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ピコリン酸アリルと様々な有機銅試薬とのアリル化反応の研究

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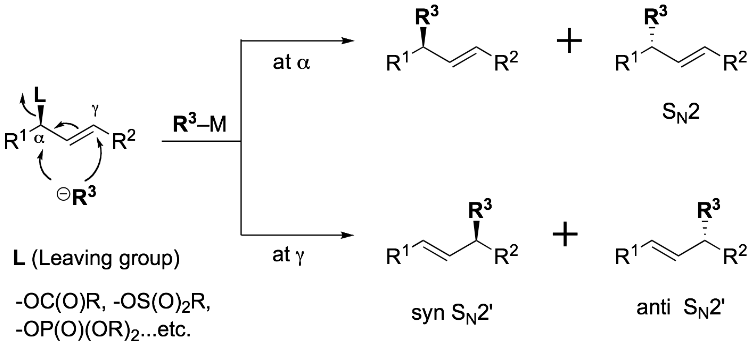
第１章「序論」

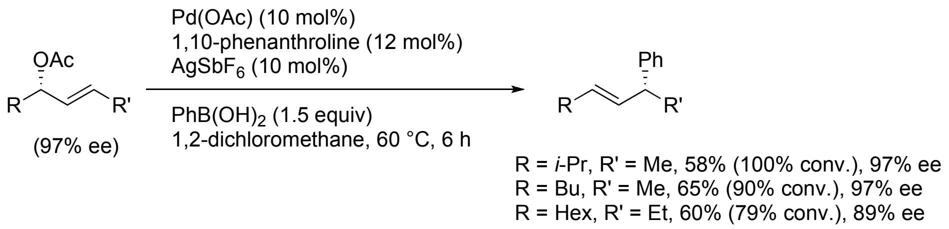
著者は博士論文研究として、ピコリン酸アリル化合物へのアリル化反応の開発研究を行った。本章では，過去の論文（知見）を引用しながら，本研究の背景・目的についてその概略を述べる。

標的化合物の合成において、光学活性な炭素－炭素結合を立体・位置選択的に構築する事は非常に重要な課題であり、新しい反応系の創出はその合成に対し新たな方法論を提供する事ができる。その不斉炭素構築方法の一つとして、著者は、２級アリルアルコール誘導体のアリル化反応に注目した[1] (eq 1)。



(1)

アリル化反応では、反応点が脱離基の α 位及び γ 位にあるため、反応の位置・立体選択性が重要である。アリル化反応では様々な求核剤と遷移金属の組み合わせが研究されている。一例として、パラジウム触媒を用いたソフトな求核剤のアリル化反応は、辻–Trost 反応として著名である。有用な反応ではあるが、π–アリル中間体を経る為に、その位置選択性の制御は基質の立体的／電子的な環境に大きく影響を受ける。2008 年に澤村らはカチオン性 Pd (II) 錯体触媒を用いたアリールボロン酸との反応で、シン S_N2' 選択的にアリール基を導入することに成功している (eq 2)[2]。しかし、反応は基質の置換基 R’ と導入するベンゼン環の置換基の立体的な影響を大きく受け、転化率や生成物の光学純度が低下してしまうのが課題である。

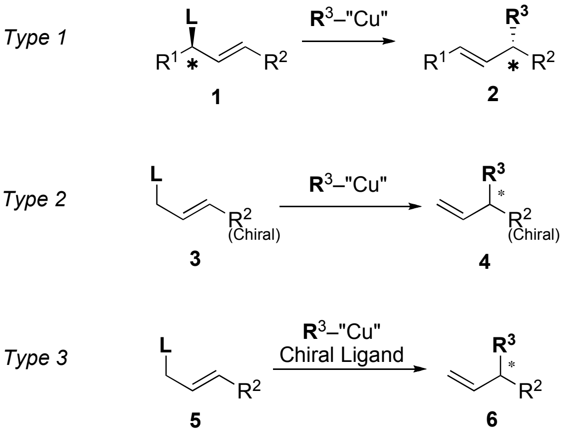


(2)

一方，有機銅試薬（ハードな求核剤）による２級アリルアルコール誘導体のアリル置換反応は、一般的にアンチ S_N2' 生成物を優先する事が知られている。この事から、光学活性な炭素－炭素結合を形成する有用な方法の１つとして精力的な研究がなされてきた。なお、主に求核性の高い sp^3 炭素アニオンである、アルキル銅試薬について研究がなされている。

ここで、有機銅試薬によるアリル化反応によって不斉炭素を構築する方法に着目すると、Scheme 1 に示すような３つの形式がある。

Scheme 1. Three types of allylic substituton.[a]



[a] **L** = leaving group.

Type 1：２級のアリル化合物 **1** に有機銅を反応させ、不斉転写により新たな不斉中心を得る (cf. eq 1)[3-8]。

Type 2：R^2 に不斉を有する１級のアリル化合物 **3** に対して有機銅を反応させ、R^2 の不斉誘起により新たな不斉を構築する[9]。

Type 3：アキラルな１級のアリル化合物 **5** に有機銅と不斉リガンドを作用させ、キラルな生成物を得る[10]。

しかし、Type 2, 3 の生成物 **4, 6** に着目すると、生成物が末端ビニル基に限定され、加えて、R^2 基もある程度限定されるため、その適応範囲は狭いといえる。

それに比べて、Type 1 では、生成物は２つの置換基 R^1, R^2 を有している。つまり、ターゲット分子の合成をデザインする際に、より柔軟性が高いと言える。また、アリル化合物 **1** に変換できる光学活性アリルアルコールの合成法が種々確立しており、得られる光学純度が高い事も魅力的である[11]。そのような理由から、著者は Type 1 の形式に着目する事にした。

しかしながら、Type 1 の反応の位置・立体選択性は、基質 **1** の置換基 R^1, R^2 の立体的及び電子的な影響の差や、試薬の求核性に大きく影響を受ける。その課題を改善するために、今日までに次のような脱離基／試薬系が開発されてきた。

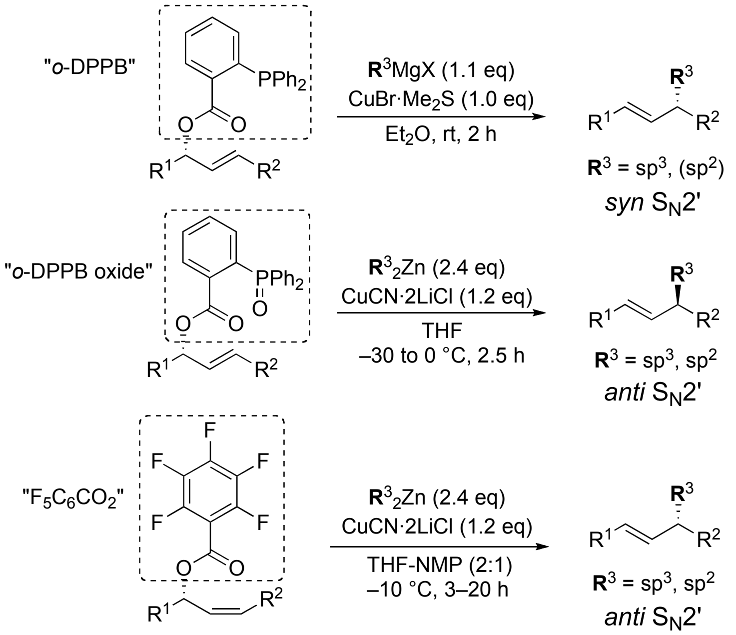
$C_6F_5CO_2$-, 2,6-$F_2C_6H_3CO_2$- (in one occasion[3f]) with $R_2Zn/CuCN{\cdot}2LiCl$;[3]
o-$(Ph_2(O)P)C_6H_4CO_2$- (*o*-DPPB oxide group) with $R_2Zn/CuCN{\cdot}2LiCl$;[4]
$(RO)_2P(O)O$- with $R_2Zn/CuCN{\cdot}2LiCl$;[5]
MsO in γ-mesyloxy-α,β-unsaturated esters with $R_2Cu(CN)Li_2{\cdot}BF_3$ or $RCu(CN)Li{\cdot}BF_3$;[6]
o-$(Ph_2P)C_6H_4CO_2$- (o-DPPB group) with $RMgX/CuBr{\cdot}Me_2S$;[4,7] etc.[8]

これらの脱離基のうち、*o*-DPPB 基は、小過剰の試薬でさも良好な選択性と反応性を示すが、他の脱離基では、多くの試薬量が必要である。例えば、2 当量以上の $Ph_2Zn/CuCN{\cdot}2LiCl$ が用いられている事が多いが、これは Ph アニオンが 4 当量以上必要であるという事である。

導入する炭素団に目を向けると、上で述べた反応系は sp^3-C 銅試薬である、アルキル銅試薬について開発されてきた。不幸な事に、その反応系を sp^3-C 銅試薬より求核性が低いアリールやアルケニル銅試薬 (sp^2-C 銅試薬) に適用すると、反応性及び（又は）選択性が低下してしまうことが知られている[5d,12]。例外としていくつかの成功例はあるが、反応性や立体的に偏りがある基質に限られており、基質の一般性は高いとは言えない[3f,13]。さらに反応性が低いアルキニル銅試薬 (sp-C 銅試薬) では反応例さえ知られていない。

しかし、近年、新しい脱離基 *o*-DPPB, *o*-DPPB oxide, $F_5C_6CO_2$ 基を用いると、選択性良く sp^2 炭素であるアリール基の導入ができるようになったと報告された (Scheme 2)。

Scheme 2. Recently developed leaving groups.



o-DPPB 基では、有機銅試薬がリン原子に配位して反応するため、シン S_N2' 生成物が得られる。また、*o*-DPPB oxide, $F_5C_6CO_2$ 基は電子吸引性置換基で活性化された脱離基で、有機亜鉛由来の銅試薬にてアンチ S_N2' 生成物が得られる。しかし、これらの反応系でも、まだ以下の課題 (1) ~ (3) は残されており、完全に満足できる結果は得られていない。

(1) アルキル基と比べ低反応性なアリール、アルケニル基など sp^2 炭素求核種の場合、*o*-DPPB 基ではアルケニル基の選択的導入ができない事や、光学活性体で不斉転写が明らかにされていない[14]。$F_5C_6CO_2$ 基ではアルケニル基の導入例がない。

(2) R^3 基の当量：亜鉛試薬では、R^3 に着目すると 4 当量以上必要であり、特に貴重な R^3 の場合に問題となりうる。

(3) これらの脱離基は大変高価であり、合成上のデメリットとなる。

そこで、これらの課題点 (1) ~ (3) を解決し、アリル化反応で sp^2 炭素や sp 炭素を選択的に導入する事が可能になれば、ターゲット合成の際の新たな選択肢となりうると考え、著者は新規反応系の開発を研究課題に決めた。

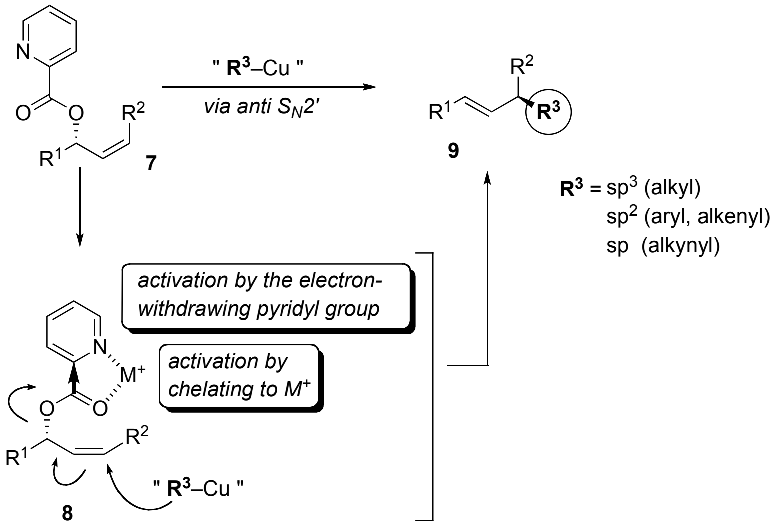
著者は、sp^2-C 銅試薬に関する困難さから、新しいメカニズムで活性化された新しい脱離基の開発が重要であると考えた。

Scheme 2 で紹介した、ある程度 sp^2-C 銅試薬の導入に成功を収めた脱離基について、その脱離基が高活性な理由を考えてみた。DPPB 基は銅試薬の配位による活性化、*o*-DPPB oxide, $F_5C_6CO_2$ 基は電子吸引性置換基により脱離能が活性化された脱離基である。しかし、１つの活性化メカニズムでは sp^2-C 銅試薬の反応性の低さを完全に克服できなかったと考えた。そこで著者は、Scheme 3 に示したような、２つの（相乗的な）活性化が期待できると考えうる、ピコリン酸（２−ピリジンカルボン酸）基に注目した。すなわち、

(a) 静電的な効果による活性化 : 電子吸引性のピリジル基によりカルボキシル基を活性化する。$C_6F_5CO_2$ 基における C_6F_5 基の場合と同様の活性化である
(b) 金属 M^+ への配位による活性化 : カルボニル酸素とピリジン環の窒素原子が M^+ へキレーションしてカルボキシル基を活性化する

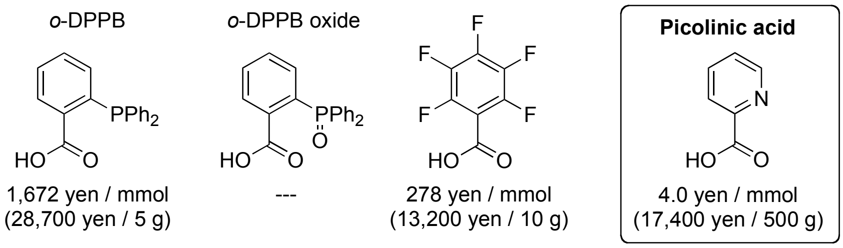
を期待した。なお、後者に関しては、真のキレート種の予測ができなかったため、シン S_N2’ あるいはアンチ S_N2’ のどちらの反応コースも想定できた。

Scheme 3. Expected activations of the picolinoxy group in the allylic substitution.



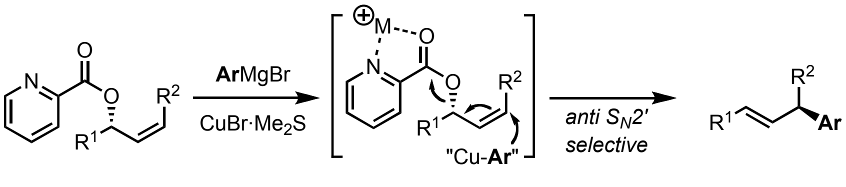
そして、著者はその仮説に基づいて検討した結果、ピコリン酸アリルと有機銅との反応で高アンチ S_N2' 選択的に生成物を得ることを見出した。この時、アルキル基だけでなく、低反応性で選択的導入の難しかったアリール基やアルケニル基の sp^2 炭素団、さらには、これまで例を見なかったアルキニル基 (sp-C) も円滑に導入できた。つまり、課題 (1) を解決できた。加えて、R^3 アニオンは２当量以下で良好な結果を与え、脱離基のコスト面においても、ピコリン酸は従来の脱離基よりはるかに安価である[15] (Figure 1)。つまり、課題 (1)~(3) について全てを解決できており、様々な面から有機合成上のメリットを示す事が出来た。それらの成果について本博士論文で述べてゆく。

Figure 1. Prices of three leaving groups.

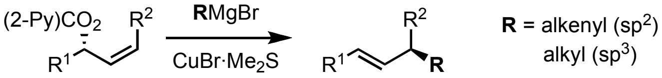


以下、各章の概略を示す。

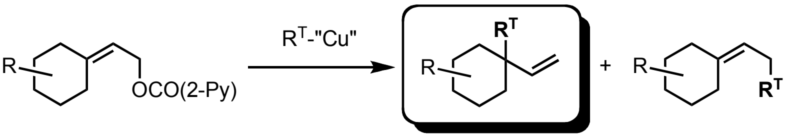
第２章「アリールグリニャール試薬と銅塩を用いたピコリン酸アリルのアリール化反応の開発」では、sp^2 アニオンであるアリールグリニャール試薬と銅塩から生じる銅試薬を用いて、試薬のタイプ（当量関係）、基質と選択性（位置／立体／不斉転写）との関係について検討した。その結果、ピコリン酸アリルがアリール基 (Ar) の導入に良好な基質であり、その反応条件を確立した事について述べている。



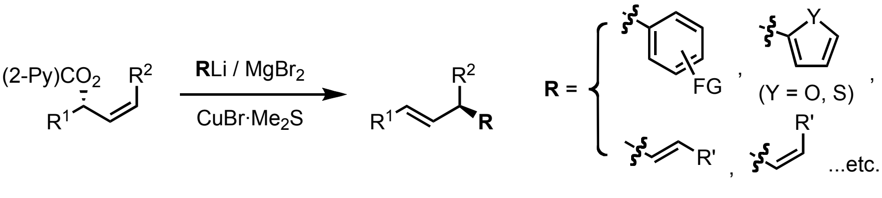
第３章「アルケニル及びアルキルグリニャール試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」では、グリニャール試薬と銅塩から生じる有機銅試薬をピコリン酸アリルと反応させ、アルケニル基 (sp^2 炭素) やアルキル基 (sp^3 炭素) を高アンチ S_N2' 選択的に導入できた事について述べている。



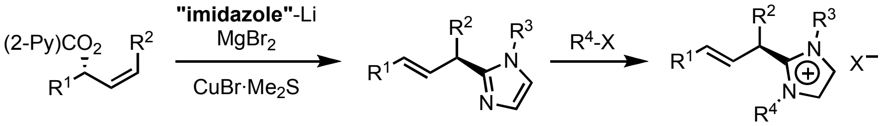
第４章「２‒シクロヘキシリデンエチルピコリン酸エステルと有機銅試薬を用いた環上４級炭素の構築」では、従来困難とされてきた環上４級炭素の構築において、ピコリン酸基を脱離基としたアリル化反応で４級炭素を高立体選択的に構築できた事について述べている。



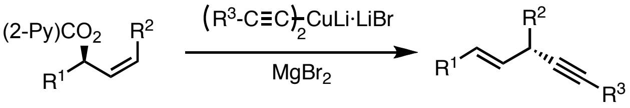
第５章「有機リチウム試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」では、グリニャール試薬の調製が難しい sp^2 炭素基（アルケニル基など）をアリル化反応に適用することを考え、リチウム試薬を用いて検討を行った。その結果、マグネシウム塩の添加が有効であり、種々の sp^2 炭素を高選択的に導入できた事について述べている。



第６章「ピコリン酸アリルのアリル化反応を活用した、光学活性なイミダゾリウム塩とピリジニウム塩の合成」では、ピコリン酸アリルのアリル化反応を活用して隣接炭素に不斉中心を有するイミダゾール、ピリジン誘導体を合成した。さらに生成物を四級塩化することで新規な構造を有するイミダゾリウム塩とピリジニウム塩の合成に成功した。本章ではこの事について述べている。



第７章「アルキニル銅試薬を用いたピコリン酸アリルのアリル化反応の開発」では、マグネシウム塩存在下でのピコリン酸基の卓越した脱離能に着目し、これまで例が知られていないアルキニル銅試薬と２級アリルアルコール誘導体でのアリル化反応を高選択的に実現できた事について述べている。



第８章「総括」では、各章の結果をまとめ、今後の展望について概観している。

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(14) Recently, the regioselection of a racemic allylic *o*-DPPB ester with sp^2-C copper reagents such as those derived from PhMgBr and CH_2=C(Me)MgBr was improved by using CH_2Cl_2 in place of Et_2O or by slow addition, but the scope of substrates to be covered by the improved conditions and the chirality transfer (CT) thereof are uncertain.[7b]

(15) Relative prices (Aldrich) of the major leaving groups as compared with picolinic acid (28 \$/mol): $C_6F_5CO_2H$, 43 times; *o*-$(Ph_2P)C_6H_4CO_2H$, 330 times; *o*-$(Ph_2P(=O))C_6H_4CO_2H$, available by oxidation of *o*-$(Ph_2P)C_6H_4CO_2H$; $(EtO)_2P(O)Cl$, 4 times. *Cf*. DCC 2.1 times.

第２章「アリールグリニャール試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」

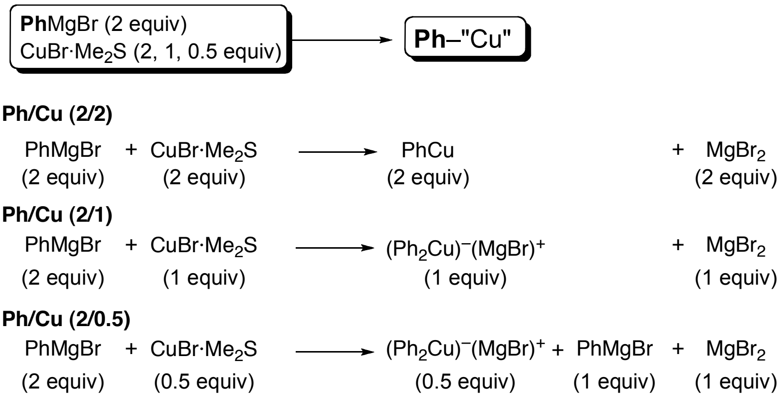
２−１．緒言

第一章で述べた様に、アルキル銅試薬 (sp^3-C 試薬) の第２級アリルアルコール誘導体へのアリル化反応ではアンチ S_N2'生成物を優先する事から、光学活性な C–C 結合の構築に大変有用な方法である。しかし、アリールやアルケニル銅試薬 (sp^2-C 試薬) は反応性が低く、選択性の低下を招くことが知られている[1,2]。例外としていくつかの成功例はあるが、反応性や立体的にバイアスがかかった基質に限られており、一般性に乏しい[3]。このような制限を克服するため、筆者はアリール銅試薬 (sp^2-C 試薬) を使うアリル化反応に有用な反応系を見出すべく研究を行った。

２−２．ラセミ体を用いた初期検討

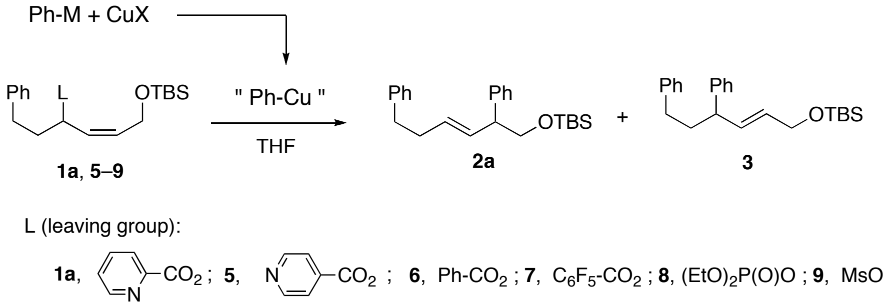
本博士論文では、便宜上、PhMgBr (2 当量) と $CuBr{\cdot}Me_2S$ (2, 1, 0.5 当量) から調製したフェニル銅試薬を、それぞれ Ph/Cu (2/2), Ph/Cu (2/1), Ph/Cu (2/0.5) 試薬と定義する。Scheme 1 にそれぞれの試薬の構造式と、同時に生成する $MgBr_2$ の当量について示した。

Scheme 1. Phenyl copper reagents derived from PhMgBr and $CuBr{\cdot}Me_2S$.

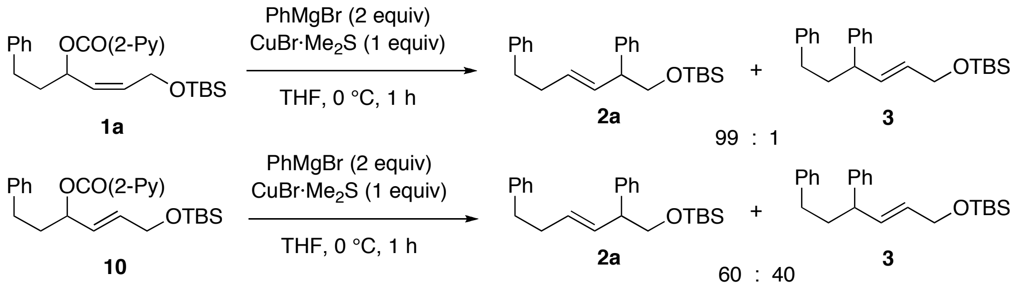


初期検討として、Scheme 2 と Scheme 3 に示した基質、すなわち、ピコリネート **1a**、**1a** のトランス異性体 **10**, および **5–9** についてアリル化反応を検討する事とした。

Scheme 2. Preliminary study.

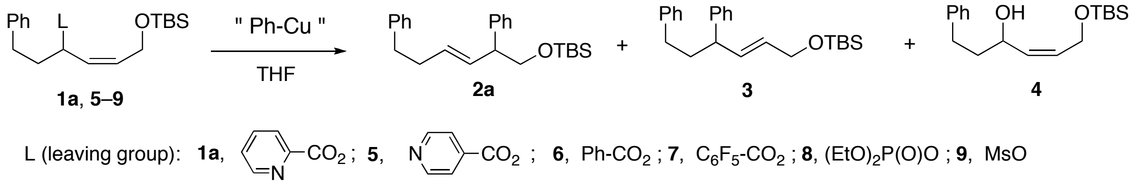


Scheme 3. Allylic substitution of allyl picolinates 1a and 10.



