48.0 mg (24 %) of (*S*)-**2i** in 74% ee.

run 7 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **39** (16.2 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 163.8 mg (80%) of **1i** and 42.2 mg (20 %) of (*R*)-**2i** in 4% ee.

run 8 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **40** (20.0 mg, 80 μmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 111.5 mg (55%) of **1i** and 91.8 mg (45 %) of (*R*)-**2i** in 0% ee.

Table 23. Oxidative Coupling of 1i with Copper-Diamine Complex

run 1 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (20.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (20.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 119.7 mg (59%) of **1i** and 81.9 mg (41 %) of (*S*)-**2i** in 51% ee.

run 2 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol)

was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 94.5 mg (45%) of **1i** and 113.6 mg (55 %) of (*S*)-**2i** in 53% ee.

run 3 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (1.25 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 108.0 mg (55%) of **1i** and 89.6 mg (45 %) of (*S*)-**2i** in 62% ee.

run 4 To a mixture of CuCl (7.9 mg, 80 μmol), H_2O (1.4 μL) and **28** (15.1 mg, 80 μmol) was added CH_2Cl_2 (0.625 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 μmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 117.9 mg (60%) of **1i** and 78.6 mg (40 %) of (*S*)-**2i** in 62% ee.

run 5 To a mixture of CuCl (7.9 mg, 80 mmol), H_2O (1.4 mL) and **29d** (17.8 mg, 80 mmol) was added CH_2Cl_2 (10.0 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 mmol) and CH_2Cl_2 (10.0 mL) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 93.6 mg (45%) of **1i** and 93.6 mg (55 %) of (*S*)-**2i** in 57% ee.

run 6 To a mixture of CuCl (7.9 mg, 80 mmol), H_2O (1.4 mL) and **29d** (17.8 mg, 80 mmol) was added CH_2Cl_2 (1.25 mL) at 20 ℃ under oxygen. The CuCl was dissolved, and the solution became green. After the solution was stirred for 1 h, **1i** (195.4 mg, 800 mmol) was added. The dark brown solution was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 111.1 mg (53%) of **1i** and 97.6 mg (47 %) of (*S*)-**2i** in 61% ee.

run 7 To a mixture of CuCl (7.9 mg, 80 mmol), H_2O (1.4 mL) and **38a** (26.0 mg, 80 mmol) was added CH_2Cl_2 (10.0 mL) under oxygen. The mixture was sonicated at 0 ℃ for 3 h to give a green suspension. After the suspension was stirred for 15 min at 20 ℃, **1i** (195.4 mg, 800 mmol) and CH_2Cl_2 (10.0 mL) was added. The dark green suspension was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was

chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 125.0 mg (62%) of **1i** and 75.0 mg (38 %) of (*S*)-**2i** in 78% ee.

run 8 To a mixture of CuCl (7.9 mg, 80 mmol), H_2O (1.4 mL) and **38a** (26.0 mg, 80 mmol) was added CH_2Cl_2 (1.25 mL) under oxygen. The mixture was sonicated at 0 ℃ for 1 h to give a green suspension. After the suspension was stirred for 15 min at 20 ℃, **1i** (195.4 mg, 800 mmol) was added. The dark green suspension was stirred at 20 ℃ for 24 h. The mixture was successively washed with aqueous 0.05N EDTA-2Na (50 mL × 1), saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL × 1). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 100:1) to afford 171.2 mg (88%) of **1i** and 20.9 mg (11 %) of (*S*)-**2i** in 78% ee.

Table 24. Oxidative Coupling of 1d with Copper-Diamine Complex

run 1 To a Copper-sparteine complex (17.0 mg, 24.3 μmol) was added CH_2Cl_2 (6.1 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (98.1 mg, 485 μmol) in CH_2Cl_2 (6.1 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 75.5 mg (75%) of **1d** and 25.5 mg (25 %) of (*S*)-**2d** in 46% ee.

run 2 To a $CuCl_2$-sparteine complex (17.0 mg, 24.3 μmol) was added CH_2Cl_2 (6.1 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (98.1 mg, 485 μmol) in CH_2Cl_2 (6.1 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 98.6 mg (100%) of **1d**.

run 3 To a $Cu(OH)_2$-sparteine complex (17.0 mg, 24.3 μmol) was added CH_2Cl_2 (6.1 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (98.1 mg, 485 μmol) in CH_2Cl_2 (6.1 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 94.8 mg (97%) of **1d** and 2.9 mg (3 %) of (*S*)-**2d** in 16% ee.

run 4 To a mixture of $CuCl_2$-sparteine complex (8.5 mg, 12.13 μmol) and $Cu(OH)_2$-sparteine complex (8.5 mg, 12.13 μmol) was added CH_2Cl_2 (6.1 mL) at room temperature under argon. The solution became pale green suspension. After the solution was stirred for 15 min, **1d** (98.1 mg, 485 μmol) in CH_2Cl_2 (6.1 mL) was added. The atmosphere was changed from argon to oxygen. The brown suspension was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silicagel column (hexanes-Et_2O, 10:1) to afford 94.8 mg (97%) of **1d** and 2.9 mg (3 %) of (*S*)-**2d** in 16% ee.

Table 25. Oxidative Coupling of 1d in Various Solvents

run 1 $[Cu(OH)TMEDA]_2Cl_2$ (7.4 mg, 15.9 μmol) was added to the solution of **1d** (68.9 mg, 319 μmol) in MeOH (8.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-AcOEt, 3:1) to afford 69.1 mg (99 %) of **2d**.

run 2 $[Cu(OH)TMEDA]_2Cl_2$ (7.4 mg, 15.9 μmol) was added to the solution of **1d** (68.9 mg, 319 μmol) in EtOH (8.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes- Et_2O, 10:1) to afford 67.6 mg (99 %) of **2f**.

run 3 $[Cu(OH)TMEDA]_2Cl_2$ (7.4 mg, 15.9 μmol) was added to the solution of **1d** (68.9 mg, 319 μmol) in 2-propanol (8.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes- Et_2O, 10:1) to afford 72.9 mg (99 %) of **2g**.

run 4 $[Cu(OH)TMEDA]_2Cl_2$ (7.4 mg, 15.9 μmol) was added to the solution of **1d** (68.9 mg, 319 μmol) in 2-methyl-2-propanol (8.0 mL), and the mixture was stirred under reflux for 24 under O_2. The solvent was evaporated under reduced pressure. The residue was chromatographed on silicagel column (hexanes-Et_2O, 3:1) to afford 68.9 mg (99 %) of **2d**.

Synthesis of Naphthol Derivatives

Scheme 43.

(1b-1) Under argon atmosphere, a solution of **1d** (2.02 g, 9.99 mmol) in THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (0.57 g, 15.02 mmol) in THF (100 mL) at room temperature, and the mixture was stirred for 1 h. H_2O (0.57 mL) was cautiously added, followed by aqueous 15% NaOH (0.57 mL) and H_2O (1.71 mL). The solid material was removed by filtration, and washed with THF. The filtrate and the washing were combined and concentrated under reduced pressure. The residue was chromatographed on silicagel column ($CHCl_3$-MeOH, 10:1) to afford **1b-1** as pale yellow solid (1.65 g, 95%), which was recrystallized from AcOEt to give color less plates (1.42 g): mp 191-192 ℃; IR (KBr) 3440, 3360, 1630, 1240, 1160, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, 1 H *J*=8.6 Hz), 7.70 (d, 1 H *J* = 8.9 Hz), 7.58 (s, 1 H), 7.32 (t, 1 H *J*=8.3 Hz), 7.17 (s, 1 H), 5.03 (d, 2 H *J*=5.9 Hz), 2.27 (m, 1 H), 2.79-2.71 (m, 1 H), 3.20-3.13 (m, 1 H), 2.52-2.42 (m, 2 H)), 1.97-1.74 (m, 1 H), 1.54-1.44 (t, 1 H *J*=5.9 Hz); EIMS, m/z 174 (M^+).

(1b) 1b-1 (332.3 mg, 1.91 mmol) was dissolved in EtOH (30 mL) and hydrogenated in the presence of 10 % Pd-C (30 mg). After 24 h, the catalyst was filtered off through a pad of celite, and the catalyst was washed with EtOH. The filtrate and the washing were combined and concentrated under reduced pressure to afford **1b** as color less solid (291.4 mg, 97%). The solid was recrystallized from hexanes to give color less plates (205.8 mg): mp 155-156 ℃; IR (KBr) 3530, 1630, 1510, 1090, 870, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, 1 H *J*=7.9 Hz), 7.64 (d, 1 H *J* = 8.3 Hz), 7.59 (s, 1 H), 7.39-7.29 (m, 2 H), 7.10 (s, 1 H), 4.94 (s, 1 H), 2.43 (s, 3 H); EIMS, m/z 158 (M^+).

Scheme 44.

(1f) A mixture of **1d** (2.00 g, 9.89 mmol) and H_2SO_4 (1.0 mL) in EtOH (80 mL) was stirred under reflux (Dean Stark trap, molecular sieves 3A) for 48 h. The reaction mixture was concentrated (~20 mL), diluted with Et_2O (50 mL), and successively washed with saturated aqueous $NaHCO_3$ (100 mL × 3), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to afford yellow oil. The oil was purified by Kugelrohr distillation (280 ℃, 0.25 Torr) to give 2.09 g (98%) of colorless oil, which crystallized on standing. The solid was recrystallized (pentane/Et_2O = 5/1) to give pale yellow cubes: IR (neat) 1670, 1510, 1280, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.51 (s, 1 H), 8.50 (s, 1 H), 7.81 (d, 1 H *J* = 8.3 Hz), 7.68 (d, 1 H *J*=8.6 Hz), 7.49 (t, 1 H *J* = 7.6 Hz), 7.35-7.29 (m 1 H), 7.31 (s, 1 H), 4.49 (q, 2 H *J*=7.1 Hz), 1.48 (t, 3 H *J*=7.1 Hz); EIMS, m/z 216 (M^+).

Scheme 45.

(1g) $SOCl_2$ (5.5 mL, 75.0 mmol) was added dropwise to a mixture of 3-hydroxy-2-naphthoic acid (4.71 g, 25.0 mmol) and DMF (0.15 mL) in benzene (80 mL) under anhydrous condition ($CaCl_2$ tube), and the mixture was stirred at 40 ℃ for 3 h. The mixture became clear, and was concentrated under reduced pressure to give orange solid. The solid was dissolved in THF (30 mL), and the solution was added dropwise to 2-propanol (150 mL) at 0℃ After the addition was complete, the mixture was stirred for 2 h at room temperature. The mixture was concentrated, and the residue was diluted with Et_2O (200 mL). The solution was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to afford yellow oil. The oil was chromatographed on silicagel column (hexanes-Et_2O, 15:1) to afford **1g** as pale yellow oil (3.57 g, 62%), which crystallized on standing. The solid was recrystallized from pentane to give pale yellow cubes: IR (neat) 3220, 2970, 1670, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.60 (s, 1 H), 8.47 (s, 1 H), 7.81 (d, 1 H *J* = 7.3 Hz), 7.68 (d, 1 H *J*=8.2 Hz), 7.48 (td, 1 H *J* = 76., 1.3 Hz), 7.34-7.28 (m, 1 H), 7.30 (s, 1 H), 2.79-2.71 (m, 1 H), 3.20-3.13 (m, 1 H), 2.52-2.42 (m, 2 H)), 1.97-1.74 (m, 1 H), 5.36 (sept, 1 H *J*=6.3 Hz), 1.46 (d, 6H *J*=6.3 Hz); EIMS, m/z 230 (M^+).

Scheme 46.

(1h) $SOCl_2$ (17.0 mL, 233.31 mmol) was added dropwise to a mixture of 3-hydroxy-2-naphthoic acid (14.63 g, 77.80 mmol) and DMF (0.30 mL) in benzene (150 mL) under anhydrous condition ($CaCl_2$ tube), and the mixture was stirred at 40 ℃ for 3 h. The mixture became clear, and was concentrated under reduced pressure to give orange solid, and the solid was dissolved in THF (150 mL). Benzyl alcohol (25.23 g, 233.31 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 233.31 mmol) at room temperature. After being sired for 15 min, the mixture was cooled to -78 ℃. To this mixture, the THF solution of acid chloride was added dropwise over 4 h, and the mixture was allowed to room temperature, stirred for 24 h. The mixture was poured into H_2O (400 mL) solution of KH_2PO_4 (21.18 g, 155.6 mmol), and the whole was extracted with Et_2O (200 mL × 2). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 3) and brine (200 mL), and the extracts was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to afford yellow oil. The oil was chromatographed on silicagel column (hexanes-Et_2O, 200:1) to afford **1h** as yellow solid (12.37 g, 57%). The solid was recrystallized from hexanes to give pale yellow prisms: IR (KBr) 3420, 3350, 1670, 1280, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.43 (s, 1 H), 7.77 (d, 1 H J = 8.3 Hz), 7.66 (d, 1 H J = 8.6 Hz), 7.66-7.36 (m, 6 H), 7.30 (s, 1 H), 7.32-7.27 (m, 1 H), 5.44 (s, 2 H); ^{13}C NMR ($CDCl_3$) 169.67, 156.35, 137.93, 135.17, 132.47, 129.20, 129.16, 128.75, 128.66, 128.45, 126.99, 126.27, 123.92, 114.14, 111.70, 67.33; EIMS, m/z 278 (M^+).

Scheme 47.

(1i) $SOCl_2$ (17.0 mL, 233.31 mmol) was added dropwise to a mixture of 3-hydroxy-2-naphthoic acid (14.63 g, 77.80 mmol) and DMF (0.30 mL) in benzene (150 mL) under anhydrous condition ($CaCl_2$ tube), and the mixture was stirred at 40 ℃ for 3 h. The mixture became clear, and was concentrated under reduced pressure to give orange solid, and the solid was dissolved in THF (150 mL). This solution was added dropwise to a mixture of KO*t*-Bu (26.18 g, 233.31 mmol) and 18-Crown-6 (100 mg) in Et_2O (200 mL) at -78 ℃ over 5h. And the mixture was allowed to room temperature, stirred for 48 h. The mixture was poured into H_2O (500 mL) solution of KH_2PO_4 (21.18 g, 155.6 mmol), and the whole was extracted with Et_2O (200 mL × 2). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 5) and brine (200 mL), and the extracts was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to afford yellow oil. The oil was chromatographed on silicagel column (hexanes-Et_2O, 300:1) to afford **1i** as yellow solid (14.42 g, 76%), which crystallized on standing. The solid was recrystallized from pentane to give pale yellow prisms: ^1H NMR ($CDCl_3$) δ 10.71 (s, 1 H), 8.39 (s, 1 H), 7.79 (d, 1 H J = 8.3 Hz), 7.67 (d, 1 H J=8.3 Hz), 7.47 (td, 1 H J = 6.9, 1.3 Hz), 7.32-7.29 (m, 1 H), 7.28 (s 1 H), 1.67 (s, 9 H); EIMS, m/z 244 (M^+).

Synthesis of Chiral Ligands

Scheme 51.

6 A mixture of **6-1** (2.41 g, 4.38 mmol), (*S*, *S*)-1,2-cyclohexanediamine (250 mg, 2.18 mmol) and K_2CO_3 (0.61 g, 4.38 mmol) in toluene was stirred under reflux for 3d. The mixture was diluted with Et_2O (100 mL), and successively washed with H_2O (40 mL × 2) and brine (40 mL), and the organic layer was dried over anhydrous K_2CO_3, filtered, and the filtrate was evaporated to afford pale yellow gum, which was chromatographed on silicagel column ($CHCl_3$-MeOH, 30:1) to afford **6** as colorless amorphous (780 mg, 68%): $[a]^{27}_D$ -48.1° (c 0.92, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.39-7.10 (m, 20 H), 3.40-3.20 (m, 8 H), 3.00-2.86 (m, 4 H), 2.57-2.49 (m, 2 H), 2.15-2.00 (m, 2 H), 1.86-1.72 (m, 2 H), 1.66-1.52 (m, 2 H), 1.49-1.32 (m, 2 H); EIMS, m/z 526 (M^+). Treating with picric acid gave **6**-picrate, which was recrystallized from AcOEt to give orange plates: Anal. Calcd for $C_{38}H_{42}N_2 \cdot C_6H_3N_3O_7$: C, 69.92; H, 6.00; N, 9.27. Found: C, 69.78; H, 6.06; N, 9.24.

Scheme 52.

16-1 Methanesulfonylchloride (12.18 g, 106.33 mmol) was added to a mixture of ethylene glycol (3.00 g, 48.33 mmol) and NEt_3 (11.74 g, 116.00 mmol) in CH_2Cl_2 at 0 ℃. The mixture was stirred for 2 h at room temperature and poured into H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic layer was successively washed with aqueous 2% HCl (100 mL), H_2O (100 mL × 2), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to afford pale yellow oil (8.91 g, 85%), which solidified on standing. The solid was recrystallized (hexanes-AcOEt) to give colorless prisms: IR (KBr) 3020, 1350, 1310, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.84 (s, 4 H), 3.07 (s, 6 H); EIMS, m/z 217 (M^+-1), 219 (M^++1).

Scheme 53.

(*S*)-2-Pyrrolidine methanol Prepared from (*S*)-proline according to the method given in the literature. Colorless oil, c.y. 74%: $[a]^{23}_D$ +32.2° (c 1.074, toluene).
Aldrich $[a]^{20}_D$ +31° (c 1, toluene).

Scheme 53.

(*S*)-2-Hydroxymethyl-1-pyrrolidinecarbaldehyde Prepared from (*S*)-2-Pyrrolidine methanol according to the method given in the literature. Pale yellow oil, c.y. 83%: $[a]^{25}_D$ -30.3° (c 2.118, benzene).
lit.[34] $[a]_D$ -18° (c 2, benzene).

Scheme 53.

(*S*)-2-Methoxymethyl-1-pyrrolidinecarbaldehyde Prepared from (*S*)-2-Hydroxymethyl-1-pyrrolidinecarbaldehyde according to the method given in the literature. Pale yellow oil, c.y. 83%: $[a]^{25}_D$ -34.4° (c 2.00, benzene).
lit.[34] $[a]_D$ -43.5° (c 2, benzene), Aldrich $[a]^{20}_D$ -34° (c 2, toluene).

Scheme 53.

(*S*)-2-Methoxymethylpyrrolidine (18) Prepared from (*S*)-2- Methoxymethyl-1-pyrrolidinecarbaldehyde according to the method given in the literature. Colorless oil, c.y. 64%: $[a]^{25}_D$ +2.2° (c 2.00, benzene).
Aldrich $[a]^{20}_D$ +2.5° (c 2, benzene).

Scheme 54.

(19-1) Under argon atmosphere, **18** (3.23 g, 25.0 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (60% oil dispersion, washed with hexanes, 1.10 g, 27.5 mmol) in THF (30 mL) at 0 ℃, and the mixture was stirred for 5 min. Benzylbromide (6.41 g, 37.5 mmol) was added dropwise to the mixture and the whole was stirred at room temperature for 24 h. Triethylamine (3 mL) was added and the whole was stirred under reflux for 3 h, cooled, and insoluble material was filterd off. The filtrate was concentrated under reduced pressure, and the residure was chromatographed on silicagel column ($CHCl_3$-MeOH, 30:1) to afford **19-1** as

colorless oil (5.1 g, quant): ^{1}H NMR ($CDCl_3$) δ 8.34, 8.26 (s, 1 H), 7.37-7.26 (m, 5 H), 4.53 (s, 2 H), 4.12, 4.05-3.96 (m, 1 H), 3.70-3.74 (m, 4 H), 2.08-1.69 (m, 4 H); EIMS, m/z 220 (M^++1).

Scheme 54.

(19) The mixture of **19-1** (1.00 g, 4.92 mmol) and 20% aqueous KOH (20 mL) was stirred under reflux for 2 h, cooled, and extracted with Et_2O (50 mL × 3). The extract was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless oil. The oil was purified by Kugelrohr distillation (200 ℃, 0.5 Torr) to give 850 mg (90%) of colorless oil.

Scheme 55.

(20) Under argon atmosphere, a solution of **19-1** (1.00 g, 4.56 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.19 g, 4.92 mmol) in THF (20 mL) at room temperature, and the mixture was stirred for 1.5 h. H_2O (0.19 mL) was cautiously added, followed by aqueous 15% NaOH (0.19 mL) and H_2O (0.57 mL). The solid material was removed by filtration, and washed with THF. The filtrate and the washing were combined and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (250 ℃, 0.35 Torr) to give 780 mg (83%) of colorless oil: $[a]^{25}_D$ -30.8° (c 1.05, MeOH); IR (neat) 2930, 1450, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35-7.26 (m, 5 H), 4.54 (s, 2 H), 3.47 (dd, 1 H J = 28.2, 5.3 Hz), 3.46 (dd, 1 H J=28.2, 5.6 Hz), 3.08-3.02 (m, 1 H), 2.41 (s, 3 H), 2.27-2.16 (m, 2 H), 1.96-1.59 (m, 4 H); EIMS, m/z 205 (M^+).

Scheme 56.

(23-1) Under argon atmosphere, (*S*)-2-Hydroxymethyl-1-pyrrolidinecarbaldehyde (2.00 g, 15.48 mmol) in THF (40 mL) was added dropwise to a suspension of NaH (60% oil dispersion, washed with hexanes, 0.68 g, 17.03 mmol) in THF (20 mL) at 0 ℃, and the mixture was stirred for 10 min. *p*-Xylylenedilbromide (2.02 g, 7.74 mmol) in THF (20 mL) was added dropwise to the mixture and the whole was stirred at room temperature for 24 h. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silicagel column ($CHCl_3$-MeOH, 70:1) to afford **23-1** as colorless oil (2.92 g, quant): $[a]^{23}_D$ -28.6° (c 1.084, MeOH); IR (neat) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.37, 8.26 (2 H), 7.29 (s, 4 H), 4.52 (s, 4 H), 4.21, 4.02 (m, 2 H), 3.69-3.33 (m, 8 H), 2.09-1.71 (m, 8 H); ^{13}C NMR ($CDCl_3$) 161.92, 161.08, 137.99, 137.25, 136.93, 127.69, 127.58, 127.51, 73.10, 73.05, 72.89, 72.81, 70.03, 56.86, 54.68, 49.96, 43.60, 27.91, 27.84, 27.77, 23.85, 22.73; EIMS, m/z 360 (M^+).

Scheme 56.

(23) The mixture of **23-1** (2.23 g, 6.19 mmol) and 20% aqueous KOH (30 mL) was stirred under reflux for 1.5 h, cooled, and extracted with Et_2O (50 mL × 3). The extract was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless oil. The oil was purified by Kugelrohr distillation (320 ℃, 0.2 Torr) to give 1.05 g (56%) of colorless solid: mp 35-40 ℃; $[a]^{23}_D$ +5.3° (c 1.122, MeOH); IR (KBr) 2940, 2850, 1400, 1100, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 4 H), 4.53 (s, 4 H), 3.48-3.27, 3.02-2.81 (m, 10 H), 1.91 (s, 2 H), 1.71-1.67 (m, 6 H), 1.47-1.38 (m, 2 H); ^{13}C NMR ($CDCl_3$) 137.79, 127.73, 73.84, 72.99, 57.90, 46.47, 27.91, 25.20; EIMS, m/z 305 (M^++1); Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.22; H, 9.32; N, 9.33.

Scheme 57.

(24-1) Under argon atmosphere, (*S*)-2-Hydroxymethyl-1-pyrrolidinecarbaldehyde (2.50 g, 19.36 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60% oil dispersion, washed with hexanes, 0.83 g, 21.29 mmol) in THF (10 mL) at 0 ℃, and the mixture was stirred for 20 min. *m*-Xylylenedilbromide (2.55 g, 9.68 mmol) in THF (20 mL) was added dropwise to the mixture and the whole was stirred at room temperature for 48 h. The mixture was poured into H_2O (70 mL), and the whole was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was washed with brine (200 mL), and the extracts was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to afford yellow oil. The oil was chromatographed on silicagel column

(AcOEt, then $CHCl_3$-MeOH 200:1) to afford **24-1** as yellow oil (3.20 g, 92%): $[a]^{23}_{D}$ -27.5° (c 3.228, MeOH); IR (neat) 2860, 1660, 1380, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38, 8.26 (2 H), 7.33-7.24 (m, 4 H), 4.53 (s, 4 H), 4.25-4.17, 4.07-3.96 (m, 2 H), 3.67-3.33 (m, 8 H), 2.09-1.72 (m, 8 H); ^{13}C NMR ($CDCl_3$) 161.90, 161.06, 138.58, 137.93, 137.74, 128.63, 128.52, 126.92, 126.74, 126.65, 126.58, 73.23, 73.14, 72.87, 72.81, 70.06, 56.82, 54.63, 46.90, 43.56, 27.91, 27.73; EIMS, m/z 360 (M^+).

Scheme 57.

(24) The mixture of **24-1** (1.45 g, 4.02 mmol) and KOH (85%, 2.66 g, 10.23 mmol) in 85% aqueous MeOH (35 mL) was stirred under reflux for 3 h, cooled, and evaporated to 5 mL. The residue was diluted with H_2O, and extracted with Et_2O (50 mL × 3). The extract was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless oil. The oil was purified by Kugelrohr distillation to give 1.15 g (94%) of colorless oil: $[a]^{23}_{D}$ +6.9° (c 2.774, MeOH); IR (neat) 3280, 2950, 2850, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.27 (m, 4 H), 4.53 (s, 4 H), 3.49-3.28, 3.01-2.85 (m, 4 H), 1.99 (s, 2 H), 1.81-1.73, 1.47-1.41 (m, 8 H); ^{13}C NMR ($CDCl_3$) 137.40, 128.21, 127.04, 126.67, 73.75, 72.94, 57.68, 46.27, 27.74, 25.02; EIMS, m/z 305 (M^++1); HRMS calcd for $C_{18}H_{28}N_2O_2$: 304.2151, found 304.2137.

Scheme 57.

(25) Under argon atmosphere, a solution of **24-1** (1.21 g, 3.36 mmol) in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (382 mg, 10.07 mmol) in THF (15 mL) at room temperature, and the mixture was stirred under reflux for 19 h. H_2O (0.38 mL) was cautiously added, followed by aqueous 15% NaOH (0.38 mL) and H_2O (1.14 mL). The solid material was removed by filtration, and washed with THF. The filtrate and the washing were combined and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (250 ℃, 0.2 Torr) to give colorless oil: $[a]^{25}_{D}$ +38.6° (c 2.764, MeOH); IR (neat) 2940, 2760, 1450, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.24 (m, 4 H), 4.53 (s, 4 H), 3.50 (dd, 2 H J=9.2, 5.6 Hz), 3.40 (dd, 2 H J=9.2, 5.6 Hz), 3.05 (m, 2 H), 2.41 (s, 6 H), 2.41-2.16 (m, 4 H), 1.96-1.63 (m, 8 H); ^{13}C NMR ($CDCl_3$) 138.49, 128.23, 126.77, 126.69, 73.42, 73.17, 57.68, 41.51, 27.65, 22.66, 54.75; EIMS, m/z 332 (M^+); HRMS calcd for $C_{20}H_{32}N_2O_2$: 332.2464, found 332.2464.