まず、シス体のピコリン酸アリル **1a** (L = (2-Py)CO_2) とそのトランス体 **10** に対し、Ph/Cu (2/1) を THF 中, 0 °C, 1 時間反応させた (Scheme 3)。シス体の基質 **1a** からは高い位置選択性で **2a** が生成した。この際、位置異性体も微量生成したが (**2a** : **3** = 99 : 1 by ^{1}H NMR, Table 1, entry 2)、**2a** と **3** のシス異性体 (**2a’** と **3’**) およびアルコール体 **4** の生成は認められなかった。なお、位置異性体 **3** は後述する方法で合成し (Table 2, entry 10)、シス異性体は Scheme 4 の方法を使って合成した。一方、トランス体 **10** からは、**2a** と **3** を 60 : 40 の割合で生成した (Scheme 3)。トランス体では反応が遅く、一部 π アリル中間体を経る事によって位置選択性が低下したと考えている。以上の結果から、基質の二重結合の立体はシス型が適していることがわかった。よって、以下の検討はシス体 **1a** を用いて行うことにした。

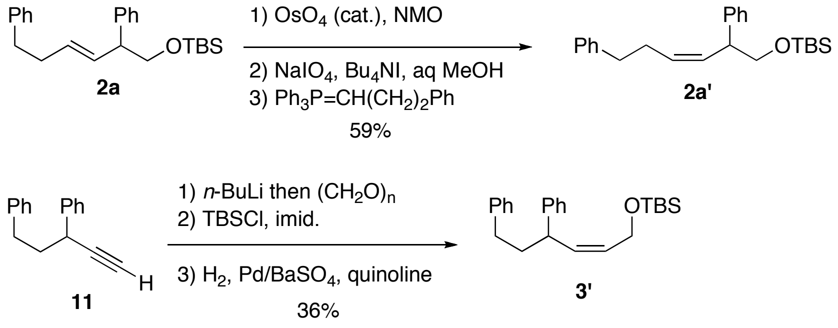
Table 1. Allylic Substitution of 1a and 5–8 with “Ph-Cu” derived from Ph-M and CuX.



entry	substrate	reagent sources (equiv)	temp, °C	time, h	ratio of **2a** : **3** : **4** : **SM**[a]	yield,[b,c] %
1	**1a**	PhMgBr (2), CuBr·Me_2S (0.5)	0	1	99 : 1 : 0 : 0	85
2	**1a**	PhMgBr (2), CuBr·Me_2S (1)	0	1	99 : 1 : 0 : 0	91
3	**1a**	PhMgBr (2), CuBr·Me_2S (2)	0	1.5	98 : 2 : 0 : 0	84
4	**1a**	PhMgBr (1.2), CuBr·Me_2S (0.5)	0	1	98 : 0 : 1 : 1	92
5	**1a**	PhMgBr (2), CuBr (0.5)	0	1	97 : 3 : 0 : 0	nd
6	**1a**	PhMgBr (3), CuBr (1.5)	–50 to –20	1	90 : 0 : 0 : 10	83
7	**1a**	PhMgBr (2), CuCl (0.5)	0	1	98 : 2 : 0 : 0	nd
8	**1a**	PhMgBr (2), CuI (0.5)	0	1	90 : 2 : 8 : 0	nd
9	**1a**	PhMgBr (2), CuCN (0.5)	0	1	96 : 0 : 2 : 2	88
10	**1a**	PhMgBr (3), CuCN (1.5)	–50 to –20	1	99 : 1 : 0 : 0	86
11	**5**	PhMgBr (2), CuBr·Me_2S (1)	0 to rt	13	46 : 0 : 0 : 54	nd
12	**6**	PhMgBr (2), CuBr·Me_2S (1)	0 to rt	20	0 : 0 : 0 : 100	–
13	**7**	PhMgBr (2), CuBr·Me_2S (2)	0 to rt	18	60 : 0 : 40 : 0	nd
14	**8**	PhMgBr (3), CuBr·Me_2S (1)	0[d]	3	99[e] : 1 : 0 : 0	nd
15	**1a**	Ph_2Zn·2LiBr[f] (3), CuBr·Me_2S (1.5)	–15 to 0	4	31 : 0 : 46 : 23	nd
16	**1a**	Ph_2Zn·2LiBr[f] (3), CuCN·2LiCl (1.5)	–15 to 0	4	25 : 0 : 60 : 15	nd
17	**1a**	Ph_2Zn·2$MgBr_2$[g] (2), CuBr·Me_2S (1)	–15 to 0	1	99 : 1 : 0 : 0	91
18	**1a**	Ph_2Zn·2$MgBr_2$[g] (2), CuCN·2LiCl (1)	–15 to 0	1.5	85 : 1 : 5 : 10	nd
19	**1a**	PhZnBr·$MgBr_2$[g] (2), CuBr·Me_2S (1)	–15 to 0	1	85 : 2 : 0 : 13	nd
20	**1a**	PhZnBr·$MgBr_2$[g] (2), CuCN·2LiCl (1)	–15 to 0	1	93 : 1 : 0 : 6	nd

[a] SM: starting materials (substrates). Zero (0) is given in the case the product signal(s) was not detected by ^{1}H NMR spectroscopy. [b] Isolated yield of **2a** (and **3**, if produced). [c] nd: not determined. [d] Almost no reaction took place at –50 to –30 °C for 4 h. [e] An olefinic impurity (cis isomer in ca. 20%) was seen in the ^{1}H NMR spectrum. [f] Derived from PhLi and $ZnBr_2$. [g] Derived from PhMgBr and $ZnBr_2$.

Scheme 4. Synthesis of 2a' and 3'.



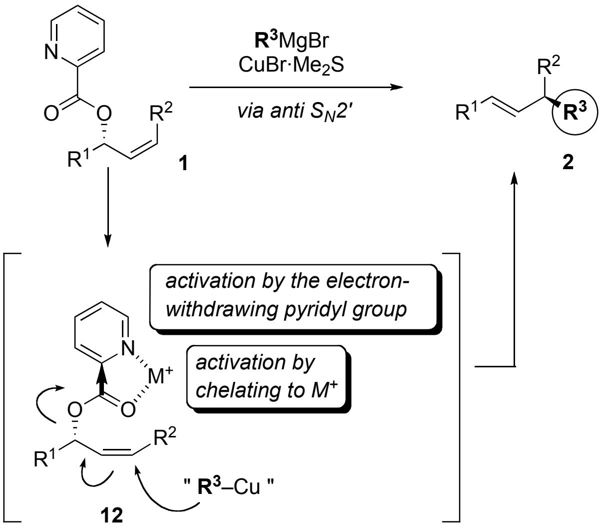
次に、PhMgBr と $CuBr·Me_2S$ の比を比較した。PhMgBr (2 当量) と $CuBr·Me_2S$ (0.5 または 2 当量) から調製した銅試薬 Ph/Cu (2/0.5) 及び Ph/Cu (2/2) を反応に用いても良好な選択性・収率を与えた (entries 1, 3)。銅試薬のアリル化反応では、一般に銅試薬の基となる有機金属試薬と銅塩の比（つまり、活性種）の違いが反応性や選択性に影響を及ぼす。これに対し、本反応では位置選択性は Ph/Cu の比に依存しなかった。よって、正確に PhMgBr と $CuBr·Me_2S$ を正確に測る必要はなく、この事は実践的なメリットであると言えよう。なお、以下の検討では銅塩の使用量が比較的少ない Ph/Cu (2/1) または Ph/Cu (2/0.5) を用いる事にした。

続いて、グリニャール試薬 PhMgBr を 1.2 当量まで減らした。この場合も反応は１時間以内に完結した (entry 4)。しかし、著者は秤量の際の誤差によるトラブルを避ける為、以下の実験では 2 当量の PhMgBr を使う事にした。

さらに、銅塩の比較検討をした。 $CuBr·Me_2S$ の代わりに CuBr, CuCl, CuI, CuCN を用いたときも同等に良好な結果を与えた (Table 1, entries 5–10)。しかし、反応を低温で行なうと、CuCN 以外では反応性が低下した (e.g. ca. 10% recovery of **2a**, entry 6)。

ここで、ピコリン酸基が良好な脱離基である理由を明らかにするために、イソニコチン酸エステル **5** と安息香酸エステル **6** を使って反応を検討した。**5** の反応は、より高い温度（0 °C一室温）にしても遅かった (entry 11)。一方、**6** は同反応条件下で反応しなかった (entry 12)。これらの結果から、ピコリン酸基が高活性な脱離基である理由として、２つの活性化機構、(1) 金属 M （後のセクションで $MgBr_2$ と判明）のキレーション効果 : **1a** > **5**、(2) 電子求引性効果 : **1a**, **5** > **6** が考えられ、これらが共同して作用していると考えている (Scheme 5)。すなわち、３種のうちピコリン酸アリル **1a** が最適である。

Scheme 5. Expected activation of the picolinoxy group in the allylic substitution.



２－３．ラセミ体を用いたさらなる検討

これまで PhMgBr を使いて良好な結果を得てきたが、他のフェニル金属種について、科学的な見地から比較してみる事にした。また、これによりピコリン酸にキレートする金属種 M を明らかにできるとも考えた。フェニル亜鉛試薬 (Ph_2Zn と PhZnBr) については、Ph–M (M = Li, MgBr) と $ZnBr_2$ から調製したものを用いアリル化を行った。驚くべきことに、 PhLi と $ZnBr_2$ より調製した $Ph_2Zn\cdot 2LiBr$ と $CuBr\cdot Me_2S$ または $CuCN\cdot 2LiCl$（Knochel試薬）[4]から調製したフェニル銅試薬は **1a** に適さなかった (entries 15, 16)。他方、PhMgBr, $ZnBr_2$ 由来の $Ph_2Zn\cdot 2MgBr_2$ を用いた時、反応は効率的に S_N2' 生成物 **2a** を与えた (entries 17, 18)。これらの結果は、PhMgBr に由来する $MgBr_2$ がピコリン酸基にキレートして反応性を上げている真の分子種であることを示唆している。同様な傾向が PhZnBr でも得られたが、Ph_2Zn に比べて反応効率は低下した (entries 19, 20)。

次に、ピコリン酸基と比較するため、他の脱離基を持つエステル **7–9** のアリル化を検討した。ペンタフルオロ安息香酸エステル **7** は競争的にアルコール **4** を副生した (entry 13)。そして、ホスホネート **8** では位置選択性は良かったが、**2a** とそのシス異性体 **2a’** の混合物が得られた (**2a** : **2a’** = 8 : 2, entry 14, Table 1, footnote e)。なお、メシラート **9** はアルコール **4** から純度良く合成する事が困

難であった。簡便な合成が出来ないため実用的でないと判断してそれ以上の検討は行わなかった。

２−４．光学活性体を用いた不斉転写についての研究

このセクションでは、光学活性なピコリン酸アリル (*S*)-**1a-d** への反応を行い、生成物の立体化学と不斉転写について明らかにした点について述べる。ここで不斉転写 (Chirality transfer) は CT と略し、不斉転写率 CT (%) は (% ee of product / % ee of substrate) x 100 と定義する。

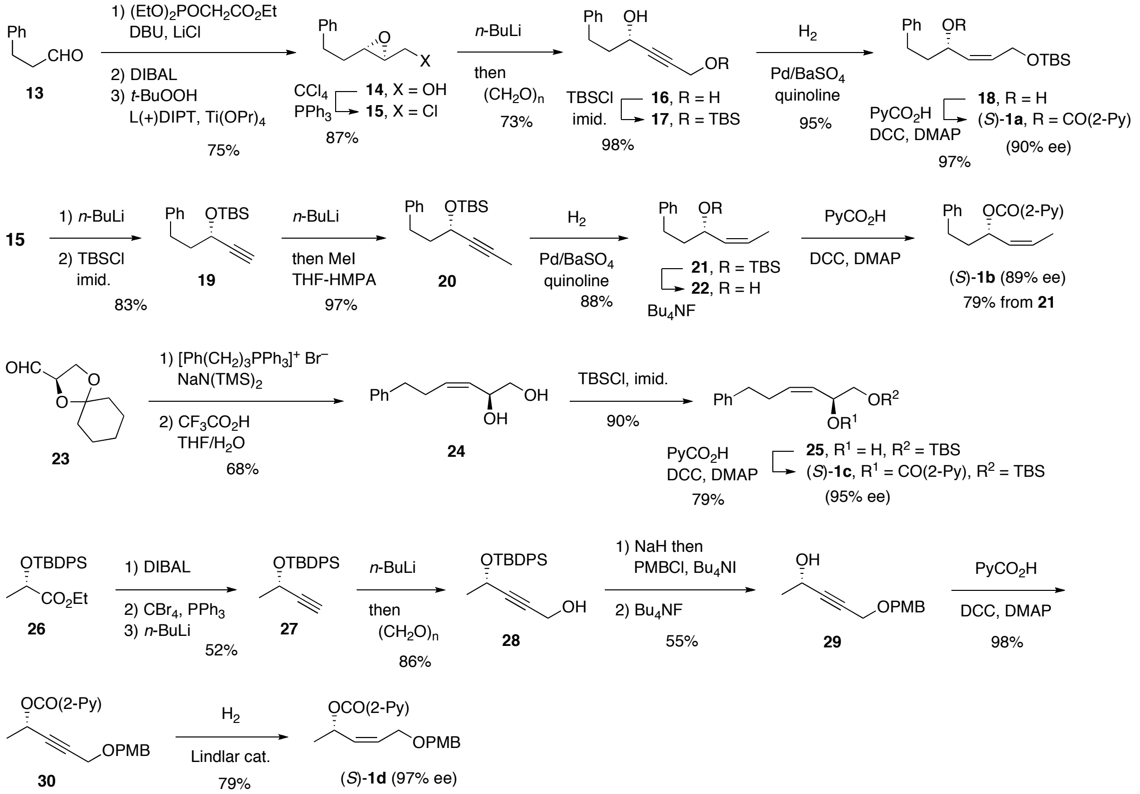
2-4-1. 基質合成

光学活性な基質 (*S*)-**1a-d** は Scheme 6 に示した方法で合成した。なお、この中で (*S*)-**1c** は (*S*)-**1a** の置換基 (R^1, R^2) が逆になっている基質である。

(*S*)-**1a** と (*S*)-**1b** の合成：アルデヒド **13** から変換したアリルアルコールに L-(+)-DIPT を使った Sharpless の不斉エポキシ化[5]を用いてエポキシアルコール **14** とした。**14** から誘導した塩化物 **15** を Yadav らの方法で[6]プロパルギルアニオンとし、パラホルムアルデヒドでトラップする事で、収率 73% でジオール **16** とした。**16** の一級水酸基の選択的な TBS 化と続くアセチレンの部分還元により、良好な収率でアリルアルコール **18** を与えた。最後に、DCC と DMAP を用いてピコリン酸と **18** を縮合し、ピコリン酸アリル (*S*)-**1a** を調製できた。合成した (*S*)-**1a** はキラルHPLC分析によって 90% ee であると決定した。(*S*)-**1b** (89% ee) は **15** から同様の方法を用いて合成した。

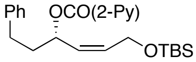
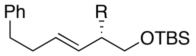
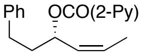
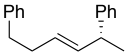
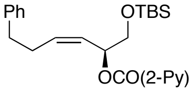
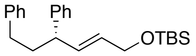
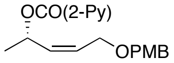
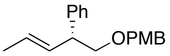
(*S*)-**1c**の合成：マンニトールから合成したアルデヒド **23**[7]は $[Ph(CH_2)_3PPh_3]^+Br^-$ と $NaN(TMS)_2$ から調製したアニオンと Wittig 反応を行いシスオレフィンとし、続く加水分解によって 68% の収率でジオール **24** に誘導した。ジオールの１級水酸基のみ選択的に TBS 保護し、残りの２級水酸基をピコリン酸と縮合し (*S*)-**1c** (95% ee) を得た。

Scheme 6. Preparation of picolinates (*S*)-1a-d.



(*S*)-**1d** の合成 : 天然由来の不斉を持つ (*S*)-乳酸エチルの TBDPS エーテル **26** を出発原料とし、Scheme 6 に示した３段階でプロパルギルアルコール体 **27** に変換した。末端アセチレンを *n*-BuLi を用いアニオン化し、パラホルムアルデヒドに作用させてアルコール **28** とした。そして、生じた水酸基の PMB 保護と続く脱 TBDPS によって **29** に変えた。ピコリン酸と縮合し、生じたエステル **30** を Lindlar触媒 (Pd/$CaCO_3$, Pb-poisoned) を用いて水素添加し、97% ee の (*S*)-**1d** を合成した。なお、**30** の部分還元で触媒として Pd/$BaSO_4$-quinoline を使用した場合、キノリンがシリカゲルクロマトグラフィーによるキノリンと (*S*)-**1d** との分離が困難であったため、ここでは Pb で被毒した Pd/$CaCO_3$ 触媒を使用した。

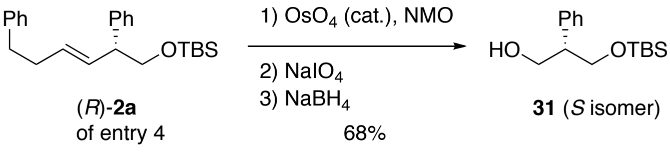
Table 2. Allylic substitution of enantiomerically enriched allylic picolinates.

entry	substrate (% ee)	reagent (equiv)	$CuBr\cdot Me_2S$, equiv	temp, °C	time, h	product[a,b]	yield, %	CT,[c] %
1	 (*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	0	1	 (*R*)-**2a**, R = Ph	85	53
2	(*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	−20 ~ −15	1	(*R*)-**2a**	84	71
3	(*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	−60 ~ −40	1	(*R*)-**2a**	83	98
4	(*S*)-**1a** (90% ee)	PhMgBr (2)	1	−60 ~ −40	1	(*R*)-**2a**	89	98
5	(*S*)-**1a** (98% ee)	PhMgBr (2)	1	−60 ~ −40	1	(*R*)-**2a**	93	99
6	(*S*)-**1a** (97% ee)	PhMgBr (1.2)	0.5	−60 ~ −40	1	(*R*)-**2a**	83	98
7	(*S*)-**1a** (90% ee)	*o*-MeC_6H_4MgBr (2)	1	−60 ~ −40	1	(*R*)-**2b**, R = *o*-MeC_6H_4	81	99
8	(*S*)-**1a** (90% ee)	*o*-$MeOC_6H_4MgBr$ (2)	1	−60 ~ −40	1	(*R*)-**2c**, R = *o*-$MeOC_6H_4$	85	98
9	 (*S*)-**1b** (89% ee)	PhMgBr (2)	1	−60 ~ −40	1	 (*R*)-**2d**	86	99
10	 (*S*)-**1c** (95% ee)	PhMgBr (2)	1	−40	1	 (*S*)-**2e**	93	97
11	 (*S*)-**1d** (97% ee)	PhMgBr (2)	1	−60 ~ −40	1	 (*R*)-**2f**	83	99

[a] Absolute configurations of **2a**, **2d**, and **2e** were determined unambiguously (for **2a**, see eq 1; for **2d**,**e**, see Scheme 8), while that of the products **2b**, **2c**, and **2f** were determined by analogy. [b] Regioselectivities of > 98 : 2 were determined by ^{1}H NMR spectroscopy. [c] Chirality transfers were determined by chiral HPLC analysis of the derivatives.

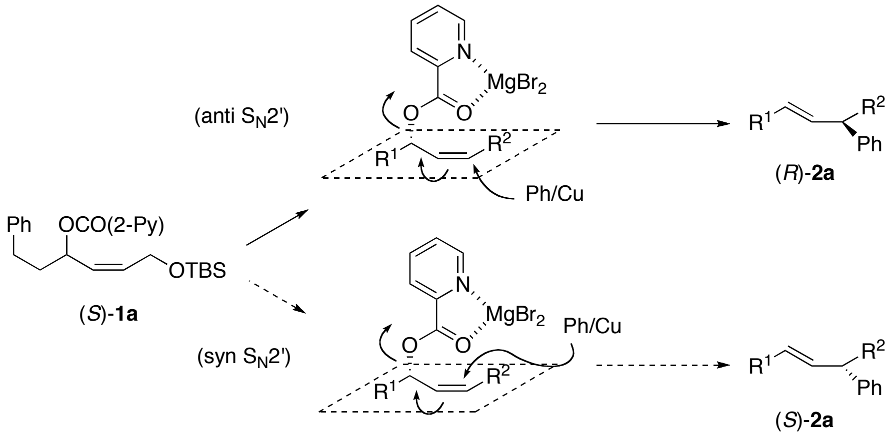
2-4-2. アリル化反応

(*S*)-**1a** (90% ee) に対して Ph/Cu (2/0.5) と Ph/Cu (2/1) を 0 °C もしくはそれ以下の温度で反応させた (Table 2, entries 1–4)。このうち、Ph/Cu (2/1) を用いて得られた生成物 **2a** (entry 4) の立体配置を決定する為に、**2a** のオレフィンを酸化的に切断して生じたアルデヒドを還元し、文献既知のアルコール **31** へと変換した (eq 1)。旋光度を測定したところ $[\alpha]^{23}_{D}$ −13 (c 0.12, $CHCl_3$) であり、*R* 体の文献値は $[\alpha]^{23}_{D}$ +14.6 (c 1.03, $CHCl_3$)[8]であった。よって、**31** は *S* 体であり、**2a** の絶対構造が *R* であると決定した。すなわち、反応はシン S_N2' ではなく、アンチ S_N2' 経路である事が確定できた (Scheme 7)。



(1)

Scheme 7. Anti- and syn-S_N2' pathways.[a]



[a] $R^1 = (CH_2)_2Ph$, $R^2 = CH_2OTBS$.

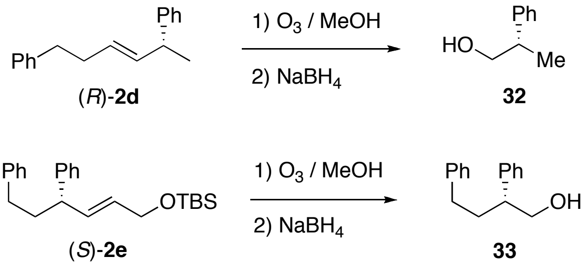
Ph/Cu 試薬 (2/0.5) から得られた生成物については entry 4 の生成物とキラル HPLC の保持時間を比較して *R* 体と決定した (entries 1–3)。

続いて、反応の不斉転写率を求めた。予想外な事に、Ph/Cu (2/0.5) による反応を 0 °C で行うと不斉転写率は低いものであった (entry 1)。しかし、反応温度を低くすると不斉転写率は向上し、–60〜–40°C で 98% CT に達した (entry 3, cf. entry 2)。また、Ph/Cu (2/1) でも高い不斉転写が得られた (entry 4)。その上、98% ee の (*S*)-**5a** でも同様の不斉転写率が得られ、基質の光学純度が不斉転写に影響しない事を確認した (entry 5)。さらに、試薬量を減らした Ph/Cu (1.2/0.5) でも高い不斉転写率で生成物が得られた (entry 6)。

次に、アリル化反応の適応範囲を調べるために、電子的及び立体的に異なるアリール銅試薬をピコリン酸アリルと反応させた。*o*-Meと*o*-MeO-C_6H_4MgBr由来のアリール銅試薬による反応はどちらの場合もよく進行し、(*R*)-**2b** 及び (*R*)-**2c** を生成した (entries 7, 8)。重要なことに、収率、不斉転写率と位置選択性は、ベンゼン環オルト位の置換基の嵩高さに影響されなかった。

つづいて、幾つかのピコリン酸アリルに対してアリル化を行った。(*S*)-**1a** と同様に、基質 (*S*)-**1b** と (*S*)-**1c** のアリル化では (*R*)-**2d** と (*S*)-**2e** をそれぞれ効率的に生成した (entries 9, 10)。生成物の立体は、(*S*)-**1a** と同様に文献既知の化合物へと変換し、その旋光度から決定した (Scheme 8)。これらの結果は、アンチ S_N2' 選択性と反応性が α 及び γ 位のメチレン置換基の影響を全く受けないことを明らかにしている。Entry 11 の結果もこの一般性と一致している。

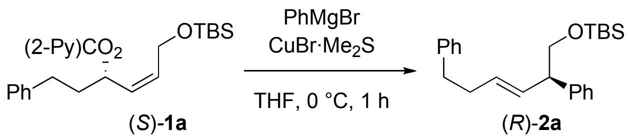
Scheme 8. Determination of the absolute configuration of (*R*)-2d and (*S*)-2e.



２−５．反応機構（一部ラセミ化）についての実験と考察

本説では、Table 2 の entry 1 (Ph/Cu (2/0.5), 0 °C) で不斉転写率が低かった理由を明らかにすべく、実験と考察を行った。Ph/Cu (2/0.5) では、銅が触媒としてサイクルするのが原因ではないかと考え、様々な比率の Ph/Cu を用いて反応を行った。結果を Table 3 に示す。

Table 3. Allylation of (*S*)-1a with PhMgBr/CuBr·Me$_2$S in various ratios.[a]



entry	PhMgBr, equiv	CuBr·Me$_2$S, equiv	yield, %	CT, %
1	2	0.5	85	53
2	2	1	89	97
3	3	1	92	49
4	4	1	80	38
5	5	1	79	32
6	4	2	91	96
7	2	0	2	61

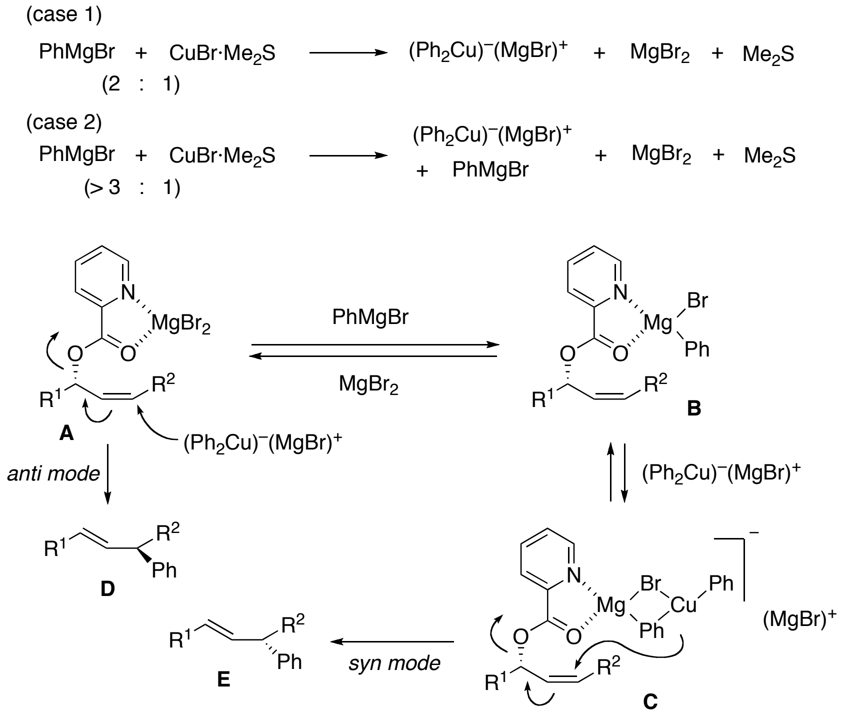
[a] All regioselectivities were >95 : 5 by ^{1}H NMR.