Scheme 58.

(26-1) Under argon atmosphere, (*S*)-2-Hydroxymethyl-1-pyrrolidinecarbaldehyde (2.50 g, 19.36 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60% oil dispersion, washed with hexanes, 0.85 g, 21.29 mmol) in THF (10 mL) at 0 ℃, and the mixture was stirred for 20 min. *o*-Xylylenedilbromide (2.55 g, 9.68 mmol) in THF (20 mL) was added dropwise to the mixture and the whole was stirred at room temperature for 24 h. The mixture was poured into H_2O (50 mL), and the whole was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was washed with brine (200 mL), and the extracts was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to afford yellow oil. The oil was chromatographed on silicagel column (AcOEt, then $CHCl_3$-MeOH 30:1) to afford **26-1** as yellow oil (2.73 g, 78%): $[a]^{24}_{D}$ -32.7° (c 2.17, MeOH); IR (neat) 2860, 1660, 1380, cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.36, 8.26 (2 H), 7.37-7.28 (m, 4 H), 4.58-3.97 (m, 4 H), 4.02-3.97 (m, 2 H), 3.70-3.33 (m, 8 H), 2.12-1.71 (m, 8 H); ^{13}C NMR ($CDCl_3$) 161.87, 161.08, 136.15, 135.76, 135.65, 128.72, 128.06, 128.37, 128.01, 127.84, 127.64, 72.99, 70.94, 70.84, 70.78, 70.19, 56.86, 54.66, 46.92, 43.58, 28.02, 27.78, 27.75, 23.81, 22.77; EIMS, m/z 360 (M^+).

Scheme 58.

(26) The mixture of **26-1** (2.15 g, 5.96 mmol) and 20% aqueous KOH (25 mL) was stirred under reflux for 4 h, cooled, and extracted with Et_2O (50 mL × 3). The extract was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless oil. The oil was purified by Kugelrohr distillation to give 1.62 g (90%) of colorless oil: $[a]^{24}_{D}$ +3.8° (c 1.610, MeOH); IR (neat) 3300, 2950, 2800, 1660, 1090, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.36 (m, 2 H), 7.31-7.26 (m, 2 H), 4.60 (s, 4 H), 3.50-3.24 (m, 6 H), 3.02-2.81 (m, 4 H), 2.08-2.18 (s, 2 H), 1.89-1.67, 1.48-1.38 (m, 8 H); ^{13}C NMR ($CDCl_3$) 136.42, 128.64, 127.64, 73.93, 70.78, 57.86,

46.40, 27.91, 25.12; EIMS, m/z 305 (M^++1); HRMS calcd for $C_{18}H_{28}N_2O_2$, 304.2151, found 304.2129.

Scheme 58.

(27) Under argon atmosphere, a solution of **26-1** (1.087 g, 3.02 mmol) in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (343 mg, 9.05 mmol) in THF (10 mL) at room temperature, and the mixture was stirred for 24 h. H_2O (0.34 mL) was cautiously added, followed by aqueous 15% NaOH (0.34 mL) and H_2O (1.00 mL). The solid material was removed by filtration, and washed with THF. The filtrate and the washing were combined and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (180 ℃, 0.15 Torr) to give colorless oil: $[a]^{24}_D$ -37.3°(c 2.088, MeOH); IR (neat) 2940, 2860, 2760, 1450, 1090, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.37 (m, 2 H), 7.28-7.25 (m, 2 H), 4.62 (d, 2 H *J* =12.5 Hz), 4.58 (d, 2 H *J*=12.5 Hz), 3.55-3.50, 3.14-3.36 (m, 4 H), 3.08-3.02 (m, 2 H), 2.41-2.16 (m, 4 H), 1.97-1.62 (m, 8 H); ^{13}C NMR ($CDCl_3$) 136.41, 128.43, 127.49, 73.71, 70.57, 64.82, 57.72, 41.60, 28.84, 22.73; EIMS, m/z 331 (M^+-1), 3333 (M^++1); HRMS calcd for $C_{20}H_{32}N_2O_2$, 332.2464, found 332.2450.

Scheme 59.

(28) Under argon atmosphere, BH_3-THF (1 M solution in THF, 167.7 mL, 167.7 mmol) was added dropwise to a solution of **28-2** (14.50 g, 67.06 mmol) in THF(330 mL) precooled by ice bath, and the whole was stirred under reflux for 24 h. MeOH (80 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (134 mL) and the whole was heated at 90 ℃ for 0.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (200 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 2), H_2O (200 mL) and brine (200 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 12.28 g (97%) of colorless solid. The solid was recrystallized from hexanes to give 9.79 g of colorless needles: mp 109-110 ℃; $[a]^{23}_D$ -207.9° (c 1.156, MeOH); IR (KBr) 3340, 2950, 2930, 2780, 1620, 1290, 870, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14-7.05 (m, 2 H), 6.82 (t, 1 H *J* = 7.6 Hz), 6.72 (d, 1 H *J* = 7.9 Hz), 3.85 (br, 1 H), 3.82 (d, 1 H *J* = 13.7 Hz), 3.33 (d, 1 H *J*=13.7 Hz), 3.35-3.30 (m, 1 H), 2.79-2.71 (m, 1 H), 3.20-3.13 (m, 1 H), 2.52-2.42 (m, 2 H)), 1.97-1.74 (m, 1 H), 1.54-1.44 (m, 1 H); ^{13}C NMR ($CDCl_3$) 149.70, 130.63, 129.62, 127.75, 120.78, 119.09, 68.58, 59.24, 55.99, 52.83, 28.92, 21.78; EIMS, m/z 188 (M^+); Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.89; H, 8.57; N, 14.88. Found: C, 76.86; H, 8.57; N, 15.03.

Scheme 62.

(29f-1) Acetic anhydride (2.00 mL, 10.62 mmol) was added to a solution of **28** (2.00 g, 10.62 mmol), triethylamine (2.96 mL, 21.24 mL) and 4-dimethylaminopyridine (39 mg, 0.32 mmol) in CH_2Cl_2 (50 mL) at room temperature, and stirred for 24 h. The CH_2Cl_2 layer was successively washed with saturated aqueous $NaHCO_3$ (50 mL × 2) and brine (50 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford a pale yellow oil. The oil was purified by column chromatography ($CHCl_3$-MeOH, 100:1) to afford a colorless oil (2.51 g, quant): IR (neat) 2920, 2790, 1650, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.16 (m, 4 H), 4.81 (d, 1 H *J* = 11.2 Hz), 3.75 (d, 1 H *J* = 13.2 Hz), 3.56 (d, 1 H *J*=13.2 Hz), 3.14-3.06 (m, 1 H), 2.64-2.45 (m, 1 H), 2.64-2.45 (m, 2 H), 1.91 (s, 3 H), 1.97-1.76 (m, 3 H), 1.50-1.39 (m, 1 H)); ^{13}C NMR ($CDCl_3$) 169.34, 142.95, 136.86, 130.28, 128.23, 127.84, 127.66, 66.25, 57.20, 54.99, 50.06, 28.36, 22.43, 21.00; EIMS, m/z 230 (M^+). Treating with MeOH-HCl gave **29f-1**-HCl, which was recrystallized from 2-propanol to give colorless prisms: $[a]^{22}_D$ -136.7°(c 1.034, MeOH);

IR (KBr) 2920, 2790, 1650, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.16 (m, 4 H), 4.81(d, 1 H *J* = 11.2 Hz), 2.64-2.45 (m, 1 H), 3.75(d, 1 H *J* = 13.2 Hz), 3.56 (d, 1 H *J* = 13.2 Hz), 3.14-3.06 (m, 1 H), 2.64-2.45 (m, 1 H), 1.91 (s, 3 H), 1.97-1.76 (m, 3 H), 1.50-1.39 (m, 1 H); ^{13}C NMR ($CDCl_3$) 169.34, 142.95, 136.86, 130.28, 128.23, 127.66, 66.25, 57.20, 54.99, 50.06, 28.36, 22.43, 20.90; EIMS, m/z 230 (M^+);

Scheme 62.

(29f-2) A solution of **29-f-1** (1.00 g, 4.34 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice bath and conc. sulfuric acid (5.00 mL) was carefully added, and then fuming nitric acid (d=1.52, 0.90 mL) was added. The mixture was stirred at room temperature for 3 d, and poured into H_2O (100 mL) and the whole was cooled and K_2CO_3 was added until the solution was basic (pH 10). The mixture was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and the extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to afford 1.12 g of orange solid. The solid was chromatographed on silicagel column (AcOEt-hexanes 1:1) to afford **29f-2** as orange solid (1.02 g, 86%), which was recrystallized from 2-propanol to give orange prisms: IR (KBr) 2770, 1650, 1510, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23-8.16 (m, 2 H), 7.35 (d, 1 H J = 8.3), 4.86 (d 1 H J =13.2 Hz), 3.89 (d 1 H J=13.5 Hz), 3.62 (d, 1 H J = 13.5 Hz), 3.12 (m, 1 H), 2.65-2.53 (m, 1 H), 2.65-2.53 (m, 1H), 1.94 (s, 3 H), 2.06-1.78 (m, 3 H), 1.51-1.40 (m, 1 H); ^{13}C NMR ($CDCl_3$) 168.64, 148.86, 147.00, 138.94, 129.00, 125.75, 123.63, 66.25, 56.98, 55.18, 50.17, 28.54, 22.68, 21.94; EIMS, m/z 275 (M^+); Anal. Calcd for $C_{14}H_{17}N_2O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.13; H,6.46; N, 15.05.

Scheme 62.

(29f) A mixture of **29-f-2** (0.50 g, 1.82 mmol) and 1N hydrochloric acid (20 mL) was stirred under reflux for 4 h. The resulting solution was cooled and $NaHCO_3$ was added until the solution was basic (pH 9). The mixture was extracted with CH_2Cl_2 (70 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (70 mL) and brine (70 mL), and the extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to afford orange solid. The solid was chromatographed on silicagel column (CH_2Cl_2-EtOH 80:1) to afford **29f** as orange solid (467 mg, 96%), which was recrystallized from 2-propanol-cyclohexane (1:1) to give yellow prisms: mp 163-164 ℃; IR (KBr) 3260, 1600, 1580, 1480, 1320, 1290, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (s, 1 H), 7.95 (dd, 1 H J = 8.9, 2.6), 6.68 (d 1 H J =8.9 Hz), 4.56 (s 1 H), 3.96 (d, 1 H J = 14.2 Hz), 3.61 (d, 1 H J=14.2 Hz), 3.50 (ddd, 1 H J = 13.2, 6.3, 5.0), 3.15-3.08 (m, 1H), 2.94 (d, 1 H J =12.9, 8.6 Hz), 2.70-2.64 (m, 1 H), 2.63-1.95 (m, 1 H), 1.89-1.74 (m, 2H), 1.61-1.50 (m, 1H); ^{13}C NMR ($CDCl_3$) 155.62, 139.93, 127.31, 127.01, 123.97, 118.08, 66.45, 58.26, 55.64, 51.79, 29.11, 22.41; EIMS, m/z 233 (M^+); Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 62.08; H,6.70; N, 17.79.

Scheme 62.

(29a-1) **29f-2** (4.30 g, 15.62 mmol) was dissolved in EtOH (150 mL) and hydrogenated in the presence of 10 % Pd-C (0.40 g). After 3 h, the catalyst was filtered off, and the filtrate was stirred under reflux for 72 h. The solvent was evaporated to give colorless oil. Treating with EtOH-HCl gave **29a-1**-2HCl, which was recrystallized from 2-propanol to give colorless prisms.

Scheme 62.

(29a-2) To a stirred solution of **29a-1**-2HCl (2.00 g, 6.28 mmol) and 37% aqueous formaldehyde (5.5 mL, 62.8 mmol) in acetonitrile was added sodium cyanoborohydride (1.18 g, 18.84 mmol). Glacial acetic acid (0.628 mL) was added over 10 min, and the reaction was stirred at room temperature for 2 h. An additional glacial acetic acid (0.628 mL) was added and stirring was continued for 1 h. The reaction mixture was poured into CH_2Cl_2 (150 mL) and then successively washed with 1N aqueous KOH (100 mL × 3), brine (100 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid, which was used for next step without further purification.

Scheme 62.

(29a) A mixture of crude **29a-2** (6.28 mmol) and 2N hydrochloric acid (50 mL) was stirred under reflux for 4 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The mixture was extracted with $CHCl_3$ (100 mL × 4), and the organic layer was washed with brine (100 mL), and the extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was recrystallized from hexanes to give colorless

needles (680 mg, 47%): mp 118-119 ℃; ^{1}H NMR ($CDCl_3$) δ 6.68-6.54 (m, 3 H), 3.75 (d, 1 H J = 13.2), 3.61 (br 1 H), 3.54 (d 1 H J = 13.2 Hz), 3.27 (d, 1 H J = 12.5 Hz), 3.16 (td, 1 H J=10.9 ,2.3 Hz), 2.83 (s, 6 H), 2.62 (dd, 1H J = 12.5, 2.6 Hz), 2.52-2.39 (m, 2 H), 1.96-1.72 (m, 3 H), 1.52-1.37 (m, 1 H); ^{13}C NMR ($CDCl_3$) 146.13, 140.97, 130.87, 120.05, 116.53, 113.50, 69.02, 59.48, 55.99, 53.28, 41.76, 28.84, 21.58.

Scheme 63.

(29b-2) The mixture of 2-amino-5-iodobenzoic acid (10.00 g, 38.02 mmol) and triphosgene (3.76 g, 12.67 mmol) in 1,4-dioxane was heated at reflux. Reflux was continued until no more gas was generated (~3 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 10.64 g (97%) of **29b-2** as colorless needles: EIMS, m/z 289 (M^+).

Scheme 63.

(29c-2) The mixture of 5-bromoanthranillic acid (6.96 g, 32.22 mmol) and triphosgene (3.19 g, 10.74 mmol) in 1,4-dioxane was heated at reflux. Reflux was continued until no more gas was generated (~3 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 7.86 g (quant) of **29c-2** as pale brown needles: IR (KBr) 3240, 3180, 1770, 1690, 1410, 1330, 1030, 840 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1 H), 7.99 (s, 1 H), 7.90 (d 1 H J =8.6 Hz), 7.10 (d 1 H J =8.6 Hz); EIMS, m/z 241 (M^+), 243 (M^++2).

Scheme 63.

(29e-2) The mixture of 2-amino-5-fluorobenzoic acid (2.00 g, 12.89 mmol) and triphosgene (1.28 g, 4.30 mmol) in 1,4-dioxane was heated at reflux. Reflux was continued until no more gas was generated (~2 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 2.40 g (quant) of **29e-2** as pale brown needles: IR (KBr) 3180, 1750, 1510, 1040 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.75 (s, 1 H), 7.69-7.60 (m, 2 H), 7.19 (dd 1 H J =8.6 Hz, 4.3 Hz, H-F coupling), 7.10 (d 1 H J =8.6 Hz); EIMS, m/z 181 (M^+).

Scheme 64.

(11a*S*)-7-Iodo-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10*H*, 11a*H*)dione (29b-3). A mixture of 2.51 g (8.68 mmol) of 5-iodo isatoic anhydride (**29b-2**), 1.25 g (10.85 mmol, 1.25 equiv) of L-proline, and 4.0 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2.5 h). The dark brown solution was cooled and poured in to 50 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure left a pale yellow oil. The oil was purified by column chromatography (AcOEt-CH_2Cl_2, 1:1) to afford a colorless solid. The solid was recrystallized from AcOEt to give 2.50 g (84 %) of colorless needles: [a] $^{22}_D$ +382.6° (c 1.036, $CHCl_3$), ^{1}H NMR ($CDCl_3$) d 8.76 (s, 1 H), 8.29 (d, 1 H J = 2.0 Hz), 7.75 (dd, 1 H J = 8.6, 2.3 Hz), 6.78 (d, 1 H J = 8.6 Hz), 4.05 (d, 1 H J = 7.3 Hz), 3.84-3.76 (m, 1 H), 3.65-3.53 (m, 1 H), 2.79-2.73 (m, 1 H), 2.07-1.99 (m, 3 H); ^{13}C NMR ($CDCl_3$) 170.96, 163.88, 141.15, 139.77, 134.93, 128.79, 122.82, 88.55, 56.64, 47.48, 26.26, 23.43; EIMS, m/z 342 (M^+); Anal. Calcd for $C_{12}H_{11}N_2O_2I$: C, 42.13; H, 23.24; N, 8.19. Found: C, 42.09; H, 3.10; N, 7.92.

Scheme 64.

(29b) Under argon atmosphere, BH_3-THF (1 M solution in THF, 90 mL, 90 mmol) was added dropwise to a solution of **29b-3** (2.45 g, 7.16 mmol) in THF(50 mL) precooled by ice bath, and the whole was stirred under reflux for 3 h. MeOH (70 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under

reduced pressure. To the resulting residue was added aqueous 2 N-HCl (50 mL) and the whole was heated at 90 ℃ for 1 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (70 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 7.51 g (quant.) of colorless solid. The solid was recrystallized from hexanes to give 2.21 g of colorless prisms: mp 145-146 ℃; $[a]^{23}_{D}$ -122.3° (c 1.048, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1 H *J*=2.0 Hz), 7.33 (dd, 1 H *J* = 8.3, 2.0 Hz), 6.48 (d 1 H *J* = 8.3 Hz), 3.86 (d 1 H *J*=5.9 Hz), 3.46 (d, 1 H *J* = 13.5 Hz), 3.31 (ddd, 1 H *J* = 12.9, 6.3, 9.6 Hz), 3.13 (td, 1 H *J* = 8.9, 3.0 Hz), 2.73 (dd, 1 H *J*=12.9, 9.6 Hz), 2.52-2.41 (m, 2 H), 1.99-1.74 (m, 3 H), 1.53-1.38 (m, 1 H); ^{13}C NMR ($CDCl_3$) 149.51, 138.96, 136.30, 132.17, 121.17, 121.20, 82.61, 68.12, 58.44, 55.83, 52.65, 28.92; Anal. Calcd for $C_{12}H_{15}N_2I$: C, 45.88; H, 4.81; N, 8.92. Found: C, 45.81; H, 4.59; N, 8.66.

Scheme 64.

(11a*S*)-7-Bromo-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11 (10*H*, 11a*H*)dione (29c-3). A mixture of 7.71 g (31.86 mmol) of 5-bromo isatoic anhydride (**29c-2**), 4.59 g (35.04 mmol, 1.1 equiv) of L-proline, and 15.9 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 3 h). The dark brown solution was cooled and poured in to 500 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure left a pale yellow solid. The solid was recrystallized from AcOEt to give 7.82 g (83 %) of colorless prisms: EIMS, m/z 294 (M^+), 296 (M^++2); Anal. Calcd for $C_{12}H_{11}N_2O_2Br$: C, 48.84; H, 3.76; N, 9.49. Found: C, 48.82; H, 3.69; N, 9.37.

Scheme 64.

(29c) Under argon atmosphere, BH_3-THF (1 M solution in THF, 265 mL, 265 mmol) was added dropwise to a solution of **29c-3** (7.82 g, 26.50 mmol) in THF(50 mL) precooled by ice bath, and the whole was stirred under reflux for 30 h. MeOH (150 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 2 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (200 mL) and the whole was heated at 90 ℃ for 2.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (200 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 2), H_2O (200 mL) and brine (200 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was recrystallized from hexanes to give 6.80 g (96%) of colorless prisms: mp 135-136 ℃; $[a]^{24}_{D}$ -130.3° (c 1.042, $CHCl_3$); IR (KBr) 2940, 2800, 1480, 1320, 1290, 1260, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (d, 1 H *J*=2.3 Hz), 7.16 (dd, 1 H *J* = 8.6, 2.6 Hz), 6.59 (d 1 H *J* = 8.3 Hz), 3.86 (br 1 H), 3.48 (d, 1 H *J* = 13.5 Hz), 3.75 (d, 1 H *J* = 13.9 Hz), 3.31 (d, 1 H *J* = 12.9 Hz), 2.76-2.68 (m, 1 H), 2.72 (dd, 1 H *J* = 12.9, 9.6 Hz), 2.52-2.43 (m, 2 H), 1.99-1.74 (m, 3 H), 1.53-1.26 (m, 1H); ^{13}C NMR ($CDCl_3$) 148.79, 133.66, 130.30, 120.72, 112.58, 68.18, 58.5, 55.99, 52.63, 28.88, 21.78; Anal. Calcd for $C_{12}H_{15}N_2Br$: C, 53.95; H, 5.66; N, 10.49. Found: C, 53.95; H, 5.52; N, 10.23.

Scheme 64.

(11a*S*)-7-Chloro-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11 (10*H*, 11a*H*)dione (29d-3). A mixture of 12.50 g (63.26 mmol) of 5-chloro isatoic anhydride (**29d-2**), 8.79 g (67.06 mmol, 1.06 equiv) of L-proline, and 32 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The dark brown solution was cooled and poured in to 600 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford 19.51 g of colorless solid. The solid was recrystallized from AcOEt to give 14.13 g (89 %) of colorless needles: $[a]^{23}_{D}$ +461.8° (c 1.178, $CHCl_3$); IR (KBr) 3200, 3150, 1700, 1610, 1470, 1450, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 9.37 (s, 1 H), 7.26 (d, 1 H *J* = 2.6 Hz), 7.43 (dd, 1 H *J* = 8.6, 2.6 Hz),

7.04 (d, 1 H J = 8.6 Hz), 4.08 (d, 1 H J = 6.9 Hz), 3.89-3.76 (m, 1 H), 3.65-3.54 (m, 1 H), 2.79-2.70 (m, 1 H), 2.14-1.95 (m, 3 H); ^{13}C NMR ($CDCl_3$) 171.19, 164.11, 133.96, 132.42, 130.67, 130.53, 128.25, 122.62, 56.64, 47.44, 26.18, 23.00; EIMS, m/z 250 (M^+); Anal. Calcd for $C_{12}H_{11}N_2O_2Cl$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.54; H, 4.39; N, 11.47.

Scheme 64.

(29-d) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **29d-3** (8.36 g, 33.33 mmol) in THF(40 mL) precooled by ice bath, and the whole was stirred under reflux for 5 h. MeOH (20 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (50 mL) and the whole was heated at 90 ℃ for 0.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (200 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 2), H_2O (200 mL) and brine (200 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 7.51 g (quant.) of colorless solid. The solid was recrystallized from hexanes to give 5.65 g of colorless plates:mp 127-128 ℃; $[a]^{23}_D$ -155.6° (c 1.136, $CHCl_3$); IR (KBr) 1480, 1370, 1260, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1 H J=2.6 Hz), 7.02 (dd, 1 H J = 8.6, 2.3 Hz), 6.64 (d 1 H J = 8.3 Hz), 3.86 (d 1 H), 3.75 (d, 1 H J = 13.5 Hz), 3.75 (d, 1 H J = 13.5 Hz), 3.48 (d, 1 H J = 13.5 Hz), 3.15 (ddd, 1 H J=16.8, 9.2, 3.0 Hz), 2.72 (dd, 1 H J=12.9, 9.6 Hz), 2.53-2.42 (m, 2 H), 1.99-1.74 (m, 3 H), 1.53-1.38 (m, 1 H)), 1.54-1.44 (m, 1 H),; ^{13}C NMR ($CDCl_3$) 148.34, 131.30, 130.26, 127.37, 125.23, 120.34, 68.30, 58.67, 55.92, 52.78, 28.90, 21.78; EIMS, m/z 188 (M^+); Anal. Calcd for $C_{12}H_{15}N_2Cl$, C, 64.72; H, 6.79; N, 12.58. Found: C, 64.88; H, 6.87; N, 12.46.

Scheme 64.

(11a*S*)-7-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11 (10*H*, 11a*H*)dione (29e-3). A mixture of 0.50 g (2.76 mmol) of 5-fluoro isatoic anhydride (**29e-2**), 0.40 g (3.04 mmol, 1.1 equiv) of L-proline, and 1.4 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The brown solution was cooled and poured in to 30 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford the colorless solid. The solid was recrystallized from AcOEt to give 0.495 g (77 %) of colorless needles: $[a]^{25}_D$ +407.6° (c 1.060, $CHCl_3$); IR (KBr) 3230, 1700, 1610, 1490, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 8.96 (s, 1 H), 7.69 (dd, 1 H J = 8.9, 3.0 Hz), 7.20 (ddd, 1 H J = 8.9, 7.3, 3.0 Hz), 7.05 (dd, 1 H J = 8.6, 4.3 Hz), 4.08 (d, 1 H J = 6.3 Hz), 3.85-3.77 (m, 1 H), 3.66-3.65 (m, 1 H), 2.80-2.75 (m, 1 H), 2.13-1.96 (m, 3 H); ^{13}C NMR ($CDCl_3$) 171.12, 164.17, 159.46 (d, J = 246.6 Hz), 131.54, 128.84 (d, J = 7.4 Hz), 123.00 (d, J = 7.3 Hz), 119.87 (d, J = 23.2 Hz), 117.20 (d, J = 24.4 Hz), 56.64, 47.42, 26.22, 23.45; EIMS, m/z 234 (M^+); Anal. Calcd for $C_{12}H_{11}N_2O_2F$: 61.53; H, 4.73; N, 11.96. Found: C, 61.49; H, 4.66; N, 12.14.

Scheme 64.

(29-e) Under argon atmosphere, BH_3-THF (1 M solution in THF, 10 mL, 10 mmol) was added dropwise to a solution of **29e-3** (0.46 g, 1.96 mmol) in THF(10 mL) precooled by ice bath, and the whole was stirred under reflux for 2 h. MeOH (10 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 0.5 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 1 N-HCl (20 mL) and the whole was heated at 90 ℃ for 0.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was recrystallized from hexanes to give 376 mg (93%) of colorless needles: mp 127-128 ℃; $[a]^{23}_D$ -124.6° (c 1.018, $CHCl_3$); IR (KBr) 3350, 2940, 2780, 1500, 1480, 1260, 1080, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.86 (dd, 1 H J=8.9 H-F, 2.6 Hz), 6.77 (ddd, 1 H J = 11.5 H-F, 8.6, 3.0 Hz), 6.66 (dd 1 H J = 8.6, 5.0 H-F Hz), 3.77

(br 1 H), 3.74 (d, 1 H J = 13.2 Hz), 3.49 (d, 1 H J = 13.5 Hz),3.30 (d, 1 H J = 13.5 Hz), 3.16 (ddd, 1 H J=11.2, 9.2, 2.6 Hz), 2.70 (dd, 1 H J=12.5, 9.6 Hz), 2.53-2.40 (m, 2 H), 2.40-1.74 (m, 3 H), 1.53-1.38 (m, 1 H)); ^{13}C NMR ($CDCl_3$) 157.34, 145.82, 131.55, 120.11, 116.96, 113.87, 68.66, 56.73, 55.94, 52.94, 28.84, 21.64; EIMS, m/z 206 (M^+); Anal. Calcd for $C_{12}H_{15}N_2F$: C, 69.88; H, 7.33; N, 13.58. Found: C, 69.97; H, 7.62; N, 13.52.