Entry 1 は Table 2, entry 1 の再録である。1 当量の CuBr·Me$_2$S に対して PhMgBr の当量を増やしていくと、2 当量で得られた高い不斉転写は当量が増えると共に低下した (entries 2–5)。一方、Ph/Cu (2/1) の試薬量をそれぞれ倍にした Ph/Cu (4/2) では Ph/Cu と同じく高い不斉転写率であった (entry 2 vs 6)。すなわち、銅塩が 1 当量に対して PhMgBr を 2 当量より多く加えた時に不斉転

写の低下が見られた。不斉転写の低下は過剰の PhMgBr そのものの影響ではないかと考え、銅塩を添加せず反応を行ってみた。しかしアリル化は殆ど進行せず、その影響は小さいと言える (entry 7)。すなわち、「$(Ph_2Cu)^-MgBr^+ + PhMgBr$」という活性種が不斉転写の低下を起こしていると言える。

不斉転写率低下の原因としては、(1) アリルラジカルによるラセミ化、(2) アリルカチオンによるラセミ化、(3) シン S_N2' 反応の競合、の可能性が考えられる。しかし、アリルラジカル又はカチオンが生じるなら、その異性化が起こり位置選択性の低下が見られるはずであるが、全ての反応で位置選択性が高いため、(1), (2) は不適と解釈できる。そこで、Scheme 9 の様に考察した。

Scheme 9. Plausible mechanism of allylation of allylic picolinate.[a]



[a] $R^1 = (CH_2)_2Ph$, $R^2 = CH_2OTBS$.

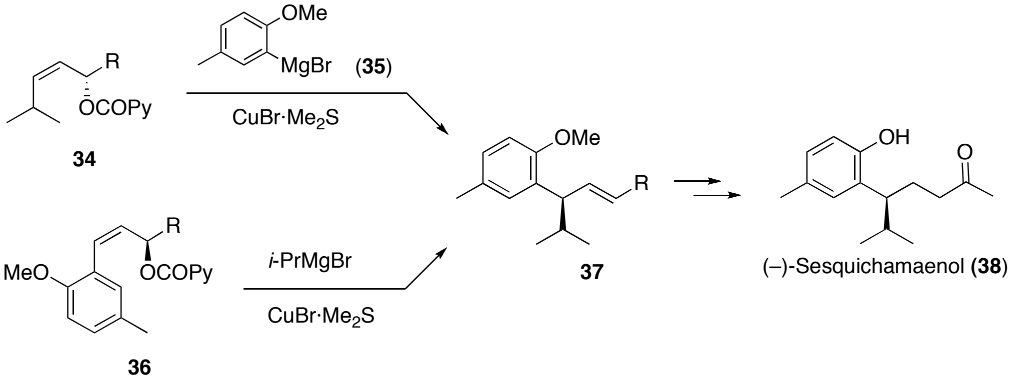
Ph/Cu (2/1) の場合、$MgBr_2$ がキレートした **A** から「anti mode」を経て生成物アンチ S_N2' 体を得る。一方、反応系に過剰な PhMgBr が存在する時、ピコリン酸基へのキレート種 $MgBr_2$ と PhMgBr の間で交換が起こり **B** が生成する。**B** 自体はアリル化を起こさないと考えられるが (cf. Table 3, entry 7)、さらに Ph/Cu が作用して **C** の様な中間体となり、「syn mode」でアリル化が進行すると考えるのが妥当と考察した。但し、Ph/Cu (2/0.5) でも低温にすると不斉

転写率が改善する事から (cf. Table 2, entries 1–3)、**B**, **C** を経て **E** に至る反応コースのどこかが低温では進行しづらいと考えられる。

２−６．セスキカマエノールの全合成

本章で見出したアリル化反応の応用研究として、光学活性な (–)-セスキカマエノール (**38**) の初の不斉全合成を達成したので本節に示す。

Scheme 10. Two possible routes to the key intermediate 37.

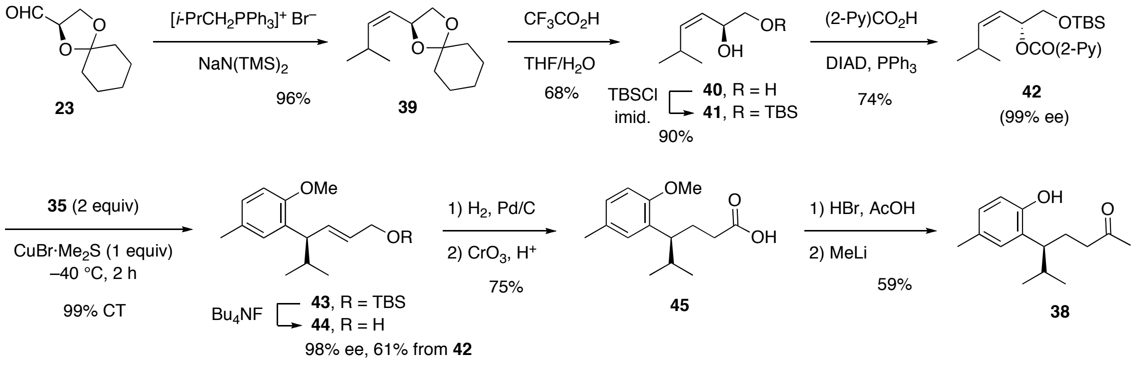


(–)-セスキカマエノール [9,10,11] はベニヒ等の植物から単離されたセスキテルペンである。非常に少量成分であった為に生理活性はほとんど研究されておらず、研究の進展の為には不斉合成によるサンプル供給が必要と考えられる。これまでに幾つかラセミ体合成の報告はあるが、不斉合成の報告は無い。そこで、(–)-セスキカマエノールの合成を行なう事とした。

ピコリン酸アリルのアンチ S_N2' 反応を鍵反応とした (–)-セスキカマエノールの合成計画は２通り考えられる (Scheme 10)。しかし、**36** のアリル化では、**36** の二重結合がベンゼン環と共役している為選択性の制御が難しいと考えられる。そこで、**34** のアリル化を鍵反応としたルートを検討した。実際の合成を Scheme 11 に示す。

出発原料の **23** に Wittig 反応を行いシスオレフィン **39** を得た。続いて、トリフルオロ酢酸を用いて加水分解した後、一級水酸基を選択的に TBS 保護し **41** とした。次に、アンチ S_N2' 反応により(–)-セスキカマエノールの立体を正しく構築するため、光延反転を行い、光学純度 99% ee のピコリン酸エステル **42** を合成した。(**42** の光学純度決定の為、$PyCO_2H$/DCC の条件で **42** のエナンチオマーを合成し、それらの HPLC 分析で光学純度を決定した。)

Scheme 11. Synthesis of (–)-sesquichamaenol (38).



42 に対して *o*-MeO-*m*-Me-C_6H_3MgBr (**35**) と CuBr·Me$_2$S から調製した銅試薬のアリル反応を行ったところ、高選択的に S$_N$2’ 反応が進行し、生成物 **43** が良好な収率で得られた。銅試薬と *i*-Pr 基の立体障害による反応速度の低下は観察されなかった。なお、銅試薬由来の残渣と生成物の分離が困難であったため、TBAF で TBS 基を除去した後に精製した。**44** の HPLC 分析を行い、非常に高い不斉転写率でアリル化が進行したことを確認できた。続いて、**44** に水素化、Jones 酸化を行い、カルボン酸 **45** へと変換した。

最後に、カルボン酸からセスキカマエノールへの変換について検討した。まず、MeLi でカルボン酸 **45** をケトンとし、HBr によるメチルエーテルの脱保護を試みた。しかしながら、反応残渣との分離が非常に困難で、高純度の (–)-セスキカマエノールを得ることは出来なかった。

そこで、**45** に先に HBr での脱メチル化を行い、続いて MeLi によるケトンへの変換を行った。その結果、非常に純度の高い (–)-セスキカマエノール (**38**) の全合成に成功した。なお、合成品の旋光度は天然体の旋光度と一致し、鍵反応である S$_N$2’ 反応も予想通りアンチ型で進行していることが確認出来た[10b]。

２－７．結論

sp^2 炭素基であるアリールグリニャール試薬と銅塩から生じるアリール銅試薬を用いてアリル化反応を検討した所、ピコリン酸基が良好な脱離基となり、反応は高いアンチ S_N2' 選択性で進行した。基質の適応範囲も広く、導入するベンゼン環も立体障害となる置換基が反応を阻害しない。加えて、応用研究として(–)-セスキカマエノールの全合成に成功した。

さらなる利点として、ピコリン酸、DCC, RMgBr と $CuBr\cdot Me_2S$ は安価であり、そして、基質のアリルアルコール類の両方の鏡像異性体は、不斉化反応又はキラルプールから簡単に合成できる事も示せた。ピコリン酸基へのキレーションによる脱離能の活性化というコンセプトに沿って研究を続ける事とし、その成果を後の章に示す。

Experimental section

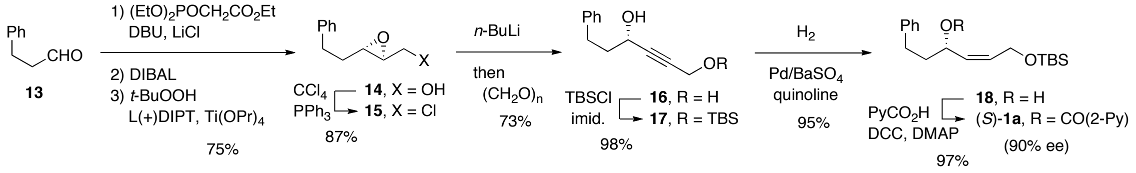
General.

Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants *(J)* are given in hertz (Hz). In some cases chemical shifts of carbons accompany plus (for C and CH_2) and minus (for CH and CH_3) signs of APT experiments. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions, organic extracts were concentrated by using a rotary evaporator and residues were purified by chromatography on silica gel (Merck, silica gel 60).

Preparation of CuBr·Me$_2$S with Modification of the Published Procedure.[12]

To a flask containing CuBr (3.00 g, 20.6 mmol) was added Me_2S (30 mL) slowly. The resulting mixture was refluxed for 1 h under argon, the resulting solution was cooled to rt and recrystallized with hexane (30 mL). The white crystals were filtered and washed with hexane several times until the washing was colorless. The residual solid was dried under vacuum to afford CuBr·Me_2S (3.74 g, 88%) as white prisms, which was stored under Ar in a refrigerator before use.

Synthesis of Picolinate (*S*)-1a.



(2*S*,3*S*)-2,3-Epoxy-5-phenylpentan-1-ol (14).

To a suspension of LiCl (2.20 g, 51.9 mmol) in MeCN (60 mL) were added DBU (6.70 mL, 44.9 mmol) and triethyl phosphonoacetate (9.70 mL, 48.5 mL) at 0 °C. The mixture was stirred 0 °C for 10 min, and a solution of aldehyde **13** (5.00 g, 37.3 mmol) in MeCN (15 mL) was added. The reaction was carried out first at 0 °C for 30 min and then at rt for 30 min, and was quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding ester (7.25 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7 Hz, 3 H), 2.48–2.57 (m, 2 H), 2.78 (t, *J* = 7 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 5.85 (dt, *J* = 16, 2 Hz, 1 H), 7.01 (dt, *J* = 16, 7 Hz, 1 H), 7.15–7.23 (m, 3 H), 7.24–7.33 (m, 2 H).

To a solution of the above ester (5.00 g, 24.5 mmol) in CH_2Cl_2 (5 mL) was added DIBAL (58.0 mL, 0.95 M in hexane, 55.1 mmol) dropwise at –78 °C. After 45 min at –78 °C, H_2O (9 mL, 500 mmol) and NaF (20.6 g, 491 mmol) were added to the solution. The resulting mixture was stirred at rt for 30 min and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding allylic alcohol (3.51 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (br s, 1 H), 2.33–2.43 (m, 2 H), 2.71 (dd, *J* = 8, 7 Hz, 2 H), 4.05–4.12 (m, 2 H), 5.66 (dd, *J* = 16, 6 Hz, 1 H), 5.75 (dt, *J* = 16, 6 Hz, 1 H), 7.15–7.23 (m, 3 H), 7.24–7.32 (m, 2 H).

To a suspension of Ti(O-*i*-Pr)$_4$ (1.17 mL, 3.99 mmol) and MS 4A (powder, 1.3 g) in CH_2Cl_2 (8 mL) was added L-(+)-DIPT (1.01 mL, 4.83 mmol) at –20 °C. The mixture was stirred at –20 °C for 20 min and cooled to –40 °C. A solution of the above alcohol (1.30 g, 8.01 mmol) dissolved in CH_2Cl_2 (8 mL) and *t*-BuOOH (2.05 mL, 5.86 M in CH_2Cl_2, 12.0 mmol) were added to the solution successively. After 4 h at –20 °C, the reaction was quenched by addition of H_2O (1.4 mL, 78 mmol) and NaF (3.4 g, 81 mmol). The mixture was stirred at rt for 30 min and filtered through a pad of Celite. To the filtrate was added 1 M NaOH (12 mL), and the mixture was stirred at rt for 30 min. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the epoxy alcohol **14** (1.29 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–1.62 (m, 1 H), 1.80–2.00 (m, 2 H), 2.67–2.89 (m, 3 H), 2.99 (ddd, *J* = 6, 6, 2 Hz, 1 H), 3.57 (ddd, *J* = 12, 8, 5 Hz, 1 H), 3.84 (ddd, *J* = 12, 6, 3 Hz, 1 H), 7.17–7.24 (m, 3 H), 7.25–7.33 (m, 2 H). The ^{1}H NMR spectrum of **14** was identical with that reported.[13] As described below, **14** was converted to (*S*)-**1a**, which was 90% ee by chiral HPLC analysis.

(*S*)-6-Phenylhex-2-yne-1,4-diol (16).

To a solution of **14** (2.00 g, 11.2 mmol) in CH_2Cl_2 (23 mL) were added CCl_4 (2.20 mL, 22.8 mmol) and PPh_3 (3.90 g, 14.9 mmol) at 0 °C. The mixture was refluxed for 6 h, diluted with hexane (30 mL), and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **15** (1.91 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86–1.95

(m, 2 H), 2.68–3.00 (m, 4 H), 3.47 (dd, J = 12, 6 Hz, 1 H), 3.53 (dd, J = 12, 6 Hz, 1 H), 7.17–7.24 (m, 3 H), 7.26–7.34 (m, 2 H).

To a solution of chloride **15** (490 mg, 2.50 mmol) in THF (5 mL) was added *n*-BuLi (4.36 mL, 2.30 M in hexane, 10.0 mmol) dropwise at –78 °C. After 1 h at –78 °C, paraformaldehyde (451 mg, 15.0 mmol) was added portionwise. The mixture was allowed to warm slowly to rt over 14 h, cooled to 0 °C, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford diol **16** (349 mg, 73%): IR (neat) 3338, 1014, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90–2.09 (m, 2 H), 2.75 (t, J = 8 Hz, 2 H), 3.73 (br s, 2 H), 4.27 (d, J = 2 Hz, 2 H), 4.37 (tt, J = 7, 2 Hz, 1 H), 7.13–7.29 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4 (+), 39.0 (+), 50.7 (+), 61.5 (–), 83.4 (+), 86.5 (+), 126.0 (–), 128.46 (–), 128.50 (–), 141.2 (+).

(*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylhex-4-yn-3-ol (17).

To a solution of **16** (440 mg, 2.28 mmol) and imidazole (230 mg, 3.38 mmol) in DMF (8 mL) at –50 °C was added TBSCl (413 mg, 2.74 mmol) in DMF (4 mL) dropwise. After 1 h at –50 °C, the solution was diluted with saturated $NaHCO_3$ and hexane. The organic layer was separated, and the aqueous layer was extracted with hexane three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **17** (680 mg, 98%): IR (neat) 3393, 1255, 1087, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 6 H), 0.92 (s, 9 H), 1.81 (br s, 1 H), 1.97–2.07 (m, 2 H), 2.79 (t, J = 8 Hz, 2 H), 4.36–4.45 (m, 1 H), 4.37 (d, J = 2 Hz, 2 H), 7.16–7.24 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.0 (–), 18.4 (+), 25.9 (–), 31.4 (+), 39.2 (+), 51.8 (+), 61.9 (–), 84.1 (+), 85.5 (+), 126.1 (–), 128.5 (–), 128.6 (–), 141.4 (+). The ^1H NMR spectrum of **17** was identical with that reported.[14]

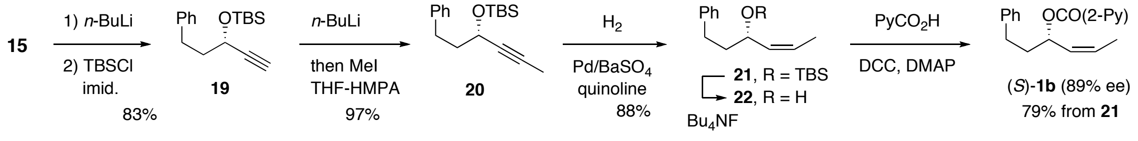
(*S*,*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylhex-4-en-3-ol (18).

To a solution of **17** (434 mg, 1.43 mmol) in MeOH (3 mL) were added 10% Pd on $BaSO_4$ (21 mg) and quinoline (85 mg, 0.66 mmol) at rt. The mixture was stirred for 30 min at rt under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **18** (415 mg, 95%): IR (neat) 3393, 1255, 1081, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.70–1.84 (m, 1 H), 1.86–1.99 (m, 1 H), 2.20 (d, J = 4 Hz, 1 H), 2.61–2.79 (m, 2 H), 4.16 (ddd, J = 14, 5, 1 Hz, 1 H), 4.25 (ddd, J = 14, 6, 1 Hz, 1 H), 4.37–4.47 (m, 1 H), 5.55 (dddd, J = 11, 8, 1, 1 Hz, 1 H), 5.65 (ddd, J = 11, 6, 5 Hz, 1 H), 7.10–7.23 (m, 3 H), 7.25–7.31 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2 (–), 18.4 (+), 26.0 (–), 31.7 (+), 38.8 (+), 59.7 (+), 67.3 (–), 125.9 (–), 128.46 (–), 128.51 (–), 131.1 (–), 134.2 (–), 141.9 (+); HRMS (FAB) calcd for $C_{18}H_{30}O_2SiK$ [(M + K)$^+$] 345.1652, found 345.1657.

(*S*,*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylhex-4-en-3-yl Pyridine-2-carboxylate ((*S*)-1a).

To an ice-cold suspension of picolinic acid (152 mg, 1.23 mmol) in CH_2Cl_2 (2 mL) were added DMAP (126 mg, 1.03 mmol) and DCC (276 mg, 1.34 mmol). After 20 min at rt, alcohol **18** (316 mg, 1.03 mmol) in CH_2Cl_2 (2 mL) was added to the mixture at 0 °C. The mixture was stirred at rt for 1 h, diluted with hexane (4 mL), and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-**1a** (411 mg, 97%): 90% ee by HPLC analysis (Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.3 mL/min, , rt; t_R (min) = 25.5 (*S*), 27.1 (*R*)); IR (neat) 1718, 1302, 1245, 1132, 1086, 836, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.90 (s, 9 H), 1.95–2.09 (m, 1 H), 2.20–2.34 (m, 1 H), 2.73 (dd, J = 8, 8 Hz, 2 H), 4.36 (dd, J = 6, 2 Hz, 2 H), 5.58 (ddt, J = 11, 9, 2 Hz, 1 H), 5.76 (dt, J = 11, 6 Hz, 1 H), 5.78–5.89 (m, 1 H), 7.14–7.23 (m, 3 H), 7.24–7.31 (m, 2 H), 7.46 (ddd, J = 8, 5, 1 Hz, 1 H), 7.82 (ddd, J = 8, 8, 2 Hz, 1 H), 8.09 (dm, J = 8 Hz, 1 H), 8.78 (dm, J = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2 (–), –5.1 (–), 18.4 (+), 26.0 (–), 31.5 (+), 36.2 (+), 59.8 (+), 71.6 (–), 125.2 (–), 126.1 (–), 126.8 (–), 127.6 (–), 128.40 (–), 128.49 (–), 134.6 (–), 136.9 (–), 141.1 (+), 148.4 (+), 150.0 (–), 164.5 (+); HRMS (FAB) calcd for $C_{24}H_{33}NO_3SiNa$ [(M + Na)$^+$] 434.2127, found 434.2118.

Synthesis of Picolinate (*S*)-1b.



(*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-2-yne (20).

To a solution of the above chloride **15** (1.68 g, 8.57 mmol) in THF (17 mL) was added *n*-BuLi (24.0 mL, 1.26 M in hexane, 30.2 mmol) dropwise over 15 min at –78 °C. After 30 min at –78 °C, the reaction was quenched by addition of saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford

(*S*)-1-phenylpent-4-yn-3-ol, which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (dd, *J* = 6, 1 Hz, 1 H), 1.95–2.13 (m, 2 H), 2.51 (dd, *J* = 2, 1 Hz, 1 H), 2.81 (t, *J* = 8 Hz, 2 H), 4.37 (dddd, *J* = 7, 7, 6, 2 Hz, 1 H), 7.16–7.33 (m, 5 H). The ^{1}H NMR spectrum of the product was identical with that reported.[15]

To an ice-cold solution of the above acetylenic alcohol and imidazole (1.20 g, 17.6 mmol) in DMF (17 mL) was added TBSCl (1.94 g, 12.9 mmol). After 2 h at rt, the solution was diluted with saturated $NaHCO_3$ and hexane. The organic layer was separated and the aqueous layer was extracted with hexane three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish silyl ether **19** (1.95 g, 83% from **15**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.95–2.04 (m, 2 H), 2.42 (d, *J* = 2 Hz, 1 H), 2.68–2.85 (m, 1 H), 4.37 (ddd, *J* = 6, 6, 2 Hz, 1 H), 7.15–7.23 (m, 3 H), 7.25–7.32 (m, 2 H).

To a solution of **19** (2.74 g, 9.98 mmol) in THF (50 mL) and HMPA (5.0 mL) was added *n*-BuLi (9.4 mL, 1.60 M in hexane, 15.0 mmol) at –78 °C. After 20 min at –78 °C, MeI (1.25 mL, 20.0 mmol) was added to the solution dropwise. The solution was allowed to warm to rt slowly. After 12 h, the reaction was quenched by addition of saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with hexane three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford methyl acetylene **20** (2.81 g, 97%): IR (neat) 1092, 836, 777, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.84 (d, *J* = 2 Hz, 3 H), 1.93 (dt, *J* = 1, 7 Hz, 1 H), 1.96 (dt, *J* = 1, 7 Hz, 1 H), 2.74 (dt, *J* = 4, 7 Hz, 2 H), 4.30–4.37 (m, 1 H), 7.14–7.23 (m, 2 H), 7.24–7.32 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9 (–), –4.3 (–), 3.6 (–), 18.3 (+), 25.9 (–), 31.6 (+), 40.6 (+), 62.6 (–), 80.4 (+), 80.8 (+), 125.8 (–), 128.4 (–), 128.5 (–), 142.0 (+); HRMS (FAB) calcd for $C_{15}H_{25}OSi$ $[(M - C_3H_3)^+]$ 249.1675, found 249.1671.

(*S*,*Z*)-1-Phenylhex-4-en-3-ol (22).

To a solution of **20** (1.38 g, 4.74 mmol) in MeOH (19 mL) were added 10% Pd on $BaSO_4$ (95 mg) and quinoline (0.284 mL, 2.40 mmol). The mixture was stirred at rt for 2.5 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **21** (1.21 g, 88%): IR (neat) 3027, 1254, 1085, 836, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 1.61 (d, *J* = 5 Hz, 3 H), 1.65–1.77 (m, 1 H), 1.80–1.93 (m, 1 H), 2.56–2.76 (m, 2 H), 4.47 (dt, *J* = 6, 7 Hz, 1 H), 5.34–5.51 (m, 2 H), 7.15–7.23 (m, 2 H), 7.24–7.32 (m, 3 H); ^{13}C NMR (75

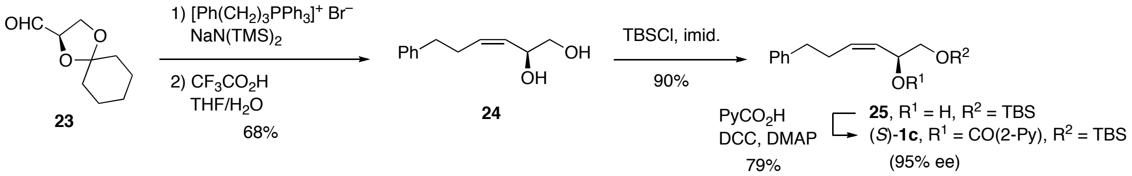
MHz, $CDCl_3$) δ –4.7 (–), –4.2 (–), 13.4 (–), 18.3 (+), 26.0 (–), 31.8 (+), 40.1 (+), 68.0 (–), 123.4 (–), 125.7 (–), 128.3 (–), 128.4 (–), 134.9 (–), 142.5 (+).

To a solution of **21** (2.48 g, 8.47 mmol) in THF (12 mL) was added Bu_4NF (12.7 mL, 1.0 M in THF, 12.7 mmol). The solution was stirred at rt for 4 h and diluted with saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford alcohol **22**, which was used for the next reaction without further purification. Analytically pure sample of **22** was obtained by chromatography on silica gel (hexane/EtOAc): IR (neat) 3347, 3026, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (br s, 1 H), 1.65 (dd, J = 7, 2 Hz, 3 H), 1.70–1.84 (m, 1 H), 1.88–2.00 (m, 1 H), 2.65–2.73 (m, 2 H), 4.46–4.52 (m, 1 H), 5.45 (ddq, J = 11, 9, 2 Hz, 1 H), 5.60 (ddq, J = 11, 1, 7 Hz, 1 H), 7.16–7.24 (m, 2 H), 7.25–7.33 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4 (–), 31.7 (+), 39.0 (+), 66.9 (–), 125.9 (–), 126.8 (–), 128.4 (–), 128.5 (–), 133.3 (–), 142.0 (+); HRMS (EI) calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1204.