Scheme 67.

(30a-2) The mixture of 2-amino-4-chlorobenzoic acid (24.50 g, 142.79 mmol) and triphosgene (14.12 g, 47.60 mmol) in 1,4-dioxane (300 mL) was heated at reflux. Reflux was continued until no more gas was generated (~ 3 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 28.68 g (quant) of **30a-2** as colorless needles: IR (KBr) 3270, 1770, 1760, 1700, 1610, 1340, 1020 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.84 (s, 1 H), 7.92 (d, 1 H J =8.3 Hz), 7.29 (d 1 H J =8.6 Hz), 7.14 (s 1 H); EIMS, m/z 197 (M^+).

Scheme 67.

(30b-2) The mixture of 2-amino-4-fluorobenzoic acid (5.00 g, 38.23 mmol) and triphosgene (3.19 g, 10.74 mmol) in 1,4-dioxane (50 mL) was heated at reflux. Reflux was continued until no more gas was generated (~ 2 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 6.22 g (90%) of **30b-2** as colorless needles: IR (KBr) 3190, 1780, 1770, 1700, 1620, 1340, 1020 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.83 (s, 1 H), 8.00 (dd, 1 H J =8.9 Hz, 6.3 Hz H-F coupling), 7.10 (ddd 1 H J =9.9 Hz, 9.9, 2.3 Hz H-F coupling), 6.89 (dd 1 H J =2.3 Hz, 9.6 Hz H-F coupling); EIMS, m/z 181 (M^+).

Scheme 67.

(11a*S*)-8-Chloro-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11 (10*H*, 11a*H*)dione (30a-3). A mixture of 3.00 g (15.18 mmol) of 4-chloro isatoic anhydride, 2.19 g (16.70 mmol, 1.1 equiv) of L-proline, and 8 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The dark brown solution was cooled and poured in to 150 mL of cold water and extracted with several portions of $CHCl_3$. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford 3.33 g of colorless solid. The solid was recrystallized from AcOEt to give 3.24 g (85 %) of colorless needles: $[a]^{24}_D$ +437.7° (c 1.034, $CHCl_3$); IR (KBr) 1700, 1610, 1470, 1440, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 8.70 (s, 1 H), 7.95 (d, 1 H J = 8.3 Hz), 7.23 (dd, 1 H J = 8.6, 1.9 Hz), 7.05 (d, 1 H J = 1.9 Hz), 4.07 (d, 1 H J = 6.9 Hz), 3.84-3.77 (m, 1 H), 3.65-3.55 (m, 1 H), 2.90-2.75 (m, 1 H), 2.20-1.95 (m, 3 H); ^{13}C NMR ($CDCl_3$) 171.01, 168.51, 138.24, 136.28, 132.63, 125.52, 125.37, 120.84, 56.71, 47.44, 26.27, 23.47; EIMS, m/z 250 (M^+); Anal. Calcd for $C_{12}H_{11}N_2O_2Cl$: 57.50; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.16; N, 11.36.

Scheme 67.

(30a) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **30a-3** (3.19 g, 12.72 mmol) in THF(20 mL) precooled by ice bath, and the whole was stirred under reflux for 14 h. MeOH (60 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 2 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 1 N-HCl (100 mL) and the whole was heated at 90 ℃ for 1 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. . The solid was recrystallized from hexanes to give 2.57 g (91%) of colorless needles: mp 131-132 ℃; IR (film) 1610, 1580, 1240, 1000, 820 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 7.02 (d, 1 H *J*=7.9 Hz), 6.77 (dd, 1 H *J* = 7.9, 3.3 Hz), 6.71 (d 1 H *J*=20. Hz), 3.89 (d 1 H *J*=5.9 Hz), 3.79 (d, 1 H *J* = 13.5 Hz), 3.44 (d, 1 H *J*=13.5 Hz), 3.31 (ddd, 1 H *J*=12.9, 6.6, 2.3), 3.14 (ddd, 1 H *J*=8.4, 8.4, 3.0), 2.74 (dd 1 H *J*=12.5, 9.2), 2.52-2.39 (m, 2 H), 1.99-1.73 (m, 3 H), 1.54-1.38 (m, 1 H); ^{13}C NMR ($CDCl_3$) 150.82,132.67, 131.66, 128.03, 120.36, 118.81, 68.21, 58.60, 55.07, 52.63, 28.88, 21.82; EIMS, m/z 222 (M^+).

Scheme 67.

(11a*S*)-8-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10*H*, 11a*H*)dione (30b-3). A mixture of 2.00 g (11.04 mmol) of 4-fluoro isatoic anhydride, 1.59 g (12.15 mmol, 1.1 equiv) of L-proline, and 5 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The brown solution was cooled and poured in to 30 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford 2.34 g of colorless solid. The solid was recrystallized from AcOEt to give 2.12 g (82 %) of colorless needles: $[a]^{23}_D$ +484.8° (c 1.0028, $CHCl_3$); IR (KBr) 1690, 1630, 1610, 1450, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 9.29 (s, 1 H), 8.03 (dd, 1 H *J* = 8.9, 6.3 Hz), 6.98 (ddd, 1 H *J* = 8.9, 7.1, 2.3 Hz), 6.81 (dd, 1 H *J* = 9.6, 2.3 Hz), 4.09 (d, 1 H *J* = 6.9 Hz), 3.84-3.76 (m, 1 H), 3.65-3.55 (m, 1 H), 2.80-2.75 (m, 1 H), 2.13-1.96 (m, 3 H); ^{13}C NMR ($CDCl_3$) 171.28, 164.67, 164.66 (d, *J* = 252.7 Hz), 137.30 (d, *J* = 11.0 Hz), 133.67 (d, *J* = 11.0 Hz), 123.32 (d, *J* = 2.5 Hz), 112.57 (d, *J* = 20.7 Hz), 107.78 (d, *J* = 24.4 Hz) 56.73, 47.39, 26.22, 23.47; EIMS, m/z 234 (M^+); Anal. Calcd for $C_{12}H_{11}N_2O_2F$: 61.53; H, 4.73; N, 11.96. Found: C, 61.40; H, 4.58; N, 12.05.

Scheme 67.

(30b) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **30b-3** (2.12 g, 9.05 mmol) in THF(110 mL) precooled by ice bath, and the whole was stirred under reflux for 5 h. MeOH (60 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 2 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (50 mL) and the whole was heated at 90 ℃ for 1 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 7.51 g (quant.) of colorless solid. The solid was recrystallized from hexanes to give 2.21 g of colorless needles: mp 137-138 ℃; $[a]^{23}_D$ -221.0° (c 1.0004, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.05 (dd, 1 H *J*=7.3 H-F, 7.3 Hz), 6.54-6.41 (m, 2 H), 3.89 (br 1 H), 3.81 (d 1 H *J*=13.5 Hz), 3.44 (d, 1 H *J* = 13.5 Hz), 3.33 (ddd, 1 H *J* = 8.3, 6.3, 2.0 Hz), 3.15 (m, 1 H), 2.77 (dd, 1 H *J*=12.5, 9.6 Hz), 2.52-2.40 (m, 2 H), 1.99-1.64 (m, 3 H), 1.54-1.39 (m, 1 H); ^{13}C NMR ($CDCl_3$) 162.00, 152.50, 131.82, 125.48, 106.95, 105.85, 68.38, 58.60, 52.76, 28.93, 21.84; EIMS, m/z 206 (M^+); Anal. Calcd for $C_{12}H_{15}N_2F$: 69.85; H, 7.33; N, 13.58. Found: C, 69.88; H, 7.35; N, 13.76.

Scheme 68.

(31) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **31-1** (3.17 g, 14.26 mmol) in THF(50 mL) precooled by ice bath, and the whole was stirred under reflux for 14 h. MeOH (30 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (120 mL) and the whole was heated at 90 ℃ for 1 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with $CHCl_3$ (100 mL × 5), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford pale yellow oil. The oil was purified by column chromatography (Al_2O_3, AcOEt-MeOH, 5:1) to afford a colorless oil (2.00 g, 72%), which was further purified by recrystallization as picrate (recrystallized from acetone-MeOH, 6.43 g, 69%). Free **31** was

purified by Kugelrohr distillation (190 ℃, 0.2 Torr) to give colorless prisms: $[a]^{24}_{D}$ +48.4° (c 1.035, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.10-2.94 (m, 3 H), 2.72-2.63 (m, 1 H), 2.57-2.46 (m 1 H), 2.37-2.22 (m 2 H), 2.08-1.62 (m, 7 H), 1.57-1.42 (m, 2 H),1.25-1.07 (m, 2 H), 0.99-0.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) 65.82, 63.31, 59.41, 57.14, 46.56, 36.23, 30.86, 25.81, 25.43, 23.40; EIMS, m/z 194 (M^+).

Scheme 69.

(32-2) The mixture of 2-amino-3-methylbenzoic acid (5.00 g, 33.08 mmol) and triphosgene (3.27 g, 11.03 mmol) in 1,4-dioxane (50 mL) was heated at reflux. Reflux was continued until no more gas was generated (~ 2 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 5.88 g (quant) of **32-2** as colorless needles: IR (KBr) 3230, 1780, 1710, 1690, 1010, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.86 (d, 1 H J=6.6 Hz), 7.56 (d, 1 H J=6.6 Hz), 7.18 (t 1 H J=7.9 Hz), 2.36 (s 3 H); EIMS, m/z 177 (M^+).

Scheme 69.

(11a*S*)-9-Methyl-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11 (10*H*, 11a*H*)dione (32-3). A mixture of 3.60 g (20.32 mmol) of 3-methyl isatoic anhydride (**32-2**), 2.93 g (22.35 mmol, 1.1 equiv) of L-proline, and 10 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 1.5 h). The dark brown solution was cooled and poured in to 200 mL of cold water and extracted with several portions of $CHCl_3$. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$ Filtration and evaporation of the solvent under reduced pressure to afford 5.59 g of colorless solid: $[a]^{25}_{D}$ +536.3° (c 1.184, MeOH); IR (KBr) 3400, 3200, 2950, 2950, 1675, 1635, 1620, 1425, 1280, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 7.94 (br, 1 H), 7.83 (d, 1 H J = 7.9 Hz), 7.35 (d, 1 H J = 7.3 Hz), 7.18 (t, 1 H J = 7.6 Hz), 4.06 (d, 1 H J = 6.9 Hz), 3.90-3.75 (m, 1 H), 3.64-3.50 (m, 1 H), 2.82-2.62 (m, 1 H), 2.37 (s, 3 H), 2.18-1.93 (m, 3 H); ^{13}C NMR ($CDCl_3$) 170.64, 165.59, 133.76, 133.48, 129.04, 128.66, 128.35, 125.10, 56.35, 47.15, 26.28, 23.54, 18.29; EIMS, m/z 230 (M^+); Anal. Calcd for $C_{13}H_{14}N_2O_2$: 67.84; H, 6.13; N, 12.17. Found: C, 67.10; H, 6.13; N, 12.01.

Scheme 69.

(32) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **32-3** (4.47 g, 19.41 mmol) in THF(40 mL) precooled by ice bath, and the whole was stirred under reflux for 4 h. MeOH (15 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (100 mL) and the whole was heated at 90 ℃ for 0.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 3.85 g (77%) of pale yellow oil. To this oil MeOH-HCl was added and the solvent was evaporated under reduced pressure. The solid was recrystallized from EtOH to give colorless prisms as mono HCl salts: $[a]^{24}_{D}$ -131.4°(c 1.0012, MeOH); IR (neat) 3400, 2920, 2780, 1590, 1470, 1290, 1100, 740 cm^{-1}; ^{1}H NMR Free amine ($CDCl_3$) δ 7.01 (d, 2 H J=7.6 Hz), 6.73 (t, 1 H J = 7.4 Hz), 3.94 (d, 1 H J = 6.3 Hz), 3.83 (d, 1 H J=13.5 Hz), 3.51 (d, 1 H J = 13.5 Hz), 3.42 (ddd, 1 H J=12.7, 6.4, 2.1 Hz), 3.14 (ddd, 1 H J=12.7, 6.4, 2.1 Hz), 2.53-2.43 (m, 2 H), 2.22 (s, 3 H), 1.98-1.74 (m, 3 H)), 1.53-1.39 (m, 1 H); ^{13}C NMR ($CDCl_3$) 147.96, 129.52, 129.86, 125.05, 120.11, 68.39, 59.07, 55.56, 52.22, 28.70, 21.78, 17.76; EIMS, m/z 202 (M^+); Anal. Calcd for $C_{13}H_{19}N_2Cl$: C, 65.40; H, 8.02; N, 11.73. Found: C, 65.45; H, 8.26; N, 11.68.

Scheme 70.

(33-2) To a solution of Cbz-Pro (6.64 g, 26.63 mmol), **33-1**[48] (5.14 g, 26.63 mmol), HOOBt (6.51 g, 39.96 mmol) in CH_2Cl_2 (300 mL) was added WSCI-HCl (5.62 g, 39.96 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 2 h and at room temperature for additional 19 h.

The solution was successively washed with saturated aqueous $NaHCO_3$ (200 mL × 2), aqueous 0.1 N-citric acid (200 mL), H_2O (100 mL), saturated aqueous $NaHCO_3$ (200 mL) and brine (100 mL), then dried over anhydrous $MgSO_4$, filtered, and evaporated to afford pale yellow oil. The oil was chromatographed on silicagel column (hexanes-AcOEt 3:2) to afford **33-2** as colorless oil (8.32 g, 74%):$[a]^{21}_D$ -13.5°(c 1.172, $CHCl_3$); IR (neat) 2940, 1720, 1700, 1640, 1400, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37-7.00 (m, 10 H), 5.20-4.99 (m, 2 H), 4.89-4.50 (m 2 H), 4.44-4.21 (m 1 H), 3.69-3.37 (m, 7H), 2.77-1.85 (m, 6H); EIMS, m/z 424 (M^+), 393 (M^+-OCH_3); Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.62; H,6.43; N, 6.56.

Scheme 70.

(33-2) Cbz-Pro (6.45 g, 25.87 mmol) and **33-1**[48] (5.00 g, 25.87 mmol) was dissolved in DMF (120 mL), and the solution was cooled to 0 ℃. To the solution was added DEPC (93%, 4.58 mL, 28.46 mmol) and then triethylamine (3.61 mL, 25.87 mmol) with stirring. After being stirred at 0 ℃ for 2 h, then at room temperature for 24 h, the mixture was diluted with H_2O (300 mL). The whole was extracted with AcOEt-benzene 2:1 (200 mL × 4) , and the organic layer was successively washed with 0.1 M aqueous citric acid (150 mL × 3), saturated aqueous $NaHCO_3$ (200 mL × 2) and brine (200 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford pale yellow oil. The oil was chromatographed on silicagel column (hexanes-AcOEt 1:1) to afford **33-2** as colorless oil (10.44 g, ~95%) which still contained impurity.

Scheme 70.

(33-3) **33-2** (10.34 g, 24.36 mmol) was dissolved in EtOH (500 mL) and hydrogenated in the presence of 10 % Pd-C (1.15 g). After 24 h, the catalyst was filtered off, and the filtrate was stirred under reflux for 72 h. The solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2-EtOH, 20:1) to give 5.37 g (85 %) of colorless oil: IR (neat) 2950, 1650, 1620, 1430, 1390, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37-7.24 (m, 5 H), 4.78 (d, 1 H *J*=14.5 Hz), 4.63 (t 1 H *J*=6.9 Hz), 4.48 (d, 1 H *J*=14.5 Hz), 3.92-3.81 (m, 1 H), 3.70-3.54 (m, 2 H), 3.24 (dt, 1 H *J*=15.8, 4.6 Hz), 2.78-2.43 (m, 3 H), 2.19-1.76 (m, 3 H); ^{13}C NMR ($CDCl_3$) 169.47, 168.07, 136.57, 128.77, 128.16, 127.80, 57.09, 50.28, 48.11, 42.25, 35.37, 28.99, 22.37.

Scheme 70.

(33-4) Under argon atmosphere, BH_3-THF (1 M solution in THF, 200 mL, 200 mmol) was added dropwise to a solution of **33-3** (5.37 g, 20.79 mmol) in THF(50 mL) precooled by ice bath, and the whole was stirred under reflux for 20 h. MeOH (60 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1.5 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (144 mL) and the whole was heated at 90 ℃ for 2 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (80 mL × 4), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 4.00 g of pale yellow oil. . To this oil MeOH-HCl was added and the solvent was evaporated under reduced pressure. The solid was recrystallized from EtOH-1,4-dioxane (2:3) to give colorless prisms as 2 HCl salts: $[a]^{25}_D$ -12.1°(c 1.147, MeOH); IR (Free amine) (neat) 2920, 2790, 1490, 1440, 1350, 1110, 730, 690 cm^{-1}; ^1H NMR(Free amine) ($CDCl_3$) δ 7.35-7.19 (m, 5 H), 3.64 (s, 2 H), 3.09-2.98 (m 2 H), 2.87-2.78 (m 2 H), 2.73-2.61 (m, 2 H), 2.51-2.32 (m, 3 H), 1.95-1.64 (m, 5 H), 1.43-1.31; ^{13}C NMR ($CDCl_3$) 139.53, 128.72, 128.07, 126.70, 63.79, 62.77, 61.92, 57.36, 53.77, 53.62, 30.51, 27.62; EIMS, (Free amine) m/z 230 (M^+); Anal. Calcd for $C_{15}H_{24}N_2Cl_2$: C, 59.41; H, 7.98; N, 9.24. Found: C, 59.19; H, 8.15; N, 9.19.

Scheme 70.

(33) **33-4** 2 HCl salt (1.08 g, 3.56 mmol) was dissolved in MeOH (150 mL) and hydrogenated in the presence of 10 % Pd-C (0.24 g). After 14 h, the catalyst was filtered off,

and the solvent was evaporated. To the residue aqueous 1 N NaOH (50 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL × 3), and the organic layer was successively washed with brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford pale yellow oil. The oil was purified by Kugelrohr distillation (100 ℃, 4 Torr) to give 330 mg (66%) of colorless oil: $[a]^{23}_{D}$ -4.0° (c 1.368, MeOH); IR (Free amine) (neat) 3270, 2900, 2790, 1450, 1160, 1120 cm^{-1}; ^1H NMR(Free amine) ($CDCl_3$) δ 3.11-2.91 (m, 5 H), 2.61-2.34 (m, 4 H), 2.00-1.68 (m 5 H), 1.48-1.40 (m 1 H); ^{13}C NMR ($CDCl_3$)67.66, 57.47, 55.29, 53.71, 47.06, 30.55, 29.99, 22.88; EIMS, (Free amine) m/z 140 (M^+).

Scheme 73.

(34-1) The mixture of 3-amino-2-naphthoic acid (1.00 g, 5.34 mmol) and triphosgene (0.53 g, 1.78 mmol) in 1,4-dioxane (20 mL) was heated at reflux. Reflux was continued until no more gas was generated (~1.5 h), and if starting material were still remained (checked by TLC, silicagel, $CHCl_3$-MeOH 10:1), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 1.17 g (quant) of **34-1** as pale brown needles: IR (KBr) 1760, 1730, 1630, 1000 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.73 (s, 1 H), 8.73 (s, 1 H), 8.13 (d 1 H J =8.3 Hz), 7.94 (d 1 H J =8.3 Hz), 7.66 (t 1 H J =8.3 Hz), 7.51 (s 1 H), 7.50 (t 1 H J =6.9 Hz); EIMS, m/z 213 (M^+).

Scheme 73.

(34-2). A mixture of 0.50 g (2.35 mmol) of **34-1**, 0.34 g (2.56 mmol, 1.1 equiv) of L-proline, and 4 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The dark brown solution was cooled and poured in to 50 mL of cold water and extracted with several portions of $CHCl_3$. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$ Filtration and evaporation of the solvent under reduced pressure to afford the pale yellow solid. The solid was recrystallized from EtOH to give 0.43 g (69 %) of colorless needles: $[a]^{25}_{D}$ +409.6° (c 0.874, $CHCl_3$); IR (KBr) 3400, 3200, 1690, 1610, 740 cm^{-1}; ^1H NMR ($CDCl_3$) d 8.59 (s, 1 H), 8.47 (s, 1 H), 7.94 (d, 1 H J = 8.3 Hz), 7.78 (d, 1 H J = 7.9 Hz), 7.24-7.45 (m, 3 H), 4.12 (m, 1 H), 3.87-3.84 (m, 1 H), 3.71-3.61 (m, 1 H), 2.90-2.70 (m, 1 H), 2.20-1.95 (m, 3 H) 1.52 (s, 9 H),; ^{13}C NMR ($CDCl_3$) 171.55, 165.43, 134.84, 132.44, 132.00, 130.33, 128.97, 128.64, 126.86, 126.79, 126.31, 118.26, 56.57, 47.46, 26.40, 23.56; EIMS, m/z 266 (M^+); Anal. Calcd for $C_{16}H_{14}N_2O_2$: 72.17; H, 5.30; N, 10.52. Found: C, 72.01; H, 5.21; N, 10.37.

Scheme 73.

(34) Under argon atmosphere, BH_3-THF (1 M solution in THF, 17.3 mL, 17.3 mmol) was added dropwise to a solution of **34-2** (0.46 g, 1.73 mmol) in THF(20 mL) precooled by ice bath, and the whole was stirred under reflux for 4 h. MeOH (20 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 0.5 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 1 N-HCl (20 mL) and the whole was heated at 90 ℃ for 0.3 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (60 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (60 mL × 2), H_2O (60 mL) and brine (60 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 390 mg of colorless solid. The solid was recrystallized from AcOEt (25 mL) to give 331 mg (81%) of colorless needles: mp 221-222 ℃; $[a]^{23}_{D}$ -246.7° (c 1.052, $CHCl_3$); IR (KBr) 3340, 2930, 2770, 1620, 1290, 870, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, 1 H J=7.9 Hz), 7.61 (d, 1 H J = 7.9 Hz), 7.62 (s 1 H), 7.36 (td 1 H J=7.6, 1.3 Hz), 7.26 (td, 1 H J = 7.4, 1.0 Hz), 7.12 (s, 1 H),4.09 (br, 1 H), 4.01 (d, 1 H J=13.5 Hz), 3.69 (d, 1 H J=13.2 Hz), 3.38 (d, 1 H J=12.5 Hz), 3.21 (ddd, 1 H J=8.4, 8.4, 3.0), 2.82 (dd, 1 H J=12.5, 9.6), 2.65-2.01 (m, 2 H), 2.00-1.72 (m, 3 H), 1.56-1.41 (m, 1 H); ^{13}C NMR ($CDCl_3$) 148.70, 134.16, 132.13, 129.87, 129.87, 127.87, 126.38, 126.13, 123.90, 68.90, 59.61, 56.35, 53.68, 29.83, 22.32; EIMS, m/z 238 (M^+); Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.42; H, 7.46; N, 11.68.

Scheme 74.

(35-3) The mixture of **35-2** (24.73 g, 139.57 mmol) and triphosgene (13.81 g, 46.52 mmol) in 1,4-dioxane (300 mL) was heated at reflux. Reflux was continued until no more gas was generated (~3 h), and if starting material were still remained (checked by TLC, silicagel, AcOEt-hexanes 1:1), additional triphosgene was added. The mixture was cooled and the solvent was evaporated under reduced pressure. The residual solid was collected by filtration, and successively washed with Et_2O, hexanes, and dried to give 27.41 g (97%) of **35-3** as pale brown needles: IR (KBr) 1760, 1720, 1590, 1480, 1300, 1020, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.82 (d, 1 H J =7.6 Hz), 7.61 (d, 1 H J =7.6 Hz), 7.21 (t 1 H J =7.6 Hz), 3.88 (t 2 H J =5.8 Hz), 2.86 (t 2 H J =6.1 Hz), 1.99 (qui 2 H J =5.9 Hz); EIMS, m/z 203 (M^+).

Scheme 74.

(35-4). A mixture of 5.00 g (24.72 mmol) of **35-3**, 3.57 g (27.20 mmol, 1.1 equiv) of L-proline, and 12 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The brown solution was cooled and poured in to 240 mL of cold water and extracted with several portions of $CHCl_3$. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$ Filtration and evaporation of the solvent under reduced pressure to afford 10.92 g of pale yellow solid. The solid was purified by column chromatography (AcOEt-hexanes 1:1) to give 5.08 g (80 %) of colorless solid The solid was recrystallized from AcOEt to give 4.15 g of colorless needles: $[a]^{23}_D$ +551.7° (c 1.064, $CHCl_3$); IR (KBr) 1660, 1620, 1420, 750 cm^{-1}; ^1H NMR ($CDCl_3$) d 7.77 (d, 1 H J = 7.6 Hz), 7.29 (d, 1 H J = 7.9 Hz), 7.19 (t, 1 H J = 7.6 Hz), 4.58-4.48 (m, 1 H),, 4.09-4.05 (m, 1 H), 3.85-3.76 (m, 1 H), 3.63-3.52 (m, 1 H), 3.13-3.07 (m, 1 H), 2.96-2.84 (m, 1 H), 2.79-2.67 (m, 2 H), 2.20-2.00 (m, 4 H), 1.99-1.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) 169.31, 165.39, 136.03, 131.75, 131.38, 129.22, 128.43, 124.78, 57.14, 46.65, 42.99, 27.42, 26.72, 23.69, 23.08; EIMS, m/z 256 (M^+); Anal. Calcd for $C_{15}H_{16}N_2O_2$: 70.29; H, 6.29; N, 10.93. Found: C, 70.24; H, 6.40; N, 10.68.

Scheme 74.

(35) Under argon atmosphere, BH_3-THF (1 M solution in THF, 72 mL, 72 mmol) was added dropwise to a solution of **35-4** (4.93 g, 19.23 mmol) in THF(70 mL) precooled by ice bath, and the whole was stirred under reflux for 20 h. MeOH (20 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 1 N-HCl (110 mL) and the whole was heated at 90 ℃ for 1.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford 1.72 g of pale yellow oil: $[a]^{23}_D$ -225.2° (c 1.066, $CHCl_3$); IR (neat) 2930, 2770, 1590, 1470, 1450, 1300, 1120, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (d, 1 H J=7.3 Hz), 6.91 (d, 1 H J = 7.3 Hz), 7.73 (d 1 H J=7.4 Hz), 3.74 (d 1 H J=12.9 Hz), 3.55 (d, 1 H J = 12.9 Hz), 3.33-3.23 (m, 1 H),3.20-3.11 (m, 1 H), 3.09-3.02 (m, 1 H), 3.05-2.99 (m, 1 H), 2.88-2.82 (m, 1 H), 2.80-2.72 (m, 1), 2.65-2.54 (m, 1 H), 2.46 (q, 1 H J=8.5 Hz), 1.96-1.68 (m, 5 H), 1.46-1.31 (m, 1 H); ^{13}C NMR ($CDCl_3$) 148.01, 131.02, 128.59, 126.36, 127.23, 120.15, 66.92, 61.28, 58.28, 55.26, 54.54, 28.57, 28.40, 21.76, 20.31; EIMS, m/z 228 (M^+); Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.70; H, 8.94; N, 12.14.