(*S*,*Z*)-1-Phenylhex-4-en-3-yl Pyridine-2-carboxylate ((*S*)-1b).

To a suspension of picolinic acid (1.15 g, 9.34 mmol) in CH_2Cl_2 (20 mL) were added DMAP (1.14 g, 9.33 mmol) and DCC (2.10 g, 10.2 mmol). After 20 min at rt, the above alcohol in CH_2Cl_2 (2 mL) was added to the mixture. The mixture was stirred at rt for 12 h, diluted with hexane, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-**1b** (1.88 g, 79% from **21**): 89% ee by HPLC analysis (Chiralcel AD-H; hexane/*i*-PrOH = 95/5, 0.5 mL/min, rt; t_R (min) = 25.5 (*S*), 28.6 (*R*)); $[\alpha]^{26}_D$ +31 (*c* 1.09, $CHCl_3$); IR (neat) 1738, 1716, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (dd, J = 7, 2 Hz, 3 H), 1.96–2.08 (m, 1 H), 2.22–2.34 (m, 1 H), 2.73 (t, J = 8 Hz, 2 H), 5.57 (ddq, J = 11, 7, 2 Hz, 1 H), 5.74 (ddq, J = 11, 2, 7 Hz, 1 H), 5.93 (dt, J = 9, 7 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.25–7.30 (m, 3 H), 7.46 (ddd, J = 8, 5, 1 Hz, 1 H), 7.82 (ddd, J = 8, 8, 2 Hz, 1 H), 8.10 (ddd J = 8, 8, 1 Hz, 1 H), 8.76 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (–), 31.4 (+), 36.0 (+), 71.3 (–), 125.1 (–), 125.9 (–), 126.7 (–), 128.30 (–), 128.35 (–), 128.38 (–), 129.4 (–), 136.8 (–), 141.2 (–), 148.4 (–), 149.9 (–), 164.5 (+); HRMS (EI) calcd for $C_{18}H_{19}NO_2$ (M^+) 281.1416, found 281.1422.

Synthesis of Picolinate (*S*)-1c.



(*S*,*Z*)-6-Phenylhex-3-ene-1,2-diol (24).

To an ice-cold suspension of $[Ph(CH_2)_3PPh_3]^+Br^-$ (5.0 g, 10.8 mmol) in THF (20 mL) was added $NaN(TMS)_2$ (10.1 mL, 1.0 M in THF, 10.1 mmol). The mixture was stirred at 0 °C for 20 min and cooled to –78 °C. Aldehyde **23** (1.23 g, 7.23 mmol) was added to the mixture. The reaction was carried out first at –78 °C for 1 h and then at rt for 12 h, and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to afford the corresponding olefin (1.64 g), which was used for the next reaction without further purification.

A solution of the above olefin (1.64 g, 6.01 mmol) in CF_3CO_2H (1.84 mL, 24.0 mmol), H_2O (3 mL), and THF (3 mL) was stirred at rt for 3 h and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish diol **24** (942 mg, 68% from **23**): IR (neat) 3354, 1684, 1206, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–1.95 (br s, 2 H), 2.32-2.54 (m, 2 H), 2.61–2.80 (m, 2 H), 3.35 (d, J = 6 Hz, 2 H), 4.33 (ddt, J = 9, 1, 6 Hz, 1 H), 5.36 (ddt, J = 9, 9, 1 Hz, 1 H), 5.61 (ddt, J = 11, 1, 8 Hz, 1 H), 7.12–7.25 (m, 3 H), 7.25–7.35 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9 (+), 35.6 (+), 66.1 (+), 68.4 (–), 126.2 (–), 128.4 (–), 128.8 (–), 128.9 (–), 133.1 (–), 141.4 (+); HRMS (FAB) calcd for $C_{12}H_{16}O_2K$ $[(M + K)^+]$ 231.0787, found 231.0783.

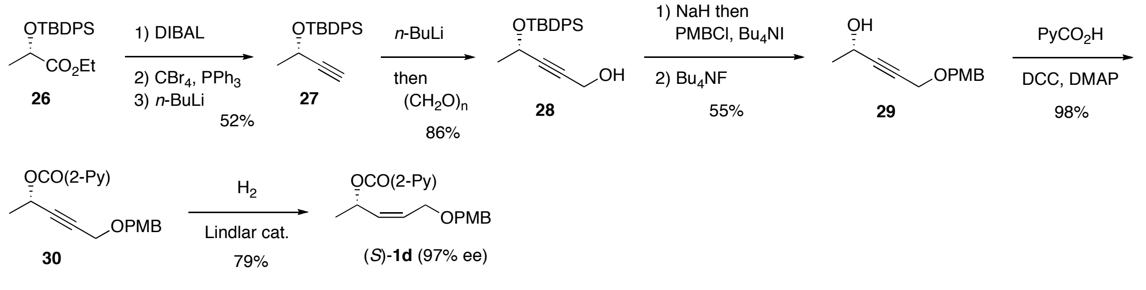
(*S*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-ol (25).

To a solution of **24** (914 mg, 4.75 mmol) and imidazole (1.07 g, 7.10 mmol) in DMF (20 mL) at –20 °C was added TBSCl (388 mg, 5.70 mmol) in DMF (2 mL) dropwise. After 1 h at –20 °C, the resulting solution was diluted with saturated $NaHCO_3$ and EtOAc with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **25** (1.31 g, 90%): IR (neat) 3441, 1256, 1107, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 2.30–2.58 (m, 3 H), 2.61–2.80 (m, 2 H), 3.31 (dd, *J* = 10, 8 Hz, 1 H), 3.38 (dd, *J* = 10, 4 Hz, 1 H), 4.38 (ddd, *J* = 8, 8, 4 Hz, 1 H), 5.36 (ddt, *J* = 11, 8, 1 Hz, 1 H), 5.61 (dt, *J* = 11, 8 Hz, 1 H), 7.15–7.24 (m, 3 H), 7.25–7.35 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.31 (–), –5.23 (–), 18.4 (+), 25.9 (–), 30.0 (+), 35.9 (+), 66.7 (+), 68.3 (–), 126.0 (–), 128.4 (–), 128.6 (–), 128.7 (–), 132.9 (–), 141.5 (+); HRMS (FAB) calcd for $C_{18}H_{30}O_2SiK$ [(M + K)$^+$] 345.1652, found 345.1654.

(*S*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl Pyridine-2-carboxylate ((*S*)-1c).

To an ice-cold solution of **25** (501 mg, 1.63 mmol) in CH_2Cl_2 (10 mL) were added DCC (437 mg, 2.12 mmol), DMAP (239 mg, 1.96 mmol), and picolinic acid (241 mg, 1.96 mmol). The mixture was stirred at rt for 2 h and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-**1c** (527 mg, 79%): 95% ee by HPLC analysis (Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.5 mL/min, rt; t_R (min) = 18.2 (*R*), 24.3 (*S*)); IR (neat) 1718, 1247, 1126, 838, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.004 (s, 3 H), 0.04 (s, 3 H), 0.83 (s, 9 H), 2.45–2.83 (m, 4 H), 3.64 (dd, *J* = 11, 5 Hz, 1 H), 3.80 (dd, *J* = 11, 7 Hz, 1 H), 5.52 (ddt, *J* = 11, 9, 1.5 Hz, 1 H), 5.72 (dt, *J* = 11, 8 Hz, 1 H), 5.93 (ddd, *J* = 9, 7, 5 Hz, 1 H), 7.10–7.32 (m, 5 H), 7.44 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.81 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.10 (dt, *J* = 8, 1 Hz, 1 H), 8.76 (ddd, *J* = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), 18.3 (+), 25.8 (–), 30.0 (+), 35.7 (+), 64.7 (+), 72.3 (–), 125.1 (–), 125.2 (–), 125.9 (–), 126.7 (–), 128.4 (–), 128.6 (–), 135.4 (–), 136.9 (–), 141.5 (+), 148.5 (+), 149.9 (–), 164.4 (+); HRMS (FAB) calcd for $C_{24}H_{34}NO_3Si$ [(M + H)$^+$] 412.2308, found 412.2299.

Synthesis of Picolinate (*S*)-1d.



(*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-butyne (27).

To an ice-cold solution of ethyl (*S*)-lactate (5.0 mL, 43.6 mmol) in DMF (46 mL) were added TBDPSCl (15 mL, 58.4 mmol) and imidazole (6.4 g, 94 mmol). After 6 h at rt, the resulting solution was cooled to 0 °C and diluted with saturated $NaHCO_3$ and hexane with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with hexane three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish silyl ether **26** (14.61 g, 94%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.14 (t, J = 7 Hz, 3 H), 1.37 (d, J = 7 Hz, 3 H), 4.02 (q, J = 7 Hz, 2 H), 4.26 (q, J = 7 Hz, 1 H), 7.30–7.48 (m, 6 H), 7.62–7.76 (m, 4 H). The ^1H NMR spectrum of **26** was identical with that reported.[16]

To a solution of silyl ether **26** (3.00 g, 12.9 mmol) in CH_2Cl_2 (24 mL) was added slowly a solution of DIBAL (13.6 mL, 0.95 M in hexane, 12.9 mmol) at –78 °C. The solution was stirred at –78 °C for 30 min. Excess hydride was destroyed by careful addition of H_2O (2.5 mL, 140 mmol). The cooling bath was removed and NaF (3.0 g, 71.4 mmol) was added to the resulting mixture. The mixture was stirred vigorously for 1 h and filtered through a pad of Celite to afford the corresponding aldehyde (2.16 g, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9 H), 1.22 (d, J = 7 Hz, 3 H), 4.09 (dq, J = 1, 7 Hz, 1 H), 7.33–7.50 (m, 6 H), 7.60–7.74 (m, 4 H), 9.64 (d, J = 1 Hz, 1 H). The ^1H NMR spectrum was identical with that reported.[17]

To an ice-cold solution of PPh_3 (16.0 g, 61 mmol) in CH_2Cl_2 (60 mL) was added CBr_4 (10.6 g, 32.0 mmol) portionwise. The solution was stirred at the same temperature for 20 min, and the above aldehyde (5.00 g, 16.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction was continued at 0 °C and hexane was added. The resulting mixture was filtered and the filtrate was concentrated to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish the corresponding dibromoalkene (5.90 g, 79%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.21 (d, J = 6 Hz, 3 H), 4.43 (dq, J = 8, 6 Hz, 1 H), 6.47 (d, J = 8 Hz, 1 H), 7.32–7.48 (m, 6 H), 7.61–7.70 (m, 4 H).

To a solution of the above dibromide (4.03 g, 8.61 mmol) in THF (35 mL) was added *n*-BuLi (11.5 mL, 2.40 M in hexane, 27.6 mmol) dropwise at –70 °C. After 1 h at –70 °C, the solution was allowed to warm slowly to –40 °C, and poured into hexane and saturated NH_4Cl with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford acetylene **27** (2.14 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.39 (d, *J* = 7 Hz, 3 H), 2.33 (d, *J* = 2 Hz, 1 H), 4.45 (dq, *J* = 2, 7 Hz, 1 H), 7.33–7.47 (m, 6 H), 7.66–7.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (+), 25.2 (–), 26.9 (–), 59.8 (–), 71.6 (+), 86.2 (+), 127.6 (–), 127.7 (–), 129.78 (–), 129.83 (–), 133.5 (+), 133.7 (+), 135.8 (–), 136.0 (–); HRMS (EI) calcd for $C_{20}H_{24}OSi$ (M^+) 308.1596, found 308.1597.

(*S*)-5-(4-Methoxybenzyloxy)-3-pentyn-2-ol (29).

To a solution of **27** (3.98 g, 12.9 mmol) in THF (26 mL) was added *n*-BuLi (9.70 mL, 1.60 M in hexane, 15.5 mmol) at –78 °C. After 20 min at –78 °C, paraformaldehyde (1.16 g, 38.6 mmol) was added portionwise. The resulting mixture was allowed to warm to rt, stirred overnight, and diluted with saturated NH_4Cl. The product was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **28** (3.77 g, 86%): IR (neat) 3307, 1105, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9 H), 1.11 (t, *J* = 6 Hz, 1 H), 1.41 (d, *J* = 7 Hz, 3 H), 4.08 (dd, *J* = 6, 2 Hz, 2 H), 4.53 (tq, *J* = 2, 7 Hz, 1 H), 7.29–7.47 (m, 6 H), 7.64–7.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (+), 25.1 (–), 26.9 (–), 51.1 (+), 60.0 (–), 82.1 (+), 88.3 (+), 127.5 (–), 127.7 (–), 129.7 (–), 129.8 (–), 133.7 (+), 134.0 (+), 135.9 (–), 136.1 (–).

To an ice-cold solution of **28** (898 mg, 2.65 mmol) in THF (6 mL) was added NaH (117 mg, 60% in mineral oil, 2.92 mmol). After 20 min at 0 °C, Bu_4NI (294 mg, 0.796 mmol) and PMBCl (0.44 mL, 2.95 mmol) were added to the mixture. The reaction was carried out at rt overnight and quenched by addition of NaOMe (72 mg, 1.33 mmol). The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to afford the corresponding PMB ether, which was used for the next reaction without further purification.

To a solution of the above PMB ether in THF (4 mL) was added Bu_4NF (4.0 mL, 1.0 M in THF, 4.0 mmol). The reaction was carried out at rt overnight, and quenched by addition of saturated NH_4Cl. The product was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish alcohol **29** (322 mg, 55% from **28**): IR (neat) 3411, 1612, 1514 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 7 Hz, 3 H), 1.89 (d, *J* = 5 Hz, 1 H), 3.80 (s, 3 H), 4.16 (d, *J* = 2 Hz, 2 H), 4.52 (s, 2 H), 4.59 (dtq, *J* = 5, 2, 7 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.28 (d, *J* = 9

Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (–), 55.3 (–), 57.0 (+), 58.3 (–), 71.3 (+), 79.9 (+), 88.5 (+), 113.9 (–), 129.4 (+), 129.8 (–), 159.4 (+); HRMS (FAB) calcd for $C_{13}H_{16}O_3Na$ [(M + Na)$^+$] 243.0997, found 243.0996. The ^{1}H NMR spectrum of **29** was identical with that reported.[18]

(*S*)-5-(4-Methoxybenzyloxy)-3-pentyn-2-yl Pyridine-2-carboxylate (30).

To an ice-cold suspension of picolinic acid (992 mg, 8.06 mmol) in CH_2Cl_2 (15 mL) were added DMAP (410 mg, 3.36 mmol) and DCC (1.80 g, 8.72 mmol). After 20 min at rt, **29** (1.48 g, 6.72 mmol) in CH_2Cl_2 (10 mL) was added to the mixture at 0 °C. The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **30** (2.14 g, 98%): IR (neat) 1719, 1514, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (d, *J* = 7 Hz, 3 H), 3.80 (s, 3 H), 4.17 (d, *J* = 2 Hz, 2 H), 4.52 (s, 2 H), 5.84 (tq, *J* = 2, 7 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.27 (d, *J* = 9 Hz, 2 H), 7.49 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.86 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.16 (ddd, *J* = 8, 1, 1 Hz, 1 H), 8.88 (ddd, *J* = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (–), 55.3 (–), 57.0 (+), 62.0 (–), 71.2 (+), 81.5 (+), 84.5 (+), 113.8 (–), 125.4 (–), 127.1 (–), 129.4 (+), 129.8 (–), 137.0 (–), 147.9 (+), 150.1 (–), 159.4 (+), 164.1 (+); HRMS (FAB) calcd for $C_{19}H_{19}NO_4Na$ [(M + Na)$^+$] 348.1212, found 348.1214.

(*S*,*Z*)-5-(4-Methoxybenzyloxy)-3-penten-2-yl Pyridine-2-carboxylate ((*S*)-1d).

To a solution of **30** (686 mg, 2.11 mmol) in EtOAc (7 mL) was added Lindlar catalyst (Aldrich, 210 mg) at rt. The mixture was stirred at rt for 12 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**1d** (544 mg, 79%): 97% ee by HPLC analysis (Chiralcel OD-H; hexane/*i*-PrOH = 96/4, 0.5 mL/min, rt; t_R (min) = 75.6 (*S*), 85.9 (*R*)); IR (neat) 1737, 1716, 1513, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6 Hz, 3 H), 3.80 (s, 3 H), 4.16–4.30 (m, 2 H), 4.47 (s, 2 H), 5.72 (dd, *J* = 11, 7 Hz, 1 H), 5.77 (dt, *J* = 11, 6 Hz, 1 H), 5.84–5.98 (m, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.27 (d, *J* = 8 Hz, 2 H), 7.46 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.83 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.11 (dm, *J* = 8 Hz, 1 H), 8.77 (dm, *J* = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (–), 55.3 (–), 65.8 (+), 68.6 (–), 72.1 (+), 113.8 (–), 125.1 (–), 126.8 (–), 129.5 (–), 129.9 (–), 130.2 (+), 131.5 (–), 136.9 (–), 148.3 (+), 149.9 (–), 159.2 (+), 164.4 (+); HRMS (FAB) calcd for $C_{19}H_{22}NO_4$ [(M + H)$^+$] 328.1549, found 328.1540.

Allylic subtitution.

NMR spectra of 2a' and 3'.

Isomer **2a'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.07 (s, 3 H), –0.06 (s, 3 H), 0.83 (s, 9 H), 2.26–2.49 (m, 2 H), 2.52–2.70 (m, 2 H), 3.62–3.79 (m, 3 H), 5.56 (dt, *J* = 11, 7 Hz, 1 H), 5.65 (dd, *J* = 11, 8 Hz, 1 H), 7.10–7.31 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.37 (–), –5.35 (–), 18.4 (+), 26.0 (–), 29.8 (+), 35.8 (+), 46.5 (–), 67.9 (+), 125.9 (–), 126.3 (–), 128.1 (–), 128.32 (–), 128.34 (–), 128.5 (–), 130.6 (–), 130.9 (–), 142.0 (+), 142.9 (+).

Isomer **3'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.87–2.13 (m, 2 H), 2.47–2.68 (m, 2 H), 3.45–3.60 (m, 1 H), 4.15 (dd, *J* = 13, 4 Hz, 1 H), 4.27 (dd, *J* = 13, 5 Hz, 1 H), 5.54–5.66 (m, 2 H), 7.12–7.34 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.08 (–), –5.05 (–), 18.4 (+), 26.0 (–), 33.7 (+), 38.5 (+), 43.3 (–), 59.7 (+), 125.9 (–), 126.2 (–), 127.4 (–), 128.4 (–), 128.5 (–), 128.6 (–), 130.0 (–), 134.1 (–), 142.1 (+), 144.7 (+).

General Procedure of the Allylic Substitution.

(Table 2, entry 4) To an ice-cold suspension of CuBr·Me_2S (18 mg, 0.088 mmol) in THF (3 mL) was added PhMgBr (0.20 mL, 0.90 M in THF, 0.18 mmol) dropwise. After 30 min of stirring, the resulting mixture was cooled to –60 °C. A solution of (*S*)-**1a** (36.5 mg, 0.0877 mmol, 90% ee) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to –40 °C over 1 h, and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**2a** (29 mg, 89%): $[\alpha]^{26}_D$ –7.7 (*c* 0.626, $CHCl_3$); IR (neat) 1255, 1102, 836, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.06 (s, 3 H), –0.05 (s, 3 H), 0.84 (s, 9 H), 2.35 (dt, *J* = 6, 8 Hz, 2 H), 2.68 (dd, *J* = 8, 7.5 Hz, 2 H), 3.42 (ddd, *J* = 8, 7, 7 Hz, 1 H), 3.74 (dd, *J* = 10, 7 Hz, 1 H), 3.76 (dd, *J* = 10, 7 Hz, 1 H), 5.55 (dt, *J* = 15, 6 Hz, 1 H), 5.67 (dd, *J* = 15, 7 Hz, 1 H), 7.12–7.38 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 18.4, 26.0, 34.8, 36.0, 51.4, 67.6, 125.8, 126.4, 128.26, 128.34, 128.6, 131.2, 142.1, 142.6; HRMS (FAB) calcd for $C_{24}H_{34}OSiNa$ [(M + Na)$^+$] 389.2277, found 389.2278. The enantiomeric information

(88% ee, 98% CT) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.4 mL/min, rt; t_R (min) = 47.7 (*S*), 49.1 (*R*).

Determination of the absolute configuration: (eq 1) To an ice-cold solution of (*R*)-**2a** (120 mg, 0.327 mmol) in acetone-H_2O (4 : 1, 3 mL) were added NMO (50 mg, 0.43 mmol) and OsO_4 (0.33 mL, 0.02 M in *t*-BuOH, 0.0066 mmol). After 3 h at 0 °C, the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O twice. The combined extracts were dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding diol (115 mg, 87%).

To an ice-cold solution of the above diol (110 mg, 0.244 mmol) in MeOH-H_2O (4 : 1, 2.5 mL) were added Bu_4NI (27 mg, 0.073 mmol) and $NaIO_4$ (68 mg, 0.32 mmol). After 3 h at 0 °C, $NaBH_4$ (40 mg, 1.06 mmol) was added to the mixture. The mixture was stirred at 0 °C for 30 min, and diluted with saturated NH_4Cl and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O twice. The combined extracts were washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **31** (51 mg, 78%): $[\alpha]^{25}_D$ –13.0 (*c* 0.12, $CHCl_3$); cf. $[\alpha]^{23}_D$ +14.6 (*c* 1.03, $CHCl_3$) for the *R* enantiomer[19] ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 2.75 (dd, *J* = 7, 4 Hz, 1 H), 3.09 (ddd, *J* = 7, 7, 5 Hz, 1 H), 3.89 (ddd, *J* = 11, 7, 5 Hz, 1 H), 3.93 (d, *J* = 7 Hz, 2 H), 4.08 (ddd, *J* = 11, 7, 4 Hz, 1 H), 7.19–7.36 (m, 5 H). The ^1H NMR spectrum was identical with the data reported.[19]

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methylphenyl)-6-phenyl-3-hexene ((*R*)-2b).

(Table 2, entry 7) 81% yield from (*S*)-**1a** (90% ee), 89% ee, 99% CT; IR (neat) 1255, 1102, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.04 (s, 3 H), –0.02 (s, 3 H), 0.85 (s, 9 H), 2.28–2.39 (m, 2 H), 2.33 (s, 3 H), 2.67 (dd, *J* = 8, 6 Hz, 2 H), 3.67–3.84 (m, 3 H), 5.50 (dt, *J* = 15, 7 Hz, 1 H), 5.64 (dd, *J* = 15, 6 Hz, 1 H), 7.11–7.32 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.34, –5.30, 18.4, 19.9, 26.0, 34.8, 36.0, 46.6, 67.1, 125.8, 125.9, 126.1, 127.0, 128.3, 128.5, 130.3, 131.0, 131.2, 136.4, 140.6, 142.1; HRMS (FAB) calcd for $C_{25}H_{36}OSiNa$ $[(M + Na)^+]$ 403.2433, found 403.2432. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.5 mL/min, rt; t_R (min) = 39.0 (*S*), 40.7 (*R*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methoxyphenyl)-6-phenyl-3-hexene ((*R*)-2c).

(Table 2, entry 8) 85% yield from (*S*)-**5a** (90% ee), 88% ee, 98% C.T.; $[\alpha]^{28}_{D}$ –9.7 (*c* 0.682, $CHCl_3$); IR (neat) 1241, 1103, 837, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.041 (s, 3 H), –0.038 (s, 3 H), 0.84 (s, 9 H), 2.34 (dt, *J* = 7, 8 Hz, 2 H), 2.68 (dd, *J* = 8, 6 Hz, 2 H), 3.71 (dd, *J* = 10, 8 Hz, 1 H), 3.78 (dd, *J* = 10, 5 Hz, 1 H), 3.80 (s, 3 H), 3.85–3.93 (m, 1 H), 5.57 (dt, *J* = 16, 7 Hz, 1 H), 5.73 (dd, *J* = 16, 7 Hz, 1 H), 6.84 (dd, *J* = 8, 1 Hz, 1 H), 6.88 (ddd, *J* = 8, 8, 1 Hz, 1 H), 7.10 (dd, *J* = 8, 2 Hz, 1 H), 7.13–7.21 (m, 4 H), 7.22–7.29 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), 18.4 (+), 26.0 (–), 34.8 (+), 36.1 (+), 44.5 (–), 55.4 (–), 66.5 (+), 110.6 (–), 120.5 (–), 125.7 (–), 127.2 (–), 128.3 (–), 128.6 (–), 128.9 (–), 130.7 (+), 130.9 (–), 131.1 (–), 142.3 (+), 157.1 (+); HRMS (FAB) calcd for $C_{25}H_{36}O_2SiNa$ $[(M + Na)^+]$ 419.2382, found 419.2385. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel OD-H; hexane/*i*-PrOH = 97/3, 0.5 mL/min, rt; t_R (min) = 45.2 (*S*), 54.1 (*R*).

(*R*,*E*)-1,5-Diphenyl-3-hexene ((*R*)-2d).

(Table 2, entry 9) According to the typical procedure, a solution of (*S*)-**1b** (114 mg, 0.405 mmol, 89% ee) in THF (4 mL) was added to a mixture of CuBr·Me_2S (84 mg, 0.41 mmol) in THF (10 mL) and PhMgBr (0.86 mL, 0.95 M in THF, 0.82 mmol) at –60 °C, and the mixture was allowed to warm to –40 °C over 1 h to afford a mixture of (*R*)-**2d** and Ph_2 in a 83 : 17 ratio by ^1H NMR analysis (93 mg in total, 86% yield of (*R*)-**2d**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7 Hz, 3 H), 2.33 (dt, *J* = 7, 7 Hz, 2 H), 2.68 (t, *J* = 7 Hz, 2 H), 3.40 (dq, *J* = 7, 7 Hz, 1 H), 5.48 (dt, *J* = 15, 7 Hz, 1 H), 5.60 (dd, *J* = 15, 7 Hz, 1 H), 7.14–7.20 (m, 4 H), 7.23–7.28 (m, 6 H).