Scheme 75.

(2*R*, 11a*S*)-2-Hydroxy-2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10*H*, 11a*H*)dione (36-1). A mixture of 5.00 g (30.65 mmol) of isatoic anhydride, 4.26 g (32.49 mmol, 1.06 equiv) of L-hydroxyproline, and 15.3 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 2 h). The dark brown solution was cooled and poured in to 300 mL of cold water. The product slowly crystallized out of solution. The solution was chilled in an ice bath and the product was filtered as a light brown solid. The brown solid was recrystallized from water to give 6.54 g (74%) of colorless needles: $[a]^{25}_D$ +457.0° (c 0.134, MeOH); IR (KBr) 3310, 2800, 1600, 1480, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.46 (s, 1 H), 7.80 (d, 1 H J = 7.9 Hz), 7.51 (t, 1 H J = 7.3 Hz), 7.22 (t, 1 H J = 7.3 Hz),

7.14 (d, 1 H J = 7.9 Hz), 5.09 (d, 1 H J = 4.0 Hz), 4.20 (m, 1 H), 3.63 (dd, 1 H J = 11.9, 3.3 Hz), 3.49 (dd, 1 H J = 12.2, 5.0 Hz), 2.69-2.60 (m, 1 H), 2.00-1.90 (m, 1 H); ^{13}C NMR (DMSO-d_6) 170.13, 165.03, 136.90, 131.99, 130.22, 125.91, 123.79, 121.17, 55.13, 67.32, 53.89, 34.33; EIMS, m/z 232 (M^+); Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 70.56; H, 7.90; N, 11.37. Found: C, 70.57; H, 13.62; N, 13.62.

Scheme 75.

(36a) Under argon atmosphere, BH_3-THF (1 M solution in THF, 500 mL, 500 mmol) was added dropwise to a solution of **36-1** (24.17 g, 104.07 mmol) in THF(150 mL) precooled by ice bath, and the whole was stirred under reflux for 12 h. MeOH (120 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 1 N-HCl (300 mL) and the whole was heated at 90 ℃ for 2 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (200 mL × 5), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (400 mL × 2), H_2O (400 mL) and brine (400 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford pale yellow solid. The solid was recrystallized from AcOEt to give pale yellow prism: IR (KBr) 3310, 2800, 1600, 1460, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10-7.04 (m, 2 H), 6.81 (t, 1 H J = 7.8 Hz), 6.70 (d 1 H J = 7.9 Hz), 4.93-4.34 (m 1 H), 3.86 (d, 1 H J = 5.9 Hz), 3.75 (s, 2 H), 3.42 (dd, 1 H J = 9.9, 6.3 Hz), 2.45 (dd, 1 H J=9.6, 4.6 Hz), 3.34 (ddd, 1 H J=12.9, 5.9, 2.3 Hz), 2.70 (dd, 1 H J=12.9, 8.9 Hz), 2.56 (s, 1 H), 1.90-1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) 149.40, 130.58, 128.68, 127.89, 120.68, 118.83, 69.53, 65.59, 63.76, 58.04, 51.97, 39.86; EIMS, m/z 204 (M^+); Anal. Calcd for $C_{12}H_{16}N_2O$, C, 70.57; H, 8.08; N, 13.62. Found: C, 70.56; H, 7.90; N, 13.71.

Scheme 75.

(36b) Under argon atmosphere, **36-a** (1.50 g, 7.34 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60% oil dispersion, washed with hexanes, 323 mg, 8.08 mmol) in THF (15 mL) at 0 ℃, and the mixture was stirred for 15 min. 4-fluoro nitrobenzene (1.14 g, 8.08 mmol) in THF (15 mL) was added dropwise to the mixture and the whole was stirred at room temperature for 18 h. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silicagel column (AcOEt-hexanes, 2:1) to afford **36b** as pale yellow solid (1.57 g, 66%), which was recrystallized from cyclohexane-AcOEt 2:1 to give yellow needles: mp 187-188 ℃; IR (KBr) 3350, 1600, 1580, 1500, 1340, 1250, 1000, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.21-8.26 (m, 2 H), 7.13-7.08 (m, 2 H), 6.93-6.82 (m, 3 H), 6.75 (d, 1 H J=7.6 Hz), 4.94-4.89 (m, 1 H), 3.89 (s, 1 H), 3.80 (s, 1 H), 3.78 (s, 1H), 3.76-3.79 (m, 1H), 3.39 (d, 1 H J=12.9 Hz), 3.02-2.92 (m, 1H), 2.80-2.71 (m, 2H), 2.13-1.95 (m, 2H); ^{13}C NMR ($CDCl_3$) 162.73, 149.51, 141.46, 130.55, 128.82, 128.06, 125.93, 121.01, 119.14, 115.11, 76.01, 65.99, 61.12, 58.15, 52.13, 36.93; EIMS, m/z 325 (M^+); Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.51; H, 5.94; N, 12.88.

Scheme 76.

(37) To a solution of **36a** (2.00 g, 9.79 mmol) in THF (20 mL) was added dropwise a THF solution of methylmagnesium bromide (0.922 M, 10.62 mL, 9.79 mmol) at room temperature under argon atmosphere. A THF (30 mL) solution of 1,1'-(azodicarbonyl)-dipiperidine was then added dropwise at room temperature. The mixture was stirred for 14 h, quenched by addition of saturated aqueous NH_4, and extracted with AcOEt (50 mL × 3). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was chromatographed on Al_2O_3 column (Et_2O-CH_2Cl_2 20:1) to afford **37** as colorless solid, which was recrystallized from hexanes-AcOEt 15:1 to give colorless needles (760 mg, 38%): [a] $^{24}_D$ -292.5° (c 1.091, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.17-7.10 (m, 2 H), 6.89 (dd, 1 H J=8.6, 1.0 Hz), 6.78 (d 1 H J=7.3 Hz), 3.93 (br 1 H), 3.86 (d, 1H J=13.9 Hz), 3.80 (d, 1H J=13.9 Hz), 3.58 (d, 1 H J=16.8 Hz), 3.43 (dd, 1 H J=12.9, 3.0 Hz), 3.18-3.07 (m, 1 H), 3.03 (d, 1 H J=16.8 Hz), 2.88 (dd, 1 H J=12.9, 9.2 Hz), 2.52 (dd, 1 H J=17.8, 6.3 Hz), 2.15 (dd, 1 H

J=17.8, 9.6 Hz); ^{13}C NMR ($CDCl_3$) 212.65, 149.61, 130.94, 129.06, 128.59, 121.65, 119.61, 65.81, 62.61, 58.78, 52.54, 43.15; EIMS, m/z 202 (M^+); Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.10; H,6.95; N, 13.73.

Scheme 77.

(38a) Under argon atmosphere, **36a** (1.00 g, 4.90 mmol), triphenylphosphine (1.93 g, 7.34 mmol), and 4-nitrophenol (0.75 g, 5.39 mmol) were dissolved in THF (60 mL) with stirring at 0 ℃, and DEAD (1.16 mL, 7.34 mmol) was added to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 2 d. The solvent was evaporated to 20 mL, and the mixture was diluted with Et_2O (200 mL), extracted with 2N hydrochloric acid (100 mL × 4). The aqueous extract was made basic (~ pH 10) with Na_2CO_3 and extracted with CH_2Cl_2 (100 mL × 3). The extracts were combined, washed with brine (100 mL), dried, and concentrated. The residual solid was chromatographed on silicagel column (Et_2O-hexanes 1:1) to afford **38a** as pale yellow solid (470 mg, 30%), which was recrystallized from AcOEt to give pale yellow prisms: mp 220-221 ℃; $[a]^{25}_D$ -74.1° (c 1.036, $CHCl_3$); IR (KBr) 3350, 2800, 1600, 1580, 1500, 1480, 1330, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19-8.14 (m, 2 H), 7.13-7.16 (m, 2 H), 6.91-6.81 (m 3 H), 6.74 (d 1 H J =7.9 Hz), 4.90 (m, 1 H), 3.92 (s, 1 H), 3.83 (d, 1 H J = 13.2 Hz), 3.52 (d, 1 H J=13.5 Hz), 3.40 (d, 1 H J=10.9 Hz), 3.35 (d, 1 H J=16.2 Hz), 2.92-2.83 (m, 2 H), 1.76-1.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) 163.25, 149.97, 141.82, 131.29, 129.51, 128.46, 126.33, 121.53, 119.73, 115.58, 76.52, 68.73, 62.16, 59.41, 52.71, 38.03; EIMS, m/z 325 (M^+); Anal. Calcd for $C_{18}H_{19}N_3O_3$, C, 66.45; H, 5.89; N, 12.91. Found: C, 66.41; H, 5.76; N, 12.92.

Scheme 77.

(38b) Under argon atmosphere, **36a** (1.00 g, 4.90 mmol), triphenylphosphine (1.93 g, 7.34 mmol), and 2-naphthol (1.06 g, 7.34 mmol) were dissolved in THF (180 mL) with stirring at 0 ℃, and DEAD (1.16 mL, 7.34 mmol) was added to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 2 d. The solvent was evaporated to 20 mL, and the mixture was diluted with Et_2O (200 mL), extracted with 2N hydrochloric acid (200 mL × 4). The aqueous extract was made basic (~ pH 10) with Na_2CO_3 and extracted with CH_2Cl_2 (200 mL × 3). The extracts were combined, washed with brine (100 mL), dried, and concentrated. The residual solid was chromatographed on silicagel column (hexanes-AcOEt 2:1 ~ hexanes-AcOEt-THF) to afford **38b** as colorless solid (570 mg, 35%), which was recrystallized from benzene to give colorless prisms: mp 252-253 ℃; $[a]^{28}_D$ -111.3° (c 0.102, THF); IR (film) 1640, 1580, 1470, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76-7.68 (m, 3 H), 7.42 (t, 1 H J =6.9 Hz), 7.32 (t, 1 H J = 7.4 Hz), 7.14 (m 3 H), 7.00 (d, 1 H J=2.3 Hz), 6.83 (t, 1 H J = 7.4 Hz), 6.74 (d, 1 H J = 7.6 Hz), 5.00-4.94 (m, 1 H), 3.84 (d, 1 H J=13.5 Hz), 3.54 (d, 1 H J=13.5 Hz), 3.47 (d, 1 H J = 10.6 Hz), 3.34 (d, 1 H J=11.2 Hz) , 2.96-2.86 (m, 2 H) , 2.68-2.57 (m, 2 H) , 1.85-1.73 (m, 1 H); ^{13}C NMR ($CDCl_3$) 163.10, 149.50, 135.50, 130.91, 127.89, 129.45, 129.00, 127.64, 126.65, 126.31, 125.20, 123.56, 120.97, 119.73, 119.21, 107.28, 74.90, 68.37, 61.96, 59.15, 52.36, 37.84; EIMS, m/z 330 (M^+); Anal. Calcd for $C_{22}H_{22}N_2O$, C, 79.97; H, 6.71; N, 8.48. Found: C, 79.92; H, 6.71; N, 8.51.

Scheme 78.

(39-1). A mixture of 417 mg (2.322 mmol, 1.1 equiv) of isatoic anhydride, 300 mg (2.556 mmol) of L-pipecolinic acid, and 1.5 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 3 h). The brown solution was cooled and poured in to 100 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford the colorless solid. The solid was purified by column chromatography (AcOEt-hexanes, 1:1) to give 242.0 mg (45 %) of colorless solid: $[a]^{21}_D$ +327.8° (c 0.748, $CHCl_3$); ^{1}H NMR ($CDCl_3$) d 9.18 (br, 1 H), 7.92 (dd, 1 H J = 7.6, 1.3 Hz), 7.44 (td, 1 H J = 7.6, 1.7 Hz), 7.29-7.21 (m 1 H), 7.03 (d, 1 H J = 7.9 Hz), 4.52 (dt, 1 H J = 9.6, 3.3 Hz), 4.16 (dd, 1 H J = 6.6, 3.3 Hz), 2.99 (td, 1 H J = 12.2, 4.0 Hz), 2.28-2.15 (m, 1 H), 1.99-1.56 (m, 5 H); ^{13}C NMR ($CDCl_3$) 172.04, 168.46, 135.90, 132.02, 131.09, 127.49, 124.94, 120.36, 51.07, 40.24, 23.08, 22.70, 19.09.

Scheme 78.

(39) Under argon atmosphere, BH_3-THF (1 M solution in THF, 10 mL, 10 mmol) was added dropwise to a solution of **39-1** (0.23 g, 1.0 mmol) in THF(5 mL) precooled by ice bath, and the whole was stirred under reflux for 5 h. MeOH (20 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 0.25 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (20 mL) and the whole was heated at 90 ℃ for 0.75 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was recrystallized from hexanes to give 68 mg (34%) of colorless prisms: $[a]^{23}_{D}$ -133.0° (c 0.426, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.13 (d, 1 H *J*=7.6 Hz), 7.07 (td, 1 H *J*=7.6, 1.7 Hz), 6.82 (td 1 H *J*=7.6, 1.3 Hz), 6.71 (d 1 H *J*=7.6 Hz), 3.80 (br, 1 H), 3.59 (s, 2 H), 3.15 (m, 1 H), 3.13 (d, 1 H *J*=13.2 Hz), 3.00-1.55 (m, 4 H), 1.33-1.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) 150.42, 130.98, 129.40, 127.76, 120.70, 117.77, 65.59, 63.22, 56.34, 54.36, 30.75, 26.11, 23.47.