Determination of the absolute configuration and CT (Scheme 8): A stream of O_3 in O_2 was gently bubbled into a solution of the mixture of (*R*)-**2d** and Ph_2 (222 mg in total, (*R*)-**2d**/Ph_2 = 81 : 19) in MeOH at –78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at –78 °C for 10 min and $NaBH_4$ (309 mg, 8.17

mmol) was added. After stirring for 1 h at –78 °C, the resulting mixture was allowed to warm to rt, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **32**: 89% ee and 99% CT by HPLC analysis (Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 56.6 (*S*), 61.3 (*R*)); $[\alpha]^{28}_D$ –11.7 (*c* 1.2, $CHCl_3$); cf. $[\alpha]_D^{20}$ –10.8 (*c* 1.0, $CHCl_3$) for the *S* enantiomer of 78% ee;[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 7 Hz, 3 H), 2.93 (tq, *J* = 7, 7 Hz, 1 H), 3.67 (d, *J* = 7 Hz, 2 H), 7.19–7.26 (m, 2 H), 7.28–7.34 (m, 3 H). The ^{1}H NMR spectrum of the product was identical with that reported.[20]

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4,6-diphenyl-2-hexene ((*S*)-2e).

(Table 2, entry 10) According to the typical procedure, a solution of (*S*)-**1c** (59 mg, 0.143 mmol, 95% ee) dissolved in THF (1 mL) was added to a mixture of $CuBr{\cdot}Me_2S$ (29 mg, 0.14 mmol) in THF (5 mL) and PhMgBr (0.27 mL, 1.07 M in THF, 0.287 mmol) at –40 °C, and the mixture was stirred –40 °C for 1 h to furnish (*S*)-**2e** (49 mg, 93%): $[\alpha]^{24}_D$ +14 (*c* 0.59, $CHCl_3$); IR (neat) 1254, 836, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 2.05 (ddd, *J* = 8, 8, 8 Hz, 2 H), 2.48–2.68 (m, 2 H), 3.30 (ddd, *J* = 8, 8, 8 Hz, 1 H), 4.16 (d, *J* = 5 Hz, 2 H), 5.57 (dt, *J* = 15, 5 Hz, 1 H), 5.82 (dd, *J* = 15, 8 Hz, 1 H), 7.10–7.35 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.0 (–), 18.5 (+), 26.0 (–), 33.8 (+), 37.5 (+), 47.9 (–), 63.9 (+), 125.8 (–), 126.3 (–), 127.7 (–), 128.4 (–), 128.52 (–), 128.54 (–), 129.5 (–), 134.3 (–), 142.3 (+), 144.4 (+); HRMS (FAB) calcd for $C_{24}H_{34}OSiNa$ [$(M + Na)^+$] 389.2277, found 389.2287. The enantiomeric information (92% ee, 97% CT) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.3 mL/min, rt; t_R (min) = 95.4 (*S*), 99.2 (*R*).

Determination of the absolute configuration (Scheme 8): A stream of O_3 in O_2 was gently bubbled into a solution of (*S*)-**2e** (92 mg, 0.25 mmol) in MeOH at –78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at –78 °C and $NaBH_4$ (95 mg, 2.51 mmol) was added at –78 °C. The cooling bath was removed. The mixture was stirred at rt for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to furnish the alcohol **33** (56 mg, 99%): $[\alpha]^{24}_D$ –11 (*c* 0.41, $CHCl_3$); cf. $[\alpha]_D$ +6.92 (*c* 1.82, $CHCl_3$) for the (*S*)-enantiomer;[21] ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (br s, 1 H), 1.81–2.12 (m, 2 H), 2.40–2.62 (m, 2 H), 2.73–2.88 (m, 1 H), 3.67–3.80 (m, 2 H), 7.05–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5 (+), 33.7 (+), 48.2 (–), 67.7 (+), 125.9 (–), 127.0 (–), 128.25 (–), 128.39 (–), 128.45 (–), 128.8 (–), 142.0 (+), 142.1 (+). The ^1H NMR and ^{13}C NMR spectra were identical with the data reported.[21]

(*R*,*E*)-1-[(2-Phenylpent-3-enyloxy)methyl]-4-methoxybenzene ((*R*)-2f).

(Table 2, entry 11) According to the typical procedure, a solution of (*S*)-**1d** (60.0 mg, 0.183 mmol, 97% ee) in THF (1 mL) was added to a mixture of CuBr·Me_2S (40 mg, 0.195 mmol) and PhMgBr (0.50 mL, 0.75 M in THF, 0.50 mmol) in THF (5 mL) at –60 °C. The resulting mixture was allowed to warm to –40 °C over 1 h and diluted with hexane and saturated NH_4Cl to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give (*R*)-**2f** (43 mg, 83%): IR (neat) 1612, 1513, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6 Hz, 3 H), 3.53–3.68 (m, 3 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 5.51 (dq, *J* = 15, 6 Hz, 1 H), 5.63 (dd, *J* = 15, 7 Hz, 1 H), 6.85 (d, *J* = 8 Hz, 2 H), 7.15–7.23 (m, 5 H), 7.25–7.33 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (–), 48.9 (–), 55.3 (–), 72.7 (+), 73.7 (+), 113.8 (–), 126.4 (–), 126.7 (–), 128.0 (–), 128.4 (–), 129.3 (–), 130.6 (+), 131.9 (–), 142.5 (+), 159.1 (+); HRMS (EI) calcd for $C_{19}H_{22}O_2$ (M^+) 282.1620, found 282.1627. The enantiomeric information (97% ee, 99% CT) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 29.9 (*R*), 33.7 (*S*).

Synthesis of (–)-Sesqichamaenol (38). (Scheme 11)

(*S*,*Z*)-2-(3-Methylbut-1-enyl)-1,4-dioxaspiro[4.5]decane (39).

To a suspension of $[i\text{-}PrCH_2PPh_3]^+Br^-$ (10.50 g, 26.2 mmol) in THF (35 mL) was added $NaN(TMS)_2$ (24.4 mL, 1.0 M in THF, 24.4 mmol) at 0 °C. The mixture was stirred 0 °C for 20 min and cooled to –78 °C. Aldehyde **23** (2.97 g, 17.5 mmol) was added to the mixture. The reaction was carried out first at –78 °C for 1 h and then at rt for 12 h, and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **39** (3.52 g, 96%): IR (neat) 1108, 931 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7 Hz, 3 H), 0.98 (d, *J* = 7 Hz, 3 H), 1.31–1.42 (m, 2 H), 1.50–1.66 (m, 8 H), 2.53–2.71 (m, 1 H), 3.47 (dd, *J* = 8, 8 Hz, 1 H), 4.02 (dd, *J* = 8, 6 Hz, 1 H), 4.82 (ddd, *J* = 8, 8, 6 Hz, 1 H), 5.25 (dd, *J* = 11, 9 Hz, 1 H), 5.42 (dd, *J* = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (–), 23.7 (–), 23.9 (+), 24.0 (+), 25.2 (+), 27.3 (–), 35.6 (+), 36.4 (+), 69.3 (+), 71.8 (–), 109.7 (+), 125.1 (–), 142.2 (–).

(*S*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methylhex-3-en-2-ol (41).

A solution of **39** (500 mg, 2.38 mmol) in CF_3CO_2H (0.73 mL, 9.5 mmol), H_2O (1 mL), and THF (1 mL) was stirred at rt for 12 h, and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish diol **40** (210 mg, 68%): IR (neat) 3391, 1075, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7 Hz, 3 H), 0.96 (d, *J* = 7 Hz, 3 H), 2.50–2.69 (m, 1 H), 3.42 (dd, *J* = 12, 8 Hz, 1 H), 3.51 (dd, *J* = 12, 3 Hz, 1 H), 3.65 (br s, 2 H), 4.51 (ddd, *J* = 8, 8, 3 Hz, 1 H), 5.19 (dd, *J* = 11, 9 Hz, 1 H), 5.35 (dd, *J* = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (–), 23.4 (–), 27.4 (–), 66.6 (+), 68.9 (–), 125.4 (–), 141.5 (–).

To a solution of the above diol **40** (915 mg, 7.03 mmol) and imidazole (1.59 g, 10.5 mmol) in DMF (10 mL) at –40 °C was added TBSCl (573 mg, 8.42 mmol) in DMF (4 mL) dropwise. After 2 h at –40 °C, the resulting solution was diluted with saturated NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **41** (1.54 g, 90%): IR (neat) 3424, 1106, 836, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 0.94 (d, *J* = 7 Hz, 3 H), 0.99 (d, *J* = 7 Hz, 3 H), 2.56 (br s, 1 H), 2.53–2.69 (m, 1 H), 3.40 (dd, *J* = 10, 8 Hz, 1 H), 3.56 (dd, *J* = 10, 4 Hz, 1 H), 4.47 (ddm, *J* = 8, 8 Hz, 1 H), 5.19 (dd, *J* = 11, 9 Hz, 1 H), 5.39 (ddd, *J* = 11, 10, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), –5.2 (–), 18.4 (+), 23.2 (–), 23.5 (–), 26.0 (–), 27.5 (–), 67.2 (+), 68.6 (–), 125.4 (–), 141.4 (–).

(*R*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methylhex-3-en-2-yl Pyridine-2-carboxylate (42).

To a solution of PPh_3 (2.15 g, 8.20 mmol) in THF (18 mL) at –78 °C were added picolinic acid (1.01 g, 8.20 mmol) and a solution of alcohol **41** (1.54 g, 6.30 mmol) in THF (3 mL). After 15 min, DIAD (1.66 mL, 7.87 mmol) was added dropwise. The solution was warmed to rt over 12 h, and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **42** (1.63 g, 74%): 99% ee by HPLC analysis (Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 25.4 (*S*), 26.2 (*R*)); $[\alpha]^{25}_{D}$ +18 (*c* 0.188, $CHCl_3$); IR (neat) 1718, 1247, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.02 (s, 3 H), 0.05 (s, 3 H), 0.84 (s, 9 H), 0.99 (d, *J* = 6 Hz, 6 H), 2.80–2.94 (m, 1 H), 3.76 (dd, *J* = 11, 5 Hz, 1 H), 3.89 (dd, *J* = 11, 7 Hz, 1 H), 5.36 (dd, *J* = 11, 9 Hz, 1 H), 5.50 (dd, *J* = 11, 11 Hz, 1 H), 5.97 (ddd, *J* = 9, 7, 5 Hz, 1 H), 7.45 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.82 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.11 (ddm, *J* = 8, 1 Hz, 1 H), 8.76 (ddm, *J* = 5, 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.48 (–), –5.46 (–), 18.2 (+), 22.7 (–), 23.1 (–), 25.7 (–), 27.4 (–), 64.9 (+), 72.4 (–), 121.8 (–), 125.0 (–), 126.6 (–), 136.8 (–), 143.6 (–), 148.3 (+), 149.7 (–), 164.2 (+); HRMS (FAB) calcd for $C_{19}H_{31}NO_3SiNa$ [$(M + Na)^+$] 372.1971, found 372.1968.

(*R*,*E*)-4-(2-Methoxy-5-methylphenyl)-5-methylhex-2-en-1-ol (44).

To a suspension of $CuBr{\cdot}Me_2S$ (280 mg, 1.05 mmol) in THF (5 mL) was added Grignard reagent **35** (2.65 mL, 0.80 M in THF, 2.12 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min and cooled to –40 °C. Picolinate **42** (370 mg, 1.06 mmol) dissolved in THF (2 mL) was added to the mixture. The reaction was carried out at –40 °C for 2 h, and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **43**, which was used for the next reaction without further purification.

To a solution of the above compound **43** in THF (3 mL) was added Bu_4NF (1.8 mL, 1.0 M in THF, 1.8 mmol) dropwise. The solution was stirred at rt for 1 h and diluted with saturated NH_4Cl. The mixture was extracted EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish alcohol **44** (152 mg, 61% from **42**): 98% ee, 99% CT; IR (neat) 3408, 1501, 1244, 1036, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J* = 7 Hz, 3 H), 0.95 (d, *J* = 7 Hz, 3 H), 1.56–1.86 (br s, 1 H), 1.90–2.30 (m, 1 H), 2.27 (s, 3 H), 3.33 (dd, *J* = 9, 9 Hz, 1 H), 3.78 (s, 3 H), 4.08 (dd, *J* = 6, 1 Hz, 2 H), 5.65 (dt, *J* = 15, 6 Hz, 1 H), 5.91 (dd, *J* = 15, 9 Hz, 1 H), 6.75 (d, *J* = 8 Hz, 1 H), 6.90–6.99 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (–), 21.1 (–), 31.8 (–), 49.8 (–), 55.7 (–), 63.7 (+), 111.0 (–), 127.1 (–), 129.1 (–), 129.5 (–), 129.6 (+), 132.5 (+), 135.1 (–), 155.0 (+). The enantiomeric information was determined by HPLC analysis: Chiralcel AD-H; hexane/*i*-PrOH = 99/1, 0.2 mL/min, rt; t_R (min) 65.6 (*S*), 70.7 (*R*).

(*S*)-4-(2-Methoxy-5-methylphenyl)-5-methylhexanoic Acid (45).

To a mixture of 10% Pd/C (75 mg, 0.070 mmol) in EtOAc (1 mL) was added **44** (152 mg, 0.649 mmol) in EtOAc (1 mL). The mixture was stirred at rt for 2 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to afford the corresponding alcohol, which was used for the next reaction without further purification.

To an ice-cold solution of the above alcohol in acetone (4.3 mL) was added Jones reagent (0.28 mL, 4.7 M, 0.88 mmol) dropwise. The reaction was quenched by addition of *i*-PrOH and the aqueous layer was extracted EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **45** (121 mg, 75% from **44**): $[\alpha]^{30}_D$ –4.17 (*c* 0.24, $CHCl_3$); IR (neat) 2957, 1244, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J* = 7 Hz, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 1.74–1.96 (m, 3 H), 2.04–2.20 (m, 2 H), 2.27 (s, 3 H), 2.77 (dd, *J* = 9, 9 Hz, 1 H), 3.75 (s, 3 H), 6.74 (d, *J* = 8 Hz, 1 H), 6.88 (d, *J* = 2 Hz, 1 H), 6.96 (dd, *J* = 8, 2 Hz, 1 H) 9.5–11.0 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (–), 20.8 (–), 21.3 (–), 27.3 (+), 32.56 (+), 32.59 (–), 44.2 (–), 55.6 (–), 110.6 (+), 127.2 (–), 128.8 (–), 129.6 (–), 131.7 (–), 156.0 (–), 180.7 (+).

(–)-Sesquichamaenol (38).

To an ice-cold solution of **45** (130 mg, 0.523 mmol) in AcOH (2.6 mL) was added 30% HBr in AcOH (1.31 mL). The mixture was refluxed for 2 h and poured into saturated $NaHCO_3$. The organic phase was separated, and the aqueous was extracted EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to afford the corresponding phenol (103 mg), which was used for the next reaction without further purification.

To a solution of the above phenol (103 mg) in Et_2O (5 mL) was added MeLi (2.19 mL, 1.02 M in Et_2O, 2.23 mmol) dropwise at –55 °C. After 3 h at –55 °C, the resulting solution was diluted with saturated NH_4Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (–)-sesquichamaenol (**38**) (75 mg, 59% from **45**): $[\alpha]^{27}_{D}$ –8.1 (*c* 0.72, $CHCl_3$) and $[\alpha]^{27}_{D}$ –9.2 (*c* 0.72, CH_2Cl_2); cf. $[\alpha]^{25}_{D}$ –4.3 (*c* 0.6, $CHCl_3$)[10a] and $[\alpha]^{22}_{D}$ –5.95 (*c* 0.042, CH_2Cl_2);[10b] ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 1.66–1.93 (m, 2 H), 2.05 (s, 3 H), 2.04–2.24 (m, 3 H), 2.25 (s, 3 H), 2.61 (ddd, *J* = 12, 9, 3 Hz, 1 H), 5.55 (br s, 1 H), 6.68 (d, *J* = 8 Hz, 1 H), 6.85 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (–), 20.9 (–), 21.3 (–), 26.7 (+), 30.1 (–), 33.0 (–), 42.0 (+), 44.2 (–), 115.7 (–), 127.3 (–), 128.6 (–), 129.8 (+), 129.9 (+), 152.1 (+), 211.1 (+); HRMS (FAB) calcd for $C_{15}H_{22}O_2Na$ [$(M + Na)^+$] 257.1517, found 257.1512. The spectral data were consistent with those reported.[10]

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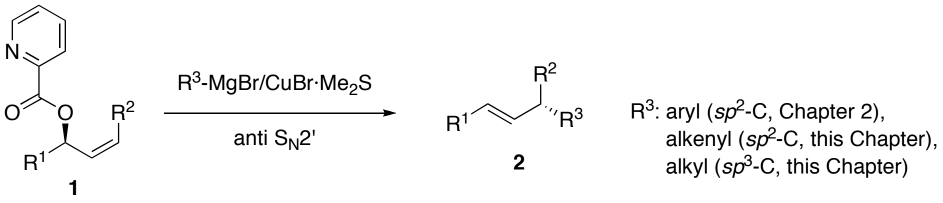
第３章「アルケニル及びアルキルグリニャール試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」

３−１．緒言

第２章で著者は、ピコリン酸基を脱離基としたアリール銅試薬のアリル化反応を見出した。そこで、本章では、このアリル化反応を用いて、アルケニル基やアルキル基を導入できるかを明らかにする事にした (Scheme 1)。

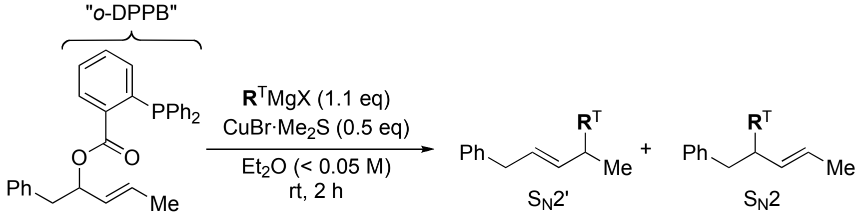
Scheme 1. Allylic substitution of picolinate 1.



初めに、アルケニル銅試薬でのアリル化の背景について、以下に紹介する。

近年 Breit らは、PhMgBr や CH_2=C(Me)MgBr 由来の sp^2-C 銅試薬を用いた、ラセミ体の *o*-DPPB アリルエステルのアリル化の位置選択性が、(1) 反応溶媒を Et_2O から CH_2Cl_2 に変更するか、または (2) 数時間に渡り slow addition する事で改善されると報告した[1] (Scheme 2)。しかし、同じ sp^2-C 銅試薬であっても、アリール銅とアルケニル銅試薬では反応性が異なり、アルケニル銅試薬ではかなりの量の脱離体が得られてしまう[1]。また、その改良法では、基質の一般性や不斉転写について明らかにされていない。

Scheme 2. Study by Breit.

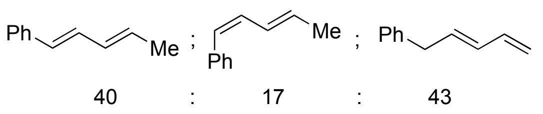


$\mathbf{R}^T$ = Ph, addition time (~5 min) : 90%, S_N2' : S_N2 = 93 : 7
$\mathbf{R}^T$ = Ph, addition time (5 h) : 84%, S_N2' : S_N2 = 97 : 3

$\mathbf{R}^T$ = H_2C=(Me)-, addition time (5 min) : 81%, S_N2' : S_N2 = 85 : 15
$\mathbf{R}^T$ = H_2C=(Me)-, addition time (3 h) : 73%^{a}, S_N2' : S_N2 = 94 : 6

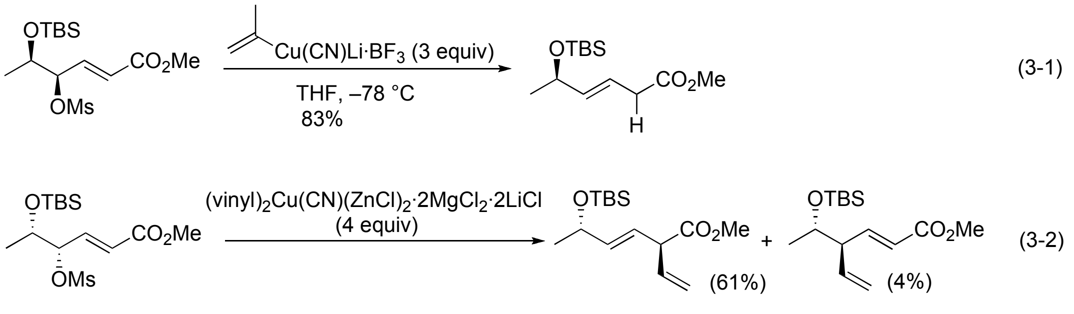
^{a} (S_N2' + S_N2) / elimination products = 60 / 40 by GC analysis

elimination products :



山本らは、γ-メシロキシ-α,β-不飽和エステルに対するアルキル及びアルケニル銅試薬の反応を報告している[2](Scheme 3)。アルキル銅試薬では良好なアンチ S_N2' 選択性を示したが、その条件をアルケニル銅に適用すると、アルケニル基ではなく水素が導入される (Scheme 3-1)。条件検討の結果、過剰な試薬及び添加剤を用いてアルケニル基を導入できてはいたが、その収率や選択性は満足いくものではない (Scheme 3-2)。さらに、第２章で示したが、アリルメシラートはこのタイプの基質を除き合成が難しいという問題がある。

Scheme 3. Study by Yamamoto.



また、ペンタフルオロ安息香酸エステルでは、アリール基の導入は行なわれていたが、アルケニル銅試薬との反応は報告されていない。

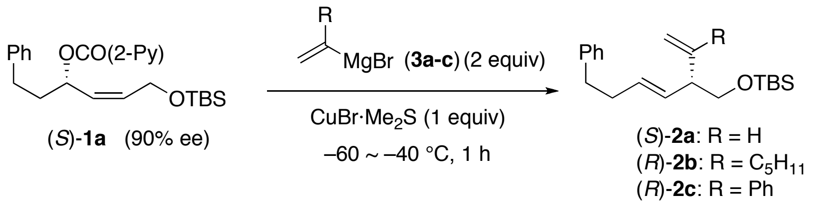
このような現状から、一般性高くアルケニル基を導入することは従来困難であったと考え、アルケニル基の導入を検討する事とした。

一方、sp^3-C アニオンであるアルキル銅試薬は sp^2-C 銅試薬より求核性が高い。よって、ピコリン酸アリルに対しても高反応性を示す事が予想されるが、ピコリン酸基を用いたこの反応系の適応範囲を確認する事は重要であると考え、こちらも検討を行った。

３－２．アルケニル銅試薬

基質に対して 2 当量のグリニャール試薬 **3a** (R = H) と CuBr·Me$_2$S (1 当量) から調製したビニル銅試薬を用いて、(*S*)-**1a** のアリル化を行った。その結果、アリール銅試薬の時と同様に、収率よく位置・立体選択的に S$_N$2’ 生成物 (*S*)-**2a** が得られた (Scheme 4, entry 1)。

Scheme 4. Allylation of (*S*)-1a with alkenyl copper reagents 3a-c.



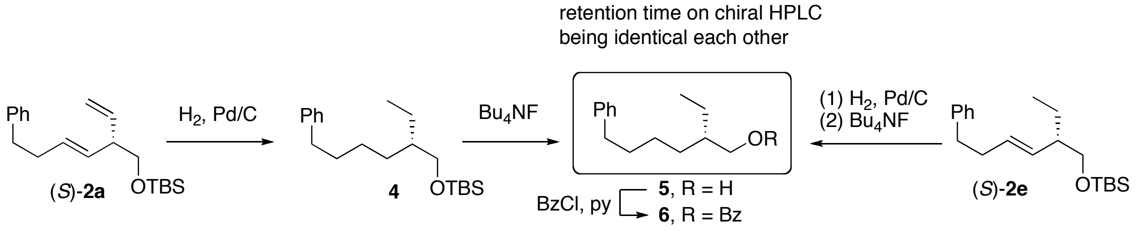
entry	product^a	yield	CT^b
1	(*S*)-**2a**	81%	98%
2	(*R*)-**2b**	75%	97%
3	(*R*)-**2c**	85%	97%

^{a} The stereochemistry of (*S*)-**2a** was determined as described in Scheme 5, while that of (*R*)-**2b**,**c** was assigned by analogy. ^{b} Chirality transfer (CT) was determined by chiral HPLC.

Scheme 5 に示すように、(*S*)-**2a** の絶対構造は **6** に変換して決定した。すなわち、絶対構造が確定している (*S*)-**2e** (Scheme 6) から３段階で変換した **6** と、(*S*)-**2a** から変換した **6** の HPLC の保持時間が一致したので、**2a** が *S* 体だと決定できた。つまり、アルケニル銅でも反応がアンチ S$_N$2’ 的に進行している事

を明らかにした。ビニル銅試薬は最も反応性が小さい試薬の 1 つであることが知られており[3]、この結果は、ピコリン酸アリルの高い反応性がビニル銅試薬の低い反応性を補うのに充分強力である事を示している。

Scheme 5. Determination of absolute configuration of (*S*)-2a.

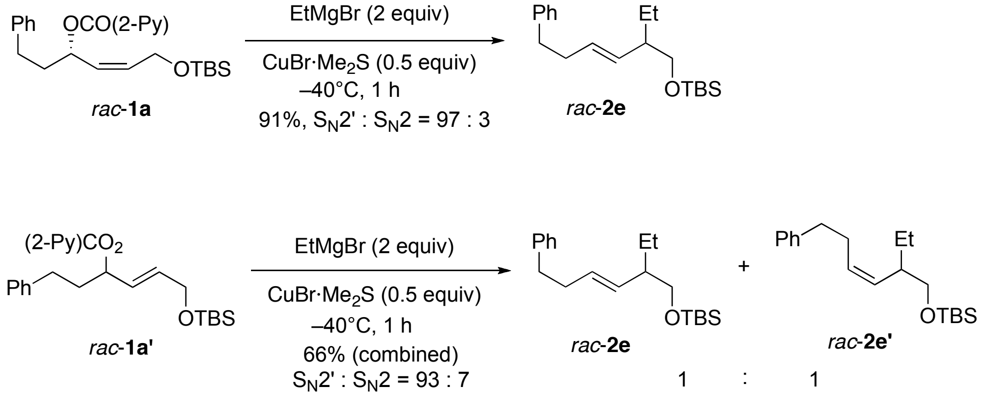


続いて、グリニャール試薬 **3b**, **3c** から調製したアルケニル銅試薬を (*S*)-**1a** に反応させると、(*S*)-**2a** と同様に、高い位置・立体選択性で (*R*)-**2b** と (*R*)-**2c** を与えた (Scheme 4, entries 2, 3)。この時、ジェミナル位に嵩高い置換基 R を持つグリニャール試薬 **3b**, **3c** のような場合でも、反応効率の低下は見られなかった。

３－３．アルキル銅試薬

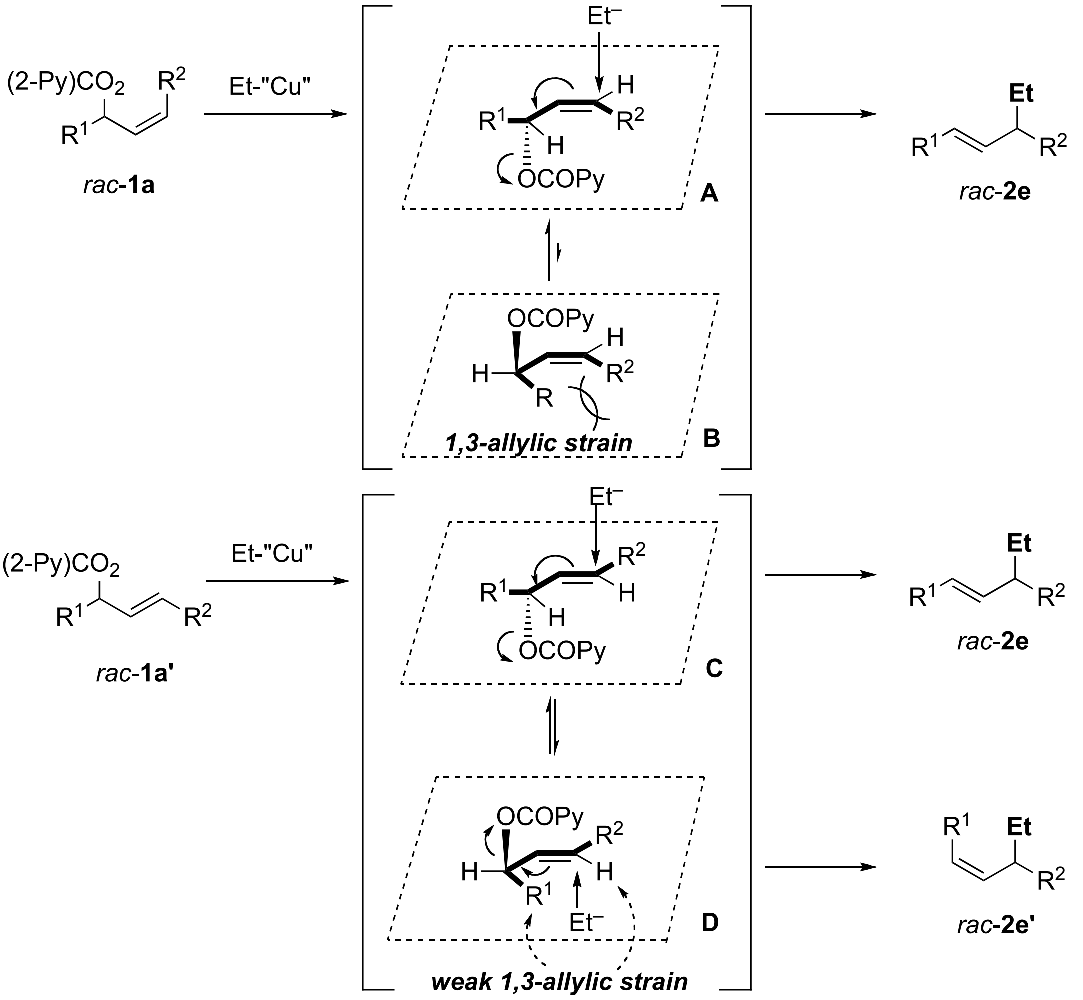
sp^2-C アニオンより求核性が高いアルキル銅試薬についても検討を行った。この際、基質としてトランスオレフィン異性体についても検討した。まず、アリール銅試薬の反応条件に従い、EtMgBr と CuBr·Me$_2$S からエチル銅試薬を２つ調製した。それぞれに対して、二重結合の立体が異なるラセミ体の基質 *rac*-**1a** と *rac*-**1a'** を加え、アリル化反応を行った (Scheme 6)。シス体の基質 *rac*-**1a** からは高い S$_N$2' 選択性で生成物 *rac*-**2e** が得られた。一方、トランス体の基質 *rac*-**1a'** の反応では、S$_N$2' 選択性は良好であったが、オレフィンの立体混合物を与えた (*rac*-**2e** : *rac*-**2e'** = 1 : 1)。よって、アルキル銅試薬に関しても基質はシス型が適していることが明らかになった。

Scheme 6. Allylation of *rac*-1a and *rac*-1a’ with EtMgBr/CuBr·Me$_2$S.



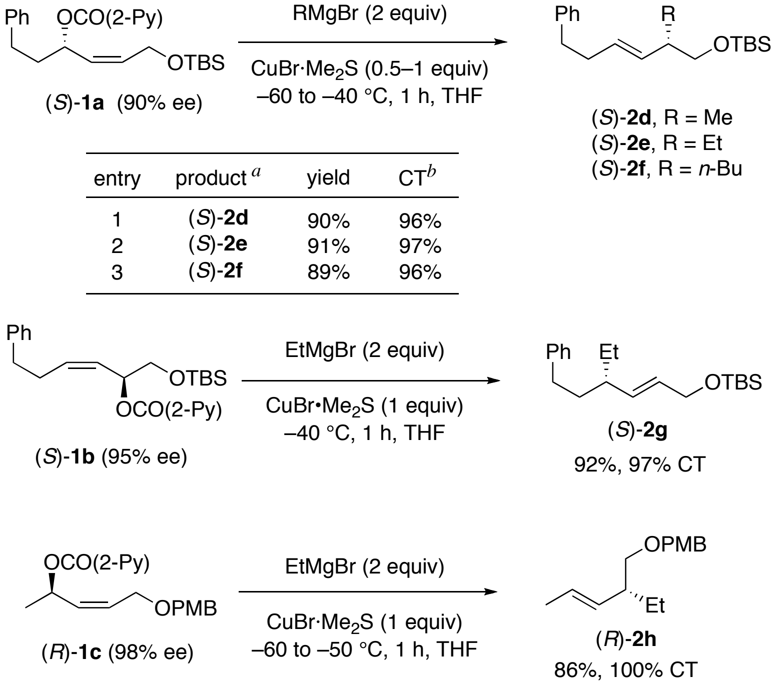
Scheme 6 で S_N2’ 生成物の二重結合の立体選択性に差があった結果について、Scheme 7 のように考察した。シス型の基質 *rac*-**1a** にアルキル銅試薬が S_N2’ 反応を起こす時、基質の配座は **A** と **B** の２通りが考えられる。しかし、配座 **B** では、置換基 R^1, R^2 の間で 1,3-アリル位の立体反発があるため形成しづらく、配座 **A** 経由の生成物 *rac*-**2e** が高い選択性で得られる。一方、トランス型の基質 *rac*-**1a’** の場合、配座 **D** の置換基 R^1, H の間の立体反発が小さいので、基質の配座は **C** と **D** の２通りを取る事ができ、*rac*-**2e** と **2e’** の混合物が得られたと解釈した。

Scheme 7. Plausible mechanisum of allylation of *rac*-1a and *rac*-1a' with EtMgBr/CuBr·Me$_2$S.



続いて、光学活性なシス型の基質 (*S*)-**1a** に、RMgBr (R = Me, Et, *n*-Bu) と CuBr·Me$_2$S から調製したアルキル銅試薬を反応させた。その結果、優れた位置選択性と不斉転写率で (*S*)-**2d~f** を与えた (Scheme 8)。また、EtMgBr と (*S*)-**1b** の反応も同様に進行し、(*S*)-**2g** を与えた。(*S*)-**2g** は、(*S*)-**1a** とエチル銅試薬とのアリル化反応での S$_N$2 生成物に相当する。(*S*)-**2e** と (*S*)-**2g** の ^{1}H NMR スペクトルを互いに比較し、(*S*)-**1a** と (*S*)-**1b** の反応物に位置異性体が混ざっていない事が分かった。この事から、ピコリン酸アリルのアルキル化は、側鎖 (Ph(CH$_2$)$_2$-, TBSOCH$_2$-) に依らず S$_N$2' 生成物を与える事が明らかとなった。さらに、(*R*)-**1c** も高選択的に反応し、(*R*)-**2g** を与えた。

Scheme 8. Allylation with alkyl copper reagents.

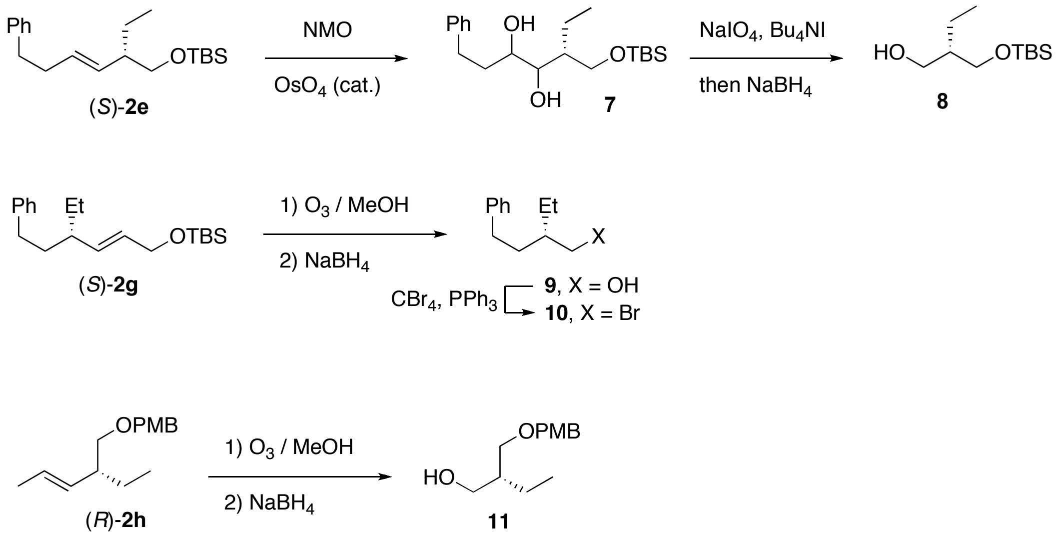


entry	product [a]	yield	CT [b]
1	(*S*)-**2d**	90%	96%
2	(*S*)-**2e**	91%	97%
3	(*S*)-**2f**	89%	96%

[a] The stereochemistry of (*S*)-**2e**, **2g** and (*R*)-**2h** was determined as described in Scheme 9, whereas that of the other products was assigned by analogy. [b] Chirality transfer (CT) was determined by chiral HPLC.

なお、(*S*)-**2e**, **2g**, (*R*)-**2h** はそれぞれ既知化合物 **8**, **10**, **11** へ変換し、$[\alpha]_D$ を比較して絶対構造を決定した (Scheme 9)。その結果から、アルキル銅試薬でもアリル化反応がアンチ S_N2' 選択的に進行している事を確定できた。

Scheme 9. Determination of absolute configuration of (*S*)-2e, 2g, and (*R*)-2h.



３－４．結論

グリニャール試薬と銅塩から生じる有機銅試薬をピコリン酸アリルと反応させ、アルケニル基 (sp^2-C) やアルキル基 (sp^3-C) も高アンチ S_N2' 選択的に導入できた。特に、これまで一般性の高い例が知られていないアルケニル基の導入を円滑に行なう事が出来た事は特筆に値する。

Experimental Section

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-ethenyl-6-phenyl-3-hexene ((*S*)-2a).

(Scheme 4, entry 1) (*S*)-**2a** was synthesized from (*S*)-**1a** according to the procedure described in Chapter 2; 81% yield, 88% ee, 98% CT; IR (neat) 1256, 1104, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 2.35 (dt, *J* = 7, 8 Hz, 2 H), 2.69 (dd, *J* = 7, 6 Hz, 2 H), 2.87 (ddt, *J* = 8, 8, 7 Hz, 1 H), 3.54 (d, *J* = 7 Hz, 2 H), 4.98–5.08 (m, 2 H), 5.40 (dd, *J* = 16, 8 Hz, 1 H), 5.55 (dt, *J* = 16, 7 Hz, 1 H), 5.79 (ddd, *J* = 17, 11, 7 Hz, 1 H), 7.15–7.23 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, 18.5, 26.0, 34.8, 36.0, 49.5, 66.6, 115.4, 125.8, 128.3, 128.5, 130.2, 131.3, 138.9, 142.1. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 30.5 (*R*), 31.9 (*S*).

Determination of the absolute configuration (Scheme 5): To a solution of (*S*)-**2a** (42 mg, 0.153 mmol) in MeOH and EtOAc (1 : 1, 2 mL) was added 10% Pd/C (20 mg). The mixture was stirred at rt for 2 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **4** (40 mg, 94%): $[\alpha]^{28}_D$ 0 (*c* 0.80, $CHCl_3$); IR (neat) 1256, 1094, 835, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.85 (t, *J* = 7 Hz, 3 H), 0.89 (s, 9 H), 1.18–1.42 (m, 8 H), 1.54–1.66 (m, 1 H), 2.60 (t, *J* = 8 Hz, 2 H), 3.46 (d, *J* = 5 Hz, 2 H), 7.15–7.20 (m, 3 H), 7.23–7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), 11.3 (–), 18.4 (+), 23.6 (+), 26.0 (–), 26.7 (+), 30.4 (+), 32.0 (+), 36.0 (+), 42.0 (–), 65.3 (+), 125.6 (–), 128.3 (–), 128.5 (–), 143.0 (+).

To an ice-cold solution of **4** (40 mg, 0.125 mmol) in THF (1 mL) was added Bu_4NF (0.19 mL, 1.0 M in THF, 0.19 mmol). The reaction was carried out at rt for 3 h, and quenched by addition of saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **5** (24 mg, 93%): $[\alpha]^{28}_D$ –1.2 (*c* 0.803, $CHCl_3$); IR (neat) 3351, 1453, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.21 (br s, 1 H), 1.26–1.45 (m, 6 H), 1.56–1.68 (m, 3 H), 2.61 (t, *J* = 8 Hz, 2 H), 3.54 (d, *J* = 4 Hz, 2 H), 7.13–7.22 (m, 3 H), 7.23–7.30 (m, 2 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 11.2 (–), 23.4 (+), 26.7 (+), 30.4 (+), 31.9 (+), 36.0 (+), 42.0 (–), 65.3 (+), 125.7 (–), 128.3 (–), 128.5 (–), 142.8 (+).

To an ice-cold solution of **5** (24 mg, 0.117 mmol) in pyridine and CH_2Cl_2 (1 : 1, 1 mL) was added BzCl (0.027 mL, 0.233 mmol). The resulting mixture was stirred at rt overnight and diluted with EtOAc and H_2O. The excess reagent was quenched with *N*,*N*-dimethyl-1,3-propanediamine (0.050 mL, 0.40 mmol). The mixture was stirred at rt for 20 min. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6** (23 mg, 63%): $[\alpha]^{28}_{D}$ –1.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 8 Hz, 3 H), 1.35–1.52 (m, 6 H), 1.58–1.77 (m, 3 H), 2.62 (t, *J* = 8 Hz, 2 H), 4.24 (d, *J* = 6 Hz, 2 H), 7.13–7.21 (m, 3 H), 7.22–7.30 (m, 2 H), 7.44 (dddd, *J* = 8, 8, 1, 1 Hz, 2 H), 7.56 (dddd, *J* = 8, 8, 1, 1 Hz, 1 H), 8.04 (ddd, *J* = 8, 1, 1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2 (–), 24.1 (+), 26.6 (+), 30.9 (+), 31.9 (+), 36.0 (+), 39.0 (–), 67.3 (+), 125.7 (–), 128.3 (–), 128.43 (–), 128.45 (–), 129.6 (–), 130.6 (+), 132.9 (–), 142.7 (+), 152.1 (+), 166.8 (+); HRMS (EI) calcd for $C_{21}H_{26}O_2$ (M^+) 310.1934, found 310.1933.

HPLC analysis (Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 32.6 (*S*), 33.8 (*R*)) showed that retention time of **6** thus synthesized was identical with that of **6** synthesized from (*S*)-**2e** (R = Et in Scheme 8) ((1) H_2, Pd/C, MeOH and EtOAc; (2) Bu_4NF; (3) BzCl, pyridine, CH_2Cl_2), while determination of the absolute configuration of (*S*)-**2e** was independently carried out as described below.

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(1-pentylethenyl)-6-phenyl-3-hexene ((*R*)-2b).

(Scheme 4, entry 2) 75% yield, 87% ee, 97% CT; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.88 (s, 9 H), 0.89 (m, 3 H), 1.21–1.48 (m, 6 H), 1.97 (t, *J* = 8 Hz, 2 H), 2.32 (ddd, *J* = 8, 8, 7 Hz, 2 H), 2.67 (t, *J* = 8 Hz, 2 H), 2.76 (ddd, *J* = 7, 7, 7 Hz, 1 H), 3.55 (dd, *J* = 10, 7 Hz, 1 H), 3.65 (dd, *J* = 10, 7 Hz, 1 H), 4.71 (s, 1 H), 4.78 (s, 1 H), 5.37 (dd, *J* = 15, 8 Hz, 1 H), 5.50 (dt, *J* = 15, 6 Hz, 1 H), 7.14–7.30 (m, 5 H). The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 26.0 (*R*), 28.0 (*S*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenyl-2-(1-phenylethenyl)-3-hexene ((*R*)-2c).

(Scheme 4, entry 3) 85% yield, 87% ee, 97% CT; IR (neat) 1256, 1103, 836 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ –0.09 (s, 6 H), 0.79 (s, 9 H), 2.22–2.32 (m, 2 H), 2.60 (dd, *J* = 8, 8 Hz, 2 H), 3.28 (ddd, *J* = 7, 7, 6 Hz, 1 H), 3.52 (dd, *J* = 10, 7 Hz, 1 H), 3.62 (dd, *J* = 10, 6 Hz, 1 H), 4.96 (s, 1 H), 5.22 (s, 1 H), 5.44 (dd, *J* = 16, 7 Hz, 1 H), 5.52 (dt, *J* = 16, 6 Hz, 1 H), 7.04–7.33 (m, 10 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ –5.3, –5.2, 18.4, 26.0, 34.7, 36.0, 50.2, 66.2, 113.7, 125.8, 126.7, 127.2, 128.1, 128.3, 128.6, 131.1, 131.3, 142.1, 142.6, 149.6; HRMS (FAB) calcd for $C_{26}H_{36}OSiNa$ [(M + Na)$^+$] 415.2433, found 415.2430. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 47.6 (*S*), 59.9 (*R*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-6-phenyl-3-hexene ((*S*)-2d).

(Scheme 8, entry 1) 90% yield from (*S*)-**1a** (90% ee), 86% ee, 96% CT; IR (neat) 1257, 1078, 837, 775 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 2.20–2.35 (m, 3 H), 2.67 (t, *J* = 7 Hz, 2 H), 3.34 (dd, *J* = 9, 7 Hz, 1 H), 3.46 (dd, *J* = 9, 6 Hz, 1 H), 5.35 (dd, *J* = 16, 7 Hz, 1 H), 5.49 (dt, *J* = 16, 7 Hz, 1 H), 7.14–7.21 (m, 3 H), 7.24–7.31 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ –5.21, –5.18, 16.8, 18.5, 26.0, 34.7, 36.2, 39.4, 68.4, 125.8, 128.3, 128.6, 129.3, 133.6, 142.2. HRMS (FAB) calcd for $C_{19}H_{32}OSiNa$ [(M + Na)$^+$] 327.2120, found 327.2122. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 30.0 (*R*), 31.3 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-6-phenyl-3-hexene ((*S*)-2e).

(Scheme 8, entry 2) 91% yield from (*S*)-**1a** (90% ee), 87% ee, 97% CT; IR (neat) 1256, 1103, 836 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.03 (s, 6 H), 0.82 (t, *J* = 7 Hz, 3 H), 0.89 (s, 9 H), 1.07–1.34 (m, 1 H), 1.46–1.62 (m, 1 H), 1.94–2.08 (m, 1 H), 2.28–2.38 (m, 2 H), 2.68 (dd, *J* = 7, 6 Hz, 2 H), 3.43 (dd, *J* = 10, 7 Hz, 1 H), 3.48 (dd, *J* = 10, 6 Hz, 1 H), 5.20 (dddd, *J* = 15, 8, 2, 2 Hz, 1 H), 5.48 (dt, *J* = 15, 7 Hz, 1 H), 7.13–7.35 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ –5.2, 11.7, 18.5, 24.0, 26.0, 34.8, 36.3, 47.3, 66.9, 125.8, 128.3, 128.6, 130.9, 132.3, 142.2; HRMS (FAB) calcd for $C_{20}H_{34}OSiNa$ [(M + Na)$^+$] 341.2277, found 341.2269. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 28.7 (*R*), 29.8 (*S*).

Determination of the absolute configuration (Scheme 9): To an ice-cold solution of (*S*)-**2e** (110 mg, 0.345 mmol) in acetone-H_2O (4 : 1, 3.5 mL) were added NMO (53 mg, 0.45 mmol) and OsO_4 (0.175 mL, 0.02 M in *t*-BuOH, 0.0035 mmol). After 5 h at 0 °C, the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O twice. The combined extracts were dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **7** (105 mg, 85%).

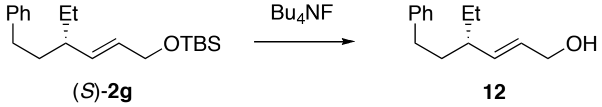
To an ice-cold solution of **7** (55 mg, 0.16 mmol) in MeOH-H_2O (5 : 1, 2 mL) was added Bu_4NI (18 mg, 0.049 mmol) and $NaIO_4$ (48 mg, 0.22 mmol). After 4 h at 0 °C, $NaBH_4$ (20 mg, 0.53 mmol) was added to the mixture. The mixture was stirred at 0 °C for 30 min, and diluted with saturated NH_4Cl and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O twice. The combined extracts were washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **8** (21 mg, 61%): $[\alpha]^{25}_{D}$ –10.0 (*c* 0.10, $CHCl_3$); cf. $[\alpha]^{26}_{D}$ –11.41 (*c* 1.42, $CHCl_3$);[4] ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 0.92 (t, *J* = 8 Hz, 3 H), 1.19–1.35 (m, 2 H), 1.58–1.72 (m, 1 H), 2.92 (dd, *J* = 6, 4 Hz, 1 H), 3.60 (dd, *J* = 10, 7 Hz, 1 H), 3.60–3.68 (m, 1 H), 3.70–3.80 (m, 1 H), 3.81 (dd, *J* = 10, 4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.55, –5.49, 11.9, 18.2, 20.7, 25.9, 43.7, 66.7, 67.4.

(*S,E*)-2-Butyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-3-hexene ((*S*)-2f).

(Scheme 8, entry 3) 89% yield, 86% ee, 96% CT; IR (neat) 1256, 1077, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.82–1.00 (br s, 12 H), 1.16–1.35 (m, 5 H), 1.44–1.54 (m, 1 H), 2.03–2.16 (m, 1 H), 2.33 (dt, *J* = 7, 7 Hz, 2 H), 2.69 (t, *J* = 7 Hz, 2 H), 3.37–3.53 (m, 2 H), 5.21 (dd, *J* = 15, 8 Hz, 1 H), 5.48 (dt, *J* = 15, 7 Hz, 1 H), 6.85–7.22 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.21, –5.17, 14.2, 18.5, 22.9, 26.0, 29.3, 30.9, 34.7, 36.2, 45.5, 67.2, 125.8, 128.3, 128.6, 130.6, 132.7, 142.2; HRMS (FAB) calcd for $C_{22}H_{38}OSiNa$ [$(M + Na)^+$] 369.2590, found 369.2594. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 25.9 (*R*), 27.6 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-diphenyl-4-ethyl-2-hexene ((*S*)-2g).

(Scheme 8) 92% yield from (*S*)-**5c** (95% ee), 92% ee, 97% CT; $[\alpha]^{23}_D$ +4.7 (*c* 0.42, $CHCl_3$); IR (neat) 1462, 1255, 1092, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.099 (s, 3 H), 0.101 (s, 3 H), 0.86 (t, *J* = 7 Hz, 3 H), 0.93 (s, 9 H), 1.18–1.80 (m, 6 H), 1.87–2.00 (m, 1 H), 2.45–2.70 (m, 2 H), 4.19 (d, *J* = 5 Hz, 2 H), 5.43 (dd, *J* = 15, 8 Hz, 1 H), 5.55 (dt, *J* = 15, 5 Hz, 1 H), 7.12–7.22 (m, 3 H), 7.24–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9 (–), 11.7 (–), 18.5 (+), 26.1 (–), 28.1 (+), 33.7 (+), 36.8 (+), 43.8 (–), 64.1 (+), 125.6 (–), 128.3 (–), 128.5 (–), 130.0 (–), 134.9 (–), 143.0 (+). The enantiomeric information was determined by HPLC analysis of the corresponding alcohol shown below.



Determination of CT: To a solution of (*S*)-**2g** (23 mg, 0.072 mmol) in THF (2 mL) was added Bu_4NF (0.14 mL, 1.0 M in THF, 0.14 mmol) dropwise. The reaction was carried out at rt for 1 h and quenched by addition of saturated NH_4Cl. The organic phase was separated and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **12** (14 mg, 95%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.24–1.78 (m, 5 H), 1.88–2.02 (m, 1 H), 2.45–2.70 (m, 2 H), 4.13 (dd, *J* = 6, 1 Hz, 1 H), 5.46 (dd, *J* = 15, 9 Hz, 1 H), 5.64 (dd, *J* = 15, 6 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.24–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7 (–), 27.9 (+), 33.7 (+), 36.6 (+), 43.9 (–), 63.9 (+), 125.7 (–), 128.4 (–), 128.5 (–), 129.6 (–), 137.0 (–), 142.8 (+); HRMS (EI) calcd for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1516. The enantiomeric information (92% ee, 97% CT) was determined by chiral HPLC analysis: Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.3 mL/min, rt; t_R (min) = 31.8 (*R*), 33.8 (*S*).

Determination of the absolute configuration (Scheme 9): A stream of O_3 in O_2 was gently bubbled into a solution of (*S*)-**2g** (78 mg, 0.245 mmol) in MeOH at –78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at –78 °C and $NaBH_4$ (93 mg, 2.45 mmol) was added. The cooling bath was removed, and the solution was stirred at rt for 1 h. Saturated NH_4Cl was added to the solution, and the resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **9** (38 mg, 87%): $[\alpha]^{23}_{D}$ 0 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, *J* = 7 Hz, 3 H), 1.36–1.54 (m, 2 H), 1.56–4.74 (m, 2 H), 2.64 (t, *J* = 8 Hz, 2 H), 3.60 (d, *J* = 5 Hz, 2 H), 7.14–7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (–), 23.3 (+), 32.6 (+), 33.5 (+), 41.8 (–), 65.3 (+), 125.9 (–), 128.6 (–), 142.9 (+). The ^1H NMR and ^{13}C NMR spectra were identical with the data reported.[5]

To an ice-cold solution of **9** (25 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) were added CBr_4 (56 mg, 0.169 mmol) and PPh_3 (48 mg, 0.183 mmol) portionwise. The mixture was stirred at 0 °C for 2 h and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish bromide **10** (20 mg, 59%): $[\alpha]^{25}_{D}$ +6 (*c* 0.2, $CHCl_3$), *cf.* $[\alpha]_D$ +10.8 (*c* 1.5, $CHCl_3$) for the same enantiomer;[6] ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 8 Hz, 3 H), 1.43–1.80 (m, 5 H), 2.53–2.73 (m, 2 H), 3.52 (d, *J* = 4 Hz, 2 H), 7.16–7.24 (m, 3 H), 7.25–7.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9 (–), 25.2 (+), 33.0 (+), 34.1 (+), 38.8 (+), 40.5 (–), 125.9 (–), 128.4 (–), 128.5 (–), 142.2 (+); HRMS (EI) calcd for $C_{12}H_{17}Br$ (M^+) 242.0514, found 242.0518. The ^1H NMR and ^{13}C NMR spectra were identical with the data reported.[6]

(*R*,*E*)-1-[(2-Ethylpent-3-enyloxy)methyl]-4-methoxybenzene ((*R*)-2h).

(Scheme 8) 86% yield from (*R*)-**1c** (98% ee), 98% ee, 100% CT; $[\alpha]^{25}_{D}$ –6.4 (*c* 0.346, $CHCl_3$); IR (neat) 1612, 1513, 1248, 1096, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 8 Hz, 3 H), 1.12–1.38 (m, 1 H), 1.46–1.63 (m, 1 H), 1.67 (dd, *J* = 6, 2 Hz, 3 H), 2.11–2.25 (m, 1 H), 3.30 (dd, *J* = 9, 7 Hz, 1 H), 3.33 (dd, *J* = 9, 7 Hz, 1 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.23 (ddq, *J* = 15, 8, 2 Hz, 1 H), 5.48 (ddq, *J* = 15, 1, 6 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5 (–), 18.2 (–), 24.6 (+), 44.6 (–), 55.3 (–), 72.6 (+), 73.8 (+), 113.7 (–), 126.2 (–), 129.2 (–), 130.9 (+), 132.6 (–), 159.1 (+); HRMS (FAB) calcd for $C_{15}H_{22}O_2Na$ [$(M + Na)^+$] 257.1517, found 257.1522. The enantiomeric information was determined by chiral

HPLC: Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 67.3 (*R*), 73.8 (*S*).

Determination of the absolute configuration (Scheme 9): A stream of O_3 in O_2 was gently bubbled into a solution of (*R*)-**2h** (25.7 mg, 0.110 mmol) in MeOH at –78 °C for 5 min. Excess O_3 remaining in the solution was purged by bubbling argon at –78 °C and $NaBH_4$ (41 mg, 1.08 mmol) was added. After stirring at –78 °C for 1 h, saturated NH_4Cl was added to the solution, and the resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give **11** (19.6 mg, 79%): $[\alpha]^{27}_{D}$ +13 (*c* 0.238, $CHCl_3$); cf. $[\alpha]^{25}_{D}$ –12.8 (*c* 1.0, $CHCl_3$) for the (*S*)-enantiomer.[7] The ^1H NMR spectrum of **11** was identical with the data reported.[7]

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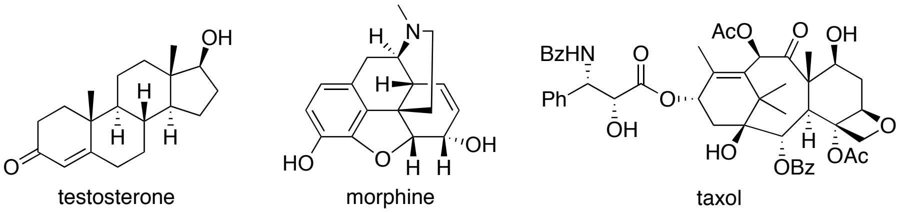
第４章「２−シクロヘキシリデンエチルピコリン酸エステルと有機銅試薬を用いた環上４級炭素の構築」

４−１．緒言

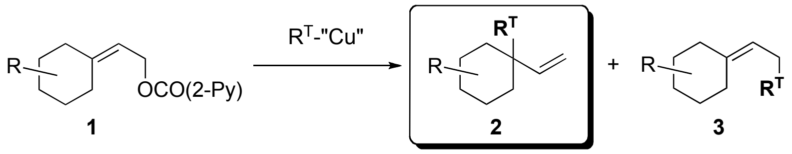
六員環上に四級炭素を有する天然物は良く知られており、４級炭素には、全てが炭素で置換されたものとヘテロ原子を含むものがある。(Figure 1)。

Figure 1. Natural products having quaternary carbon.



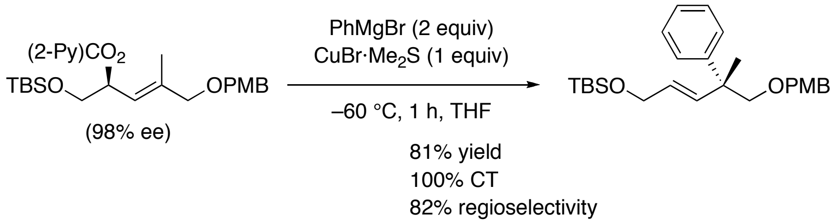
testosterone　morphine　taxol

その構築の困難さゆえに、立体選択的な４級炭素の構築法の開発は重要な課題の一つである。そこで、筆者は第２、３章で見出した知見を元に、アリル化反応を活用して環上に４級炭素を構築する研究を行う事にした。反応形式としては、合成容易な２−シクロヘキシリデンエチルピコリン酸エステルへのアリル化を選択した (eq 1)。得られる生成物 **2** は末端ビニル基を足掛りに更なる誘導化が期待され、有用であると考えられる。



(1)

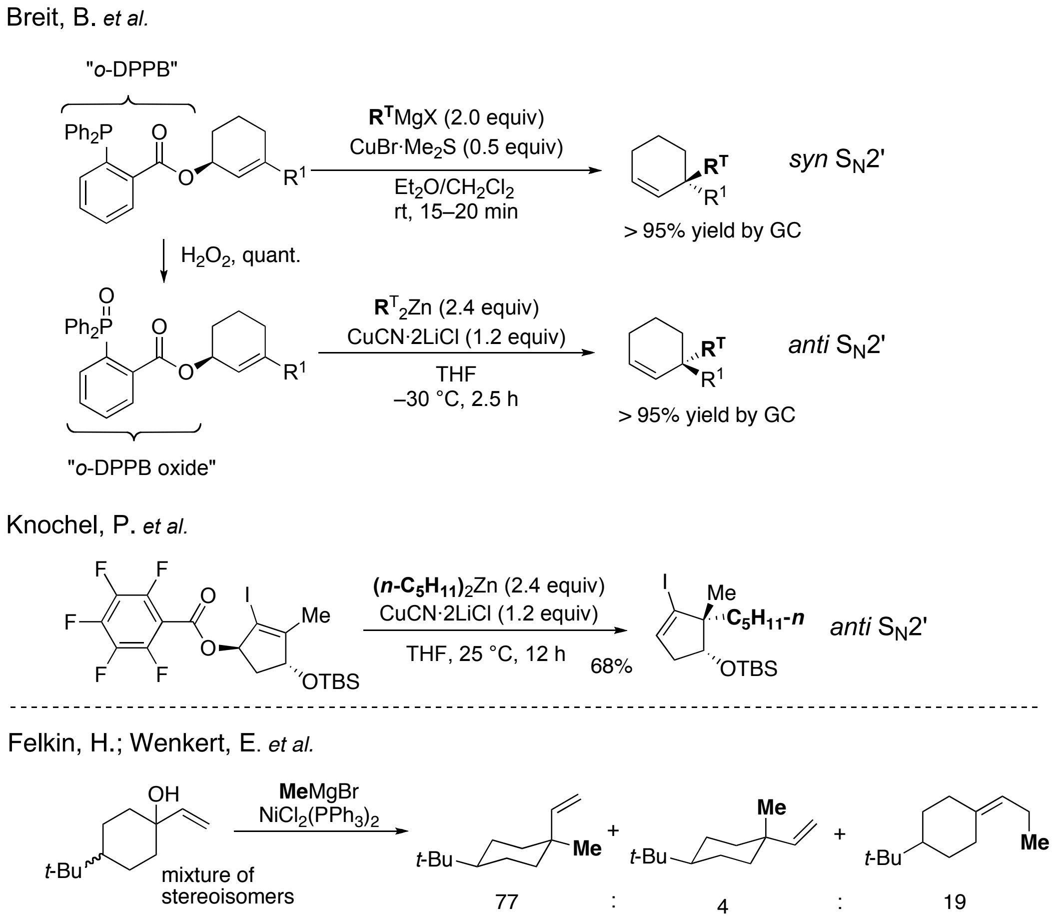
なお、鎖状の４級炭素構築については、ピコリン酸アリルのアンチ S_N2' 反応を共同研究者の片山が行い良好な結果を得ている (eq 2)[1]。



(2)

ここで、有機銅を用いたアリル化反応によって環上に４級炭素を構築した例を紹介する (Scheme 1)。Breit らは、*o*-DPPB 又は *o*-DPPB oxide 基を脱離基とした２−シクロヘキセン−１−オール誘導体の反応で、良好な選択性でシン又はアンチ S_N2' 生成物を得ている[2]。また、Knochel らは $C_6F_5CO_2$ 基を脱離基としたアリル化で五員環上に４級炭素を構築して、天然物合成に応用している[3]。一方、eq 1 の４級炭素構築法は有機銅では知られてないが、 Felkin, Wenkert らは Ni 触媒を用いて研究している。しかし、その位置及び立体選択性は満足がいくものではない[4]。

Scheme 1. Examples of other studies.

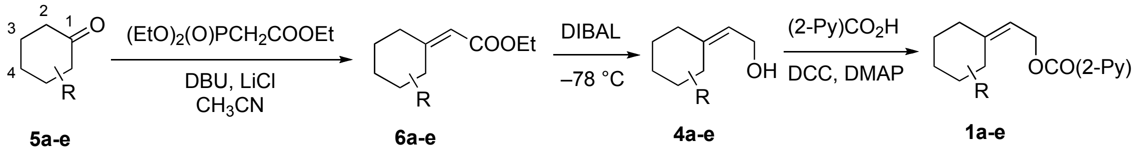


４－２．反応条件の検討

4-2-1. 基質の合成

反応基質は、市販のシクロヘキサノン誘導体から、(1) Horner-Wadsworth-Emmons 反応、(2) DIBAL による還元、(3) ピコリン酸との縮合の３工程で簡便に合成できた (Scheme 2)。なお、置換基が２位または３位にある場合、Horner-Wadsworth-Emmons 反応の段階でオレフィンの立体混合物を与えたが、分離が困難だったため、混合物のまま反応基質へと変換して反応を検討することにした。

Scheme 2. Preparation of picolinates 1a-e.

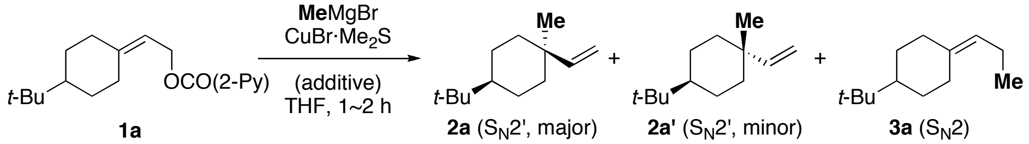


1a: 4-*t*-Bu; **1b**: 4-Ph; **1c**: 4-Me; **1d**: 2-Me; **1e**: 3-Me

4-2-2. 反応条件の検討

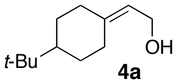
シクロヘキサン環の４位に *t*-Bu 基を有する基質 **1a** に対して、アリル化の反応条件を検討する事にした (Table 1)。このアリル化反応では、２種類の S_N2' 生成物 **2a**, **2a’** 及び S_N2 生成物 **3a** を生じる可能性がある。ここでは、位置選択性を (**2a** + **2a’**) : **3**、S_N2' 生成物の立体選択性を **2a** : **2a’** で表し、その値は ^{1}H NMR から求めた。

Table 1. Allylation of 1a with MeMgBr/CuBr·Me$_2$S.



entry	**Me**–"Cu" (equiv)	additive (equiv)	temp., °C	regio-selectivity [(**2a**+**2a'**)/**3a**]	stereo-selectivity [**2a** : **2a'**][a]	yield,[a] %
1	**Me**$_2$CuMgBr·MgBr$_2$ (1.5)	none	–40 ~ –20	18 : 82	nd	nd
2	as above	none	0	22 : 78	nd	nd
3	as above	BF$_3$·OEt$_2$ (1.5)	0	91 : 9	91 : 9	nd
4	as above	ZnBr$_2$ (1.5)	0	95 : 5	93 : 7	nd
5	as above	ZnBr$_2$ (1.5)	–40 ~ –10	99 : 1	96 : 4	nd
6	as above	ZnBr$_2$ (4)	–40 ~ 0	100 : 0	97 : 3	88
7	as above	ZnI$_2$ (1.5)	–40 ~ –10	99 : 1	99 : 1	85
8	**Me**Cu·MgBr$_2$ (1.5)	none	0	90 : 10	94 : 6	nd
9	**Me**Cu·MgBr$_2$ (1.5)	ZnBr$_2$ (1.5)	0 ~ rt (18 h)	85 : 15	94 : 6	nd[b]
10	**Me**MgBr / CuBr (3 / 0.5)	none	0	7 : 93	–	nd[b]

[a] nd: not determined. [b] Alcohol **4a** was formed competitively.



4a

まず、MeMgBr (3 当量) と CuBr·Me$_2$S (1.5 当量) から調製した Me$_2$CuMgBr·MgBr$_2$、つまり Me/Cu (3/1.5) を **1a** に反応させたところ、反応は温度に依存せず S$_N$2 生成物 **3a** を優先した (entries 1, 2)。そこで、S$_N$2' 選択性を向上させる為に幾つかのルイス酸を検討した。その中で亜鉛塩 ZnBr$_2$ を用いた場合、劇的に位置及び立体選択性が改善され、**2a** を選択的に与えた (entry 4)。MgBr$_2$ では位置選択性が約 1 : 1 と低く、LiCl ではアルコール **4a** を生成するのみであった。そこで、亜鉛塩についてさらに検討したところ、ZnX$_2$ (X = Br or I, 1.5 ~ 4 当量) を添加してより低温 (–40 ~ –10 °C) で反応させると、非常に高い位置及び立体選択性で S$_N$2' 生成物 **2a** が得られる事を見出せた (entries 5–7)。

ZnX$_2$ の添加で選択性が向上した理由として、(1) ピコリン酸基とキレートする MgX$_2$ が銅錯体から遊離する事で、ピコリン酸基の脱離能を向上させた ; (2) ZnX$_2$ が銅錯体と複合体を形成し、銅試薬の反応性が向上した、という２つの反応性を上げる効果が働いたものと考えている。

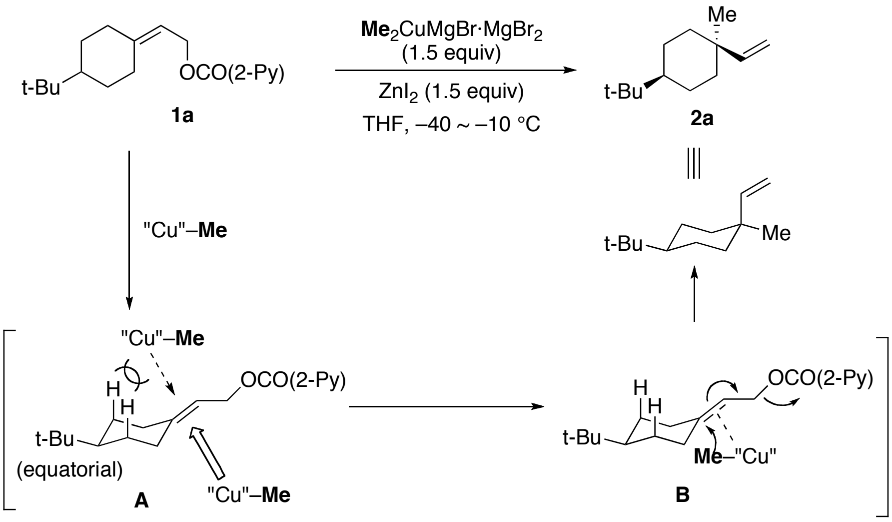
また、メチル銅試薬の活性種の比較を行った。Me/Cu (3/0.5) では S$_N$2 選択性が向上し、Me/Cu (1.5/1.5) では９割程度の S$_N$2' (位置)選択性が見られた (entries 8, 10)。興味深い事に、Me/Cu (1.5/1.5) に ZnBr$_2$ (1.5 当量) を添加しても、位置

選択性に向上は見られなかった (entry 9)。なお、これらの条件ではアルコール体 **4a** の副生が見られた。

4-2-3. 推定反応機構の考察

前節で選択的に得る事ができた S_N2'生成物の両ジアステレオマー (**2a, 2a'**) は文献既知である[4]。生成物の ^{13}C NMR を文献値と比較したところ、相対構造は **2a** であると判明した。この事から反応機構を Scheme 3 の様に推察した。

Scheme 3. Plausible mechanism for 2a

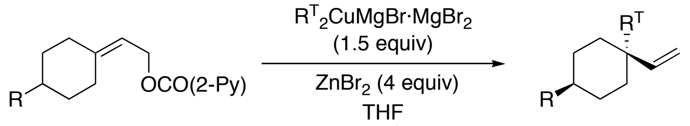


反応基質 **1a** では、シクロヘキサン環４位の *t*-Bu 基が立体障害の小さいエカトリアル位を占める。これに対して銅試薬 (Me–“Cu”) が１位の二重結合に配位すべく垂直方向から接近するが、紙面左上から接近する場合にはシクロヘキサン環の３、５位のアキシアル水素が立体障害となる（中間体 **A**）。一方、分子の外側（紙面右下）から接近する場合（中間体 **B**）、上述した立体障害はなく、速やかに S_N2' 反応して位置選択性良く **2a** を生じる。なお、entries 1, 2, 8-10 の条件下では S_N2' 反応が遅く、πアリル中間体を経て S_N2 体 **3a** を副生したと考えている。

4-2-4. 適応範囲の検討

続いて、前節で見出した条件を元に、シクロヘキサン環上の置換基効果（置換基及び置換位置）を調べる事にした。

Table 2. Allylation of 1a-c.



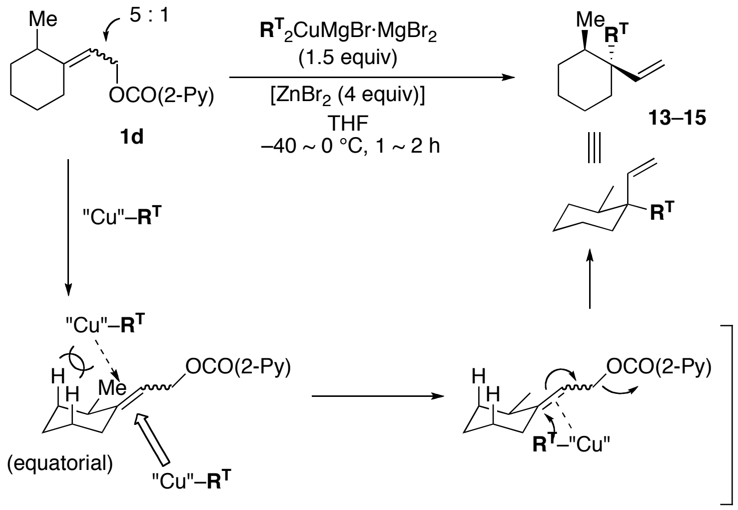
1a-c **7–12**

entry	substrate	product No.	product R	product R^T	regio-selectivity, %	stereo-selectivity, %	yield, %
1	**1a**	**7**	*t*-Bu	Et	98	98	81
2	**1a**	**8**	*t*-Bu	*i*-Pr	95	100	80
3	**1b**	**9**	Ph	Et	100	99	81
4	**1b**	**10**	Ph	*i*-Pr	100	100	83
5	**1c**	**11**	Me	Et	94	93	70
6	**1c**	**12**	Me	*i*-Pr	90	97	79

まず、４位に置換基 (R) を持つシクロヘキシリデンエチルピコリン酸エステルに対して R^T 基の導入を行なった (Table 2)。反応は全て高い位置及び立体選択性で進行し S_N2' 体を生成したが、entry 5 では若干ではあるが立体選択性の低下が見られた。この場合、基質 **1c** の置換基 (R) も試薬の R^T 基も共に小さい組合せのため、Scheme 3 に示した反応コースの選択性が低下したと考えている。この事は、R^T を Et から *i*-Pr に代えると (entry 5→6)、立体選択性が上向いた事からも納得できる。また、R^T 基が２級アルキルの *i*-Pr 基でも選択性は良好なものであった。

続いて、シクロヘキサン環上のメチル基の位置を変えた基質 **1d**, **1e** の反応を行った。原料のオレフィンの立体は混ざりであったが、選択性は良好であった。Scheme 4 に **1d** の結果を示す。シクロヘキサン環の２位が Me 基で置換されている場合、$ZnBr_2$ を添加せずに R^T = Me 基を高選択的に導入できた (entry 1)。また、R^T 基が嵩高くなると選択性の低下が見られたが (entries 2, 3)、$ZnBr_2$ を加えると選択性を向上させることができた (entries 3→4)。

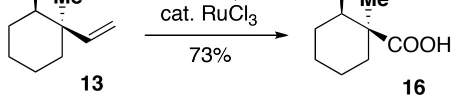
Scheme 4. Allylation of 1d.



entry	$ZnBr_2$ (equiv)	product No.	R^T	regio-selectivity, %	stereo-selectivity, %	yield,[a] %
1	none	**13**	Me	98	96	61
2	none	**14**	*n*-Bu	86	93	69
3	none	**15**	*i*-Pr	63	90	nd
4	$ZnBr_2$ (4)	**15**	*i*-Pr	92	96	69

[a] nd: not determined.

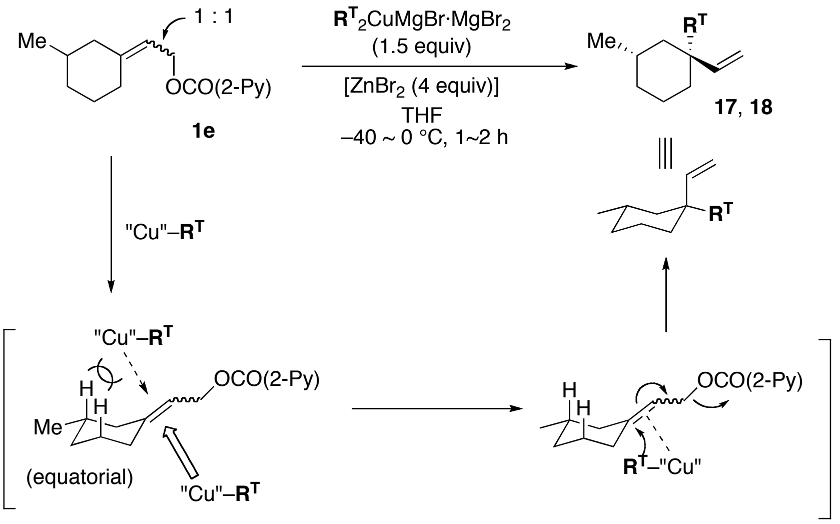
なお、生成物 **13** の立体配置を決定するため、**13** のオレフィンを酸化的に切断して文献既知[5]のカルボン酸 **16** に変換した (eq 3)。合成した **16** の ^{13}C NMR は文献値と一致した。これより、Scheme 4 に示す様に、4-*t*-Bu 基を持つ **1a** の場合と同様の反応経路で 4 級炭素が構築されたと言える。



(3)

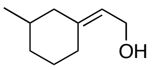
また、シクロヘキサン環の３位が Me 基で置換されている **1e** についても、そのオレフィンの立体に関係なく良好な結果が得られた (Scheme 5)。ZnBr$_2$ 無しでは位置選択性が低かったが (68%)、ZnBr$_2$ を添加する事で選択性が向上し (94%)、S$_N$2’ 反応が立体選択的に進行した (entry 1 vs entry 2)。なお、Scheme 5 に示した生成物の相対立体化学は推定であるが、反応は 2-, 4-置換体と同様の反応経路で進行したと考えている。

Scheme 5. Allylation of 1e.



entry	ZnBr$_2$ (equiv)	product No.	product R^T	regio-selectivity, %	stereo-selectivity, %	yield,^{a} %
1	none	**17**	Et	68	93	71^b
2	ZnBr$_2$ (4)	**17**	Et	94	94	84
3	ZnBr$_2$ (4)	**18**	*i*-Pr	96	96	nd

^{a} nd: not determined. ^{b} Alcohol **4e** was formed competitively.

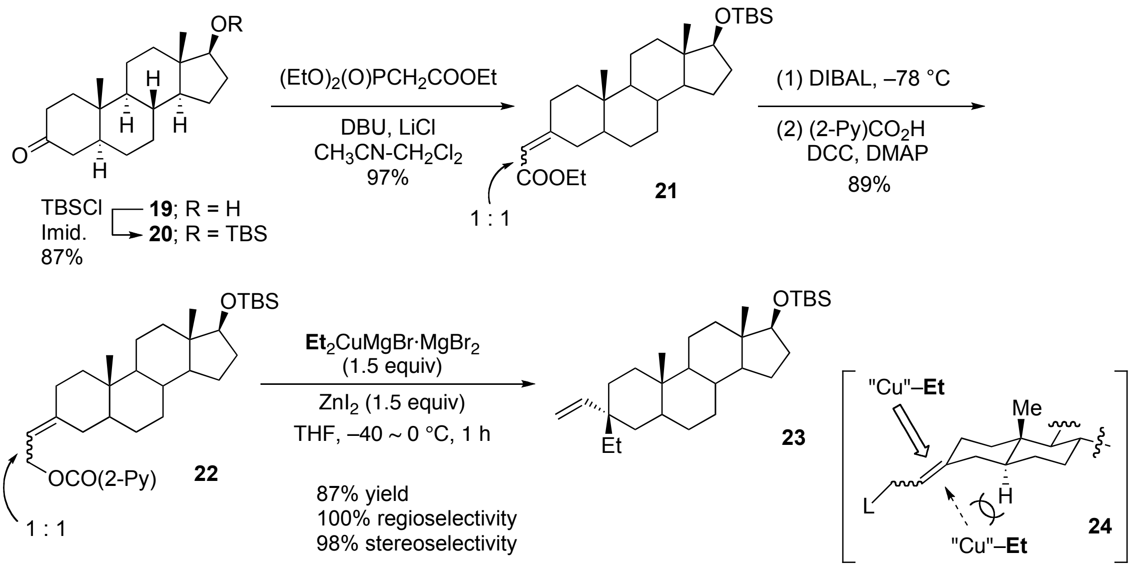


4e

４−３. 応用研究

続いて、応用研究としてステロイド骨格への４級炭素の構築に着目した。ステロイド骨格の A 環は六員環上に２つの置換基を持ち、分子自体がかなり大きい事から，アリル化反応の応用にふさわしいと考え検討を行った。その結果を Scheme 6 に示す。

Scheme 6. Construction of quaternary center on steroidal skelton.



原料のスタノロン **19** の水酸基を TBS で保護した後、Horner-Wadsworth-Emmons 反応により α,β–不飽和エステル **21** とした。合成した **21** はオレフィンの立体異性体から成る 1 : 1 の混合物であったが、前節の結果よりアリル化反応の際に問題とならないと予想し、混ざりのまま進める事にした。エステルをアルコールへ還元し、ピコリン酸と縮合して **22** とした。**22** に対し $Et_2CuMgBr\cdot MgBr_2$ を用いてアリル化を行ったところ、良好な収率、高い位置及び立体選択性で４級炭素の構築ができた。生成物の立体化学に関しては、これまでと同様に、**24** のようにステロイド骨格の外側から銅試薬が攻撃して４級炭素が得られたと考えている。

４−４．結論

本章では、六員環上の４級炭素の構築を行った。シクロヘキサン環の置換基に依らず、高い位置・立体選択性で S_N2' 生成物を得られる条件を見出した。得られる４級炭素は、容易に種々の変換が可能なビニル基を有しているため、更なる誘導化が可能であるという利点があり、今後の展開が期待できる。

Experimental section

Synthesis of Picolinates.

2-(4-*tert*-Butylcyclohexylidene)ethyl Picolinate (1a).

To a suspension of LiCl (593 mg, 14.0 mmol) in MeCN (10 mL) were added DBU (1.80 mL, 12.0 mmol) and triethyl phosphonoacetate (2.60 mL, 13.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, and **5a** (1.54 g, 9.98 mmol) was added. The reaction was carried out at rt overnight and quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6a** (2.22 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.10–1.33 (m, 3 H), 1.76–1.99 (m, 3 H), 2.16 (dt, *J* = 3, 14 Hz, 1 H), 2.31 (dm, *J* = 14 Hz, 1 H), 3.87 (dm, *J* = 14 Hz, 1 H), 4.14 (q, *J* = 7 Hz, 2 H), 5.60 (s, 1 H).

To a solution of **6a** (765 mg, 3.64 mmol) in THF (7 mL) was added DIBAL (7.80 mL, 1.03 M in hexane, 8.03 mmol) dropwise at –78 °C. After 1 h at –78 °C, the reaction was quenched by addition of water. The cooling bath was removed, and 1 N HCl was added. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated to afford the corresponding alcohol **4a** (616 mg), which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9 H), 0.82–1.26 (m, 4 H), 1.75 (t, *J* = 14 Hz, 1 H), 1.80–1.94 (m, 2 H), 2.02 (tm, *J* = 13 Hz, 1 H), 2.26 (tq, *J* = 14, 3 Hz, 1 H), 2.69 (tq, *J* = 14, 3 Hz, 1 H), 4.09–4.20 (m, 1 H), 5.36 (t, *J* = 7 Hz, 1 H). The ^{1}H NMR spectrum of **4a** was identical with that reported.[6]

To an ice-cold solution of the above **4a** (616 mg) in CH_2Cl_2 (11 mL) were added picolinic acid (538 mg, 4.37 mmol), DMAP (133 mg, 1.09 mmol), and DCC (976 mg, 4.73 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **1a** (958 mg, 92%

from **6a**): mp. 55–56 °C; IR (nujol) 1730, 1302, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9 H), 0.78–1.26 (m, 3 H), 1.74–1.96 (m, 3 H), 2.06 (tm, *J* = 13 Hz, 1 H), 2.25 (dm, *J* = 13 Hz, 1 H), 2.82 (dm, *J* = 14 Hz, 1 H), 4.95 (d, *J* = 7 Hz, 2 H), 5.46 (t, *J* = 7 Hz, 1 H), 7.47 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.84 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.15 (ddd, *J* = 8, 1, 1 Hz, 1 H), 8.77 (dm, *J* = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5 (–), 28.2 (+), 28.7 (+), 28.8 (+), 32.4 (+), 36.8 (+), 48.1 (–), 62.2 (+), 114.6 (–), 125.0 (–), 126.7 (–), 136.9 (–), 147.0 (+), 148.3 (+), 149.8 (–), 165.2 (+).

2-(4-Phenylcyclohexylidene)ethyl Picolinate (1b).

To a suspension of LiCl (240 mg, 5.66 mmol) in MeCN (16 mL) were added DBU (0.82 mL, 5.49 mmol) and triethyl phosphonoacetate (1.1 mL, 5.50 mmol) at 0 °C. The mixture was stirred 0 °C for 15 min, and a solution of **5b** (0.800 g, 4.59 mmol) in MeCN (2 mL) was added dropwise. The reaction was carried out at 0 °C for 1 h and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford the corresponding ester **6b**, which was used for the next reaction without further purification.

To a solution of the above ester **6b** in THF (18 mL) was added DIBAL (9.60 mL, 1.06 M in hexane, 10.2 mmol) dropwise at –78 °C. After 1 h at –78 °C, the resulting solution was quenched by addition of water (0.40 mL, 22 mmol) and NaF (2.0 g, 48 mmol). The mixture was stirred at rt for 30 min and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding allylic alcohol **4b** (660 mg, 71% from **5b**).

To an ice-cold suspension of DCC (2.10 g, 10.2 mmol) in CH_2Cl_2 (25 mL) were added DMAP (1.20 g, 9.82 mmol) and picolinic acid (1.30 g, 10.6 mmol). After 15 min at rt, **4b** (1.70 g, 8.40 mmol) in CH_2Cl_2 (3 mL) was added to the mixture at 0 °C. The mixture was stirred at rt for 4 h, diluted with Et_2O (28 mL), and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **1b** (2.04 g, 83%): ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.47–1.68 (m, 3 H), 1.86–2.20 (m, 2 H), 2.26 (t, *J* = 14 Hz, 1 H), 2.37 (d, *J* = 14 Hz, 1 H), 2.73 (tt, *J* = 12, 3 Hz, 1 H), 2.91 (d, *J* = 14 Hz, 1 H), 4.98 (d, *J* = 8 Hz, 2 H), 5.55 (t, *J* = 8 Hz, 1 H), 7.16–7.24 (m, 3 H), 7.25–7.33 (m, 2 H), 7.48 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.84 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.16 (dm, *J* = 8 Hz, 1 H), 8.78 (dm, *J* = 5 Hz, 1 H).

2-(2-Methylcyclohexylidene)ethyl Picolinate (1d).

To a suspension of LiCl (297 mg, 7.01 mmol) in MeCN (5 mL) were added DBU (0.90 mL, 6.03 mmol) and triethyl phosphonoacetate (1.30 mL, 6.49 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, and **5d** (0.60 mL, 4.97 mmol) was added. The reaction was carried out at rt overnight and quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding ester **6d** (647 mg, 71%), which was a 85:15 mixture of the stereoisomers by ^{1}H NMR spectroscopy: ^{1}H NMR of the major isomer (300 MHz, $CDCl_3$) δ 1.07 (d, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H), 1.01–1.92 (m, 5 H), 2.02–2.47 (m, 3 H), 3.54 (dt, *J* = 13, 5 Hz, 1 H), 4.15 (q, *J* = 7 Hz, 2 H), 5.58 (s, 1 H).

To a solution of **6d** (647 mg, 3.55 mmol) in THF (7 mL) was added DIBAL (7.60 mL, 1.03 M in hexane, 7.83 mmol) dropwise at –78 °C. After 1 h at –78 °C, the reaction was quenched by addition of water. The cooling bath was removed, and 1 N HCl was added. The mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated to afford the corresponding alcohol **4d** (477 mg), which was used for the next reaction without further purification: ^{1}H NMR of the major isomer (300 MHz, $CDCl_3$) δ 0.82–1.26 (m, 4 H), 1.75 (t, *J* = 14 Hz, 1 H), 1.80–1.94 (m, 2 H), 2.02 (tm, *J* = 13 Hz, 1 H), 2.26 (tq, *J* = 14, 3 Hz, 1 H), 2.69 (tq, *J* = 14, 3 Hz, 1 H), 4.09–4.20 (m, 1 H), 5.36 (t, *J* = 7 Hz, 1 H). The ^{1}H NMR spectrum of **4d** was identical with that reported.[6]

To an ice-cold solution of the above **4d** in CH_2Cl_2 (14 mL) were added picolinic acid (524 mg, 4.26 mmol), DMAP (130 mg, 1.06 mmol), and DCC (952 mg, 4.62 mmol).

The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **1d** (756 mg, 87% from **6d**, 85:15 mixture): IR (neat) 1739, 1717, 1307, 1289, 1128 cm^{-1}; ^{1}H NMR of the major isomer (300 MHz, $CDCl_3$) δ 1.07 (d, J = 7 Hz, 3 H), 0.80–2.20 (m, 8 H), 2.58–2.70 (m, 1 H), 4.91–5.14 (m, 2 H), 5.42 (t, J = 7 Hz, 1 H), 7.43–7.51 (m, 1 H), 7.84 (ddm, J = 8, 8 Hz, 1 H), 8.10–8.17 (m, 1 H), 8.74–8.82 (m, 1 H); ^{13}C NMR of the major isomer (75 MHz, $CDCl_3$) δ 18.3 (–), 25.3 (+), 27.9 (+), 28.7 (+), 36.4 (+), 38.4 (–), 62.2 (+), 112.4 (–), 125.0 (–), 126.6 (–), 136.8 (–), 148.1 (+), 149.7 (–), 150.7 (+), 165.0 (+).

2-(3-Methylcyclohexylidene)ethyl Picolinate (1e).

To a suspension of LiCl (297 mg, 7.01 mmol) in MeCN (5 mL) were added DBU (0.90 mL, 6.03 mmol) and triethyl phosphonoacetate (1.30 mL, 6.49 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, and **5e** (0.61 mL, 5.00 mmol) was added. The reaction was carried out at rt overnight and quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding ester **6e** (801 mg, 88%), which was a 1:1 mixture of the stereoisomers by ^{1}H NMR spectroscopy: ^{1}H NMR of the major isomer (300 MHz, $CDCl_3$) δ 0.95 and 0.98 (2 d, J = 6.5 and 6.5 Hz, 1:1, total 3 H), 1.02–2.30 (m, 11 H), 3.59–3.72 (m, 1 H), 4.14 (q, J = 7 Hz, 2 H), 5.60 and 5.61 (2 s, 1:1, total 1 H).

To a solution of the above ester (801 mg, 4.39 mmol) in THF (8 mL) was added DIBAL (9.40 mL, 1.03 M in hexane, 9.68 mmol) dropwise at –78 °C. After 1 h at –78 °C, the reaction was quenched by addition of water. The cooling bath was removed, and 1 N HCl was added. The mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated to afford the corresponding alcohol **4e** (571 mg), which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 and 0.94 (2 d, J = 7 and 7 Hz, 1:1, total 3 H), 0.87–2.04 (m, 8 H), 2.12–2.33 (m, 1 H), 2.54 (dm, *J* = 10 Hz, 1H), 4.14 (dm, *J* = 6 Hz, 2 H), 5.36 and 5.39 (2 t, *J* = 6 and 6 Hz, 1:1, total 1 H). The ^{1}H NMR spectrum of **4e** was identical with that reported.[6]

To an ice-cold solution of the above **4e** (571 mg) in CH_2Cl_2 (16 mL) were added picolinic acid (649 mg, 5.27 mmol), DMAP (161 mg, 1.32 mmol), and DCC (1.18 g, 5.72 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **1e** (997 mg, 93% from **6e**): IR (neat) 1740, 1718, 1301, 1289, 1246, 1129 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 and 0.95 (2 d, *J* = 6 and 6 Hz, 1:1, total 3 H), 0.83–2.04 (m, 7 H), 2.14–2.26 (m, 1 H), 2.59–2.72 (m, 1 H), 4.94 (d, *J* = 7 Hz, 2 H), 5.42–5.52 (m, 1 H), 7.46 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.83 (ddd, *J* = 8, 8, 1 Hz, 1 H), 8.14 (d, *J* = 8 Hz, 1 H), 8.76 (d, *J* = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0 (–), 22.1 (–), 26.4 (+), 26.8 (+), 28.3 (+), 33.5 (–), 34.0 (–), 34.7 (+), 36.3 (+), 37.0 (+), 45.0 (+), 61.9 (+), 62.0 (+), 115.0 (–), 124.9 (–), 126.6 (–), 136.8 (–), 146.4 (+), 148.1 (+), 149.6 (–), 165.0 (+).

(*E* and *Z*)-2-[(10*S*,13*S*,17*S*)-17-(*tert*-Butyldimethylsilyloxy)-10,13-dimethylhexahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*,4*H*,10*H*,12*H*,13*H*,14*H*,15*H*,16*H*,17*H*)-ylidene]ethyl Picolinate (22).

To an ice–cold solution of stanolone **(19)** (329 mg, 1.13 mmol) in DMF (4 mL) were added imidazole (369 mg, 5.42 mmol) and TBSCl (508 mg, 3.37 mmol). The mixture was stirred at rt overnight and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **20** (399 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.01 (s, 3 H), 0.00 (s, 3 H), 0.71 (s, 3 H), 0.87 (s, 9 H), 1.01 (s, 3 H), 0.64–1.94 (m, 17 H), 1.97–2.12 (m, 2 H), 2.20–2.46 (m, 3 H), 3.54 (t, *J* = 8 Hz, 1 H). The ^{1}H NMR spectrum of **20** was identical with that reported.[7]

To a suspension of LiCl (53 mg, 1.25 mmol) in MeCN (1 mL) were added DBU (0.160 mL, 1.07 mmol) and triethyl phosphonoacetate (0.23 mL, 1.15 mmol) at 0 °C.

The mixture was stirred at 0 °C for 30 min, and **20** (363 mg, 0.897 mmol) was added. The reaction was carried out at rt overnight and quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **21** (415 mg, 97%), which was a 1:1 mixture of the stereoisomers by ^1H NMR spectroscopy: ^1H NMR (300 MHz, $CDCl_3$) δ –0.012 (s, 3 H), –0.005 (s, 3 H), 0.56–2.40 (m, 21 H), 0.69 (s, 3 H), 0.86 (s, 9 H), 0.91 (s, 3 H), 1.26 (t, J = 7 Hz, 3 H), 3.47 and 3.72 (2 dm, J = 15 and 15 Hz, 1:1, total 1 H), 3.53 (t, J = 8 Hz, 1 H), 4.13 (q, J = 7 Hz, 2 H), 5.64–5.60 (m, 1 H).

To a solution of the above ester (393 mg, 0.828 mmol) in THF (2 mL) was added DIBAL (1.8 mL, 1.03 M in hexane, 1.85 mmol) dropwise at –78 °C. After 1 h at –78 °C, the reaction was quenched by addition of water. The cooling bath was removed, and 1 N HCl was added. The mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated to afford the corresponding alcohol (324 mg), which was used for the next reaction without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.06 (s, 3 H), 0.69 (s, 3 H), 0.87 (s, 12 H), 0.56–2.55 (m, 23 H), 3.53 (t, J = 8 Hz, 1 H), 4.02–4.24 (m, 2 H), 5.26–5.43 (m, 1 H).

To an ice-cold solution of the above alcohol (324 mg) in CH_2Cl_2 (3 mL) were added picolinic acid (122 mg, 0.991 mmol), DMAP (30 mg, 0.246 mmol), and DCC (222 mg, 1.08 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **22** (398 mg, 89% from **21**, 1:1 mixture): $[\alpha]^{23}_{D}$ +15 (*c* 0.72, $CHCl_3$); IR (neat) 1740, 1718, 1302, 1247, 1124, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.04 (s, 3 H), –0.03 (s, 3 H), 0.66 (s, 3 H), 0.84 (s, 9 H), 0.85 (s, 3 H), 0.52–2.36 (m, 21.5 H), 2.60 (d, J = 15 Hz, 0.5 H), 3.49 (t, J = 8 Hz, 1 H), 4.83–4.99 (m, 2 H), 5.16–5.45 (m, 1 H), 7.42 (ddd, J = 8, 5, 1 Hz, 1 H), 7.80 (ddd, J = 8, 8, 2 Hz, 1 H), 8.11 (dm, J = 8 Hz, 1 H), 8.73 (d, J = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.8 (–), –4.5 (–), 11.4 (–), 11.8 (–), 11.9 (–), 18.1 (+), 20.7

(+), 20.8 (+), 23.5 (+), 24.8 (+), 25.9 (–), 28.6 (+), 28.9 (+), 30.9 (+), 31.55 (+), 31.61 (+), 32.5 (+), 35.5 (–), 36.46 (+), 36.49 (+), 37.2 (+), 39.3 (+), 39.4 (+), 39.7 (+), 43.3 (+), 47.4 (–), 48.0 (–), 50.6 (–), 54.5 (–), 54.6 (–), 62.16 (+), 62.20 (+), 81.8 (–), 114.5 (–), 114.7 (–), 125.1 (–), 126.8 (–), 137.0 (–), 146.9 (+), 147.1 (+), 148.3 (+), 149.9 (–), 165.2 (+), 165.3 (+).

Allylation of Picolinates.

(1*s*,4*s*)-4-*tert*-Butyl-1-methyl-1-vinylcyclohexane (2a).

Allylation using ZnI_2.

To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (27.9 mg, 0.136 mmol) and ZnI_2 (43.4 mg, 0.136 mmol) in THF (1 mL) was added MeMgBr (0.29 mL, 1.0 M in THF, 0.27 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –40 °C. A solution of **1a** (26.0 mg, 0.0905 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to –10 °C over 1 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **2a** (13.9 mg, 85%): IR (neat) 3081, 1364, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77–1.03 (m, 3 H), 0.83 (s, 9 H), 0.94 (s, 3 H), 1.06–1.30 (m, 4 H), 1.46–1.59 (s, 2 H), 1.67–1.78 (m, 2 H), 4.96 (dm, *J* = 18 Hz, 1 H), 5.02 (dm, *J* = 11 Hz, 1 H), 5.76 (dd, *J* = 18, 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (–), 27.7 (+), 31.5 (+), 32.5 (–), 36.6 (–), 38.5 (–), 48.3 (+), 112.0 (–), 146.3 (+). Relative structure was determined as above by comparison of the ^{13}C NMR data reported.[4]

Allylation using $ZnBr_2$.

To an ice-cold solution of $ZnBr_2$ (308 mg, 1.37 mmol) in THF (7 mL) was added MeMgBr (1.05 mL, 1.0 M in THF, 1.05 mmol) slowly. After 30 min at 0 °C,

$CuBr·Me_2S$ (107 mg, 0.520 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1a** (100 mg, 0.348 mmol) in THF (2 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **2a** (55 mg, 88%).

(1*s*,4*s*)-4-*tert*-Butyl-1-ethyl-1-vinylcyclohexane (7).

Allylation using ZnI_2.

To an ice-cold suspension of $CuBr·Me_2S$ (39.5 mg, 0.192 mmol) and ZnI_2 (61.3 mg, 0.192 mmol) in THF (1.5 mL) was added EtMgBr (0.38 mL, 1.0 M in THF, 0.38 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –40 °C. A solution of **1a** (36.8 mg, 0.128 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 1 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **7** (21.5 mg, 86%): IR (neat) 3079, 1365, 1000, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73–1.17 (m, 5 H), 0.76 (t, J = 8 Hz, 3 H), 0.81 (s, 9 H),1.22 (q, J = 8 Hz, 2 H), 1.36–1.58 (m, 2 H), 1.73–1.81 (m, 2 H), 4.91 (dd, J = 18, 2 Hz, 1 H), 5.14 (dd, J = 11, 2 Hz, 1 H), 5.50 (dd, J = 18, 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9 (–), 23.4 (+), 27.7 (–), 32.5 (+), 36.1 (+), 36.9 (+), 40.0 (+), 48.8 (–), 114.0 (+), 144.9 (–).

Allylation using $ZnBr_2$.

To an ice-cold solution of $ZnBr_2$ (160 mg, 0.710 mmol) in THF (5 mL) was added EtMgBr (0.57 mL, 0.95 M in THF, 0.542 mmol) slowly. After 30 min at 0 °C,

$CuBr\cdot Me_2S$ (19.9 mg, 0.0968 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1a** (51.0 mg, 0.177 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **7** (27.8 mg, 81%).

(1*s*,4*s*)-4-*tert*-Butyl-1-isopropyl-1-vinylcyclohexane (8).

To an ice-cold solution of $ZnBr_2$ (315 mg, 1.40 mmol) in THF (7 mL) was added *i*-PrMgBr (1.2 mL, 0.90 M in THF, 1.08 mmol) slowly. After 30 min at 0 °C, $CuBr\cdot Me_2S$ (110 mg, 0.535 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1a** (100 mg, 0.348 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **8** (58 mg, 80%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 7 Hz, 6 H), 0.79 (s, 9 H), 0.69–0.94 (m, 2 H), 1.00–1.20 (m, 3 H), 1.24–1.40 (m, 1 H), 1.44–1.60 (m, 2 H), 1.79–1.94 (m, 2 H), 4.90 (dm, J = 18 Hz, 1 H), 5.20 (dm, J = 11 Hz, 1 H), 5.46 (dd, J = 18, 11 Hz, 1 H).

(1*s*,4*s*)-1-Ethyl-4-phenyl-1-vinylcyclohexane (9).

To an ice-cold solution of $ZnBr_2$ (243 mg, 1.08 mmol) in THF (5 mL) was added EtMgBr (0.95 mL, 0.85 M in THF, 0.81 mmol) slowly. After 30 min at 0 °C, $CuBr\cdot Me_2S$ (83.3 mg, 0.405 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 15 min and cooled to –40 °C. A solution of **1b** (80 mg, 0.274 mmol) in THF (2 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **9** (47.5 mg, 81%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 7 Hz, 3 H), 1.25–1.42 (m, 4 H), 1.56–1.76 (m, 4 H), 1.82–1.93 (m, 2 H), 2.40–2.54 (m, 1 H), 5.01 (dd, J = 18, 2 Hz, 1 H), 5.23 (dd, J = 11, 2 Hz, 1 H), 5.59 (dd, J = 18, 11 Hz, 1 H), 7.12–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 30.3, 35.8, 36.9, 39.8, 45.0, 114.5, 125.9, 126.9, 128.3, 144.6, 147.9.

(1*s*,4*s*)-4-*tert*-Butyl-1-ethyl-1-vinylcyclohexane (10).

To an ice-cold solution of $ZnBr_2$ (216 mg, 0.710 mmol) in THF (5 mL) was added *i*-PrMgBr (0.80 mL, 0.90 M in THF, 0.72 mmol) slowly. After 30 min at 0 °C, CuBr·Me_2S (74 mg, 0.36 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1b** (71.0 mg, 0.239 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **10** (45.5 mg, 83%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 7 Hz, 3 H), 1.28–1.47 (m, 3 H), 1.52–1.74 (m, 3 H), 1.96 (dm, J = 14 Hz, 2 H), 2.43 (tt, J = 16, 4 Hz, 1 H), 4.98 (dd, J = 18, 2 Hz, 1 H), 5.28 (dd, J = 11, 2 Hz, 1 H), 5.55 (dd, J = 18, 11 Hz, 1 H), 7.12–7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 30.4, 33.9, 39.1, 42.3, 44.8, 115.8, 125.9, 126.9, 128.3, 142.4, 147.9.

(1*s*,4*s*)-1-Ethyl-4-methyl-1-vinylcyclohexane (11).

Allylation with EtCu·$MgBr_2$.

To an ice-cold solution of $ZnBr_2$ (330 mg, 1.47 mmol) in THF (6 mL) was added

EtMgBr (1.40 mL, 0.80 M in THF, 1.12 mmol) slowly. After 45 min at 0 °C, CuBr·Me_2S (258 mg, 1.25 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1c** (90 mg, 0.367 mmol) in THF (1.5 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **11** (42.5 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, J = 8 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H), 0.80–1.39 (m, 7 H), 1.40–1.49 (m, 2 H), 1.66–1.77 (m, 2 H), 4.92 (dd, J = 18, 2 Hz, 1 H), 5.13 (dd, J = 11, 2 Hz, 1 H), 5.50 (dd, J = 18, 11 Hz, 1 H).

Allylation with $Et_2CuMgBr·MgBr_2$.

To an ice-cold solution of $ZnBr_2$ (330 mg, 1.47 mmol) in THF (6 mL) was