Scheme 79.

(40-1). A mixture of 2.53 g (15.52 mmol, 1.1 equiv) of isatoic anhydride, 2.50 g (14.11 mmol) of (S)-(+)-1,2,3,4-tetrahydroioquinoline-3-carboxylic acid, and 14 mL of DMSO was stirred and heated to 115 ℃ until no more CO_2 evolution was observed (~ 3 h). The brown solution was cooled and poured in to 100 mL of cold water and extracted with several portions of CH_2Cl_2. The organic layer was combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure to afford the colorless solid. The solid was recrystallized from AcOEt-EtOH to give 1.86 g (47 %) of colorless prisms: $[a]^{25}_{D}$ +605.6° (c 0.224, $CHCl_3$); ^{1}H NMR ($CDCl_3$) d 8.53 (s, 1 H), 7.96 (dd, 1 H *J* = 7.9, 1.3 Hz), 7.47 (td, 1 H *J* = 8.9, 1.7 Hz), 7.35-7.22 (m 5 H), 6.98(d, 1 H *J* = 7.9 Hz) 5.12 (d, 1 H *J* = 15.5 Hz), 4.22 (t, 1 H *J* = 6.6 Hz), 3.53 (dd, 1 H *J* = 15.5, 7.3 Hz), 3.03 (dd, 1 H *J* = 15.2, 6.3 Hz); ^{13}C NMR ($CDCl_3$) 171.01, 166.88, 135.18, 134.41, 134.18, 132.51, 131.79, 127.87, 127.69, 126.88, 126.51, 126.15, 125.12, 120.47, 52.04, 28.29; Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.50; H, 5.04; N, 10.18.

Scheme 79.

(40) Under argon atmosphere, BH_3-THF (1 M solution in THF, 100 mL, 100 mmol) was added dropwise to a solution of **40-1** (1.86 g, 6.68 mmol) in THF(50 mL) precooled by ice bath, and the whole was stirred under reflux for 5 h. MeOH (20 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 0.25 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (20 mL) and the whole was heated at 90 ℃ for 1 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (100 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid (1.68 g, quant). The solid was recrystallized from hexanes to give colorless plates: mp 184-185 ℃; ^{1}H NMR ($CDCl_3$) δ 7.24-6.98 (m, 6 H), 6.82 (t, 1 H *J*=7.3 Hz), 6.68 (d 1 H *J*=7.6, 1.3 Hz), 6.71 (d 1 H *J*=7.6 Hz), 3.80 (br, 1 H), 3.59 (s, 2 H), 3.15 (m, 1 H *J*=7.9 Hz), 4.04-3.86 (m, 4 H), 3.74 (d, 1 H *J*=15.5 Hz), 3.33 (dd, 1 H *J*=7.1, 5.3 Hz), 3.09-2.84 (m, 4 H); ^{13}C NMR ($CDCl_3$) 149.63, 134.30, 133.27, 130.85, 128.32, 127.84, 127.12, 126.13, 126.06, 125.48, 120.11, 117.68, 60.88, 60.20, 55.01, 50.75, 33.71.

Scheme 80.

(41-2) The mixture of N-methyl isatoic anhydride (192.9 mg, 1.09 mmol) and (*R*,*R*)-3,4-diphenylpyrrolidine (221.0 mg, 989.6 μmol) in THF (5 mL) was stirred for 3 h. The solvent was evaporated, and the residue was purified by column chromatography (hexanes-Et_2O, 20:1) to give 452.9 mg (quant) of colorless solid, which was recrystallized from hexanes to give colorless plates: $[a]^{25}_{D}$ -66.1° (c 1.016, $CHCl_3$); ^{1}H NMR ($CDCl_3$) d 7.32-7.17 (m, 12 H), 6.68 (d, 1 H *J* =

7.9 Hz), 6.61 (td, 1 H J = 8.1, 1.0 Hz), 5.89 (br 1 H), 4.21-3.46 (m, 6 H), 2.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) 170.01, 148.55, 139.08, 131.43, 128.14, 127.48, 127.12, 118.80, 115.06, 110.84, 60-50 (two signals), 30.03; EIMS, m/z 356 (M^+); Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 81.12; H, 6.80; N, 8.15.

Scheme 80.

(41) Under argon atmosphere, BH_3-THF (1 M solution in THF, 10 mL, 10 mmol) was added dropwise to a solution of **40-2** (352.5 mg, 989.6 μmol) in THF(5 mL) precooled by ice bath, and the whole was stirred under reflux for 18 h. MeOH (10 mL) was added to the cooled reaction mixture, and the whole was stirred under reflux for 1 h, and the solution was concentrated under reduced pressure. To the resulting residue was added aqueous 2 N-HCl (50 mL) and the whole was heated at 90 ℃ for 1.5 h. The resulting solution was cooled and K_2CO_3 was added until the solution was basic (pH 10). The solution was extracted with CH_2Cl_2 (50 mL × 3), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (100 mL × 2), H_2O (100 mL) and brine (100 mL), and the solution was dried over anhydrous K_2CO_3, filtered, and evaporated to afford colorless solid. The solid was purified by column chromatography (hexanes-Et_2O, 100:1) to give 269.6 mg (80 %) of colorless gum: $[a]^{24}_D$ -153.6° (c 1.0217, MeOH); IR (neat) 3300, 3020, 2900, 2800, 1600, 1500, 1320 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 7.28-7.13 (m, 11 H), 7.03 (d, 1 H J =6.9 Hz), 6.63 (d, 1 H J = 7.5 Hz), 6.61 (t 1 H J = 7.4 Hz), 3.77 (d, 1 H J = 12.5 Hz), 3.64 (d, 1 H J = 12.5 Hz), 3.42-3.32 (m, 2 H), 3.14-3.07 (m, 2 H), 2.93 (s, 3 H), 2.79-2.74 (m, 2 H); ^{13}C NMR ($CDCl_3$) 149.20, 144.29, 129.33, 128.53, 128.41, 127.24, 122.88, 115.99, 109.31, 62.12, 57.70, 53.08, 30.24; EIMS, m/z 342 (M^+); Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.13; H, 7.64; N, 8.47.

Binaphthol Derivatives

Scheme 83.

2f: IR (KBr) 1670, 1280, 1216, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.80 (s, 2 H), 8.69 (s, 2 H), 7.94-7.91 (m 2 H), 7.36-7.30 (m 4 H), 7.18-7.13 (m, 2 H), 4.52 (q, 4 H J = 7.1 Hz), 1.50 (t, 6 H J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) 170.13, 154.11, 137.14, 132.74, 129.74, 129.34, 127.17, 124.67, 123.88, 116.96, 114.41, 61.91, 14.29; EIMS, m/z 430 (M^+); Anal. Calcd for $C_{26}H_{22}O_6$: C, 72.55; H, 5.15; N, 0.00. Found: C, 72.63; H, 5.43; N, 0.00.

Under argon atmosphere, the mixture of **2f** (40.5 mg, 54.09 μmol, 64% ee) and sodium methoxide (77 mg, 1.41 mmol) in MeOH (5 mL) and THF (1 mL) was stirred for 1 h. Citric acid (0.45 g) was added and the mixture was partitioned with saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The organic layer was washed with brine (50 mL), dried, and concentrated to afford a pale yellow solid. The solid was purified by column chromatography (hexanes-Et_2O, 4:1) to give 36.0 mg (95%) of (S)-**2d** in 64% ee.

Scheme 84.

2g: IR (KBr) 1660, 1270, 1210, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.90 (s, 2 H), 8.66 (s, 2 H), 7.94-7.91 (m 2 H), 7.36-7.30 (m 4 H), 7.17-7.13 (m, 2 H), 5.38 (sept, 2 H J = 6.3 Hz), 1.47 (d, 12 H J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) 169.69, 154.20, 137.13, 132.65, 129.72, 129.25, 127.15, 124.67, 123.83, 116.96, 114.74, 69.76, 21.93; EIMS, m/z 458 (M^+); Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72; N, 0.00. Found: C, 73.23; H, 5.58; N, 0.00.

Under argon atmosphere, the mixture of **2g** (35.1 mg, 36.55 μmol, 64% ee) and sodium methoxide (30 mg, 555 μmol) in MeOH (5 mL) and THF (1 mL) was stirred for 1 h. Citric acid (0.30 g) was added and the mixture was partitioned with saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The organic layer was washed with brine (50 mL), dried, and concentrated to afford a pale yellow solid. The solid was purified by column chromatography (hexanes-Et_2O, 4:1) to give 21.6 mg (70%) of (S)-**2d** in 64% ee.

Scheme 85.

2h: IR (KBr) 1670, 1270, 1200, 1070 cm^{-1}; EIMS, m/z 554 (M^+).

2h (142.0 mg, 256.0 μmol, 66% ee) was dissolved in EtOH-THF 1:1 (40 mL) and hydrogenated in the presence of 10 % Pd-C (15 mg). After 14 h, the catalyst was filtered off, and the filtrate was concentrated to give pale yellow solid. The residue was dissolved in THF (4 mL) and cooled to 0 ℃. Diazomethane (generated from N-methyl-N-nitrosourea, 106.0 mg, 1.02 mmol) in Et_2O was added carefully and stirred for 5 min. Excess diazomethane was decomposed by acetic acid, and whole was successively washed with saturated aqueous $NaHCO_3$ (40 mL × 2) and brine (40 mL), and the solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to afford pale yellow solid. The solid was purified by column chromatography (hexanes-Et_2O, 4:1) to give 112.5 mg (quant) of (S)-**2d** in 66% ee.

Scheme 86.

2i: IR (KBr) 1660, 1330, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.00 (s, 2 H), 8.58 (s, 2 H), 7.92-7.88 (m 2 H), 7.33-7.29 (m 4 H), 7.18-7.02 (m, 2 H), 1.68 (s, 18 H); ^{13}C NMR ($CDCl_3$) 169.61, 154.38, 137.00, 132.65, 129.61, 129.02, 127.08, 124.64, 123.67, 116.96, 115.62, 83.36, 28.25; EIMS, m/z 486 (M^+); Anal. Calcd for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21; N, 0.00. Found: C, 74.06; H, 6.48; N, 0.00.

The mixture of **2i** (49.1 mg, 100.9 μmol, 74% ee) and trifluoroacetic acid (4 mL) was stirred at room temperature for 10 min, and trifluoroacetic acid was evaporated. The residue was dissolved in THF (4 mL) and cooled to 0 ℃. Diazomethane (generated from N-methyl-N-nitrosourea, 41.6 mg, 403.8 μmol) in Et_2O was added carefully and stirred for 5 min. Excess diazomethane was decomposed by acetic acid, and whole was successively washed with saturated aqueous $NaHCO_3$ (30 mL × 2) and brine (30 mL), and the solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to afford pale yellow solid. The solid was purified by column

chromatography (hexanes-Et_2O, 4:1) to give 39.9 mg (98 %) of (*S*)-**2d** in 74% ee.

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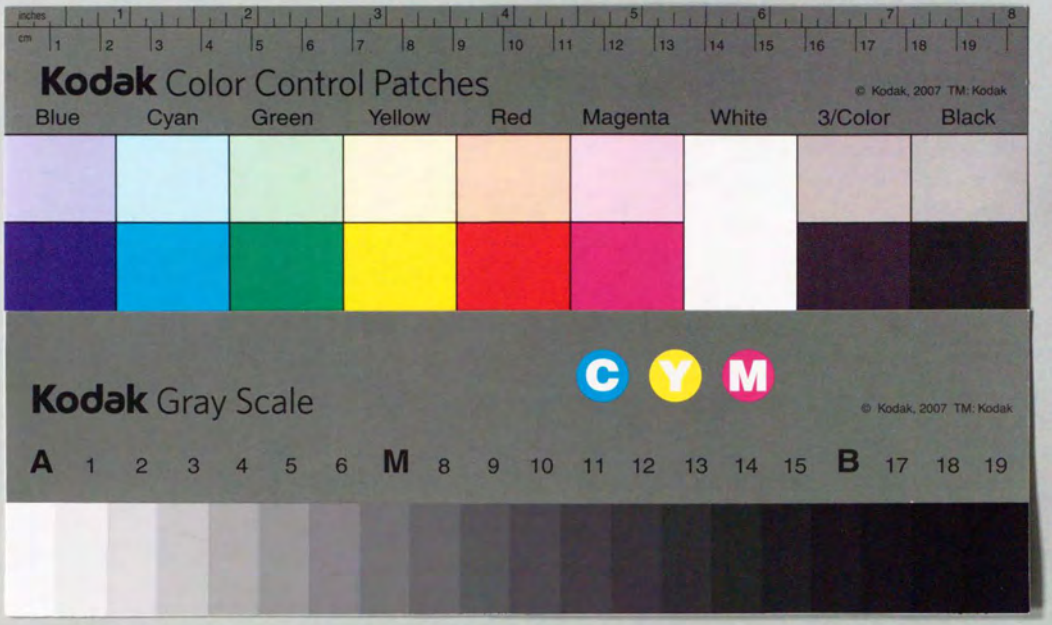
1997年　3月

野地　匡裕


inches
1 2 3 4 5 6 7 8
cm
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Kodak Color Control Patches
© Kodak, 2007 TM: Kodak
Blue
Cyan
Green
Yellow
Red
Magenta
White
3/Color
Black
Kodak Gray Scale
C
Y
M
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A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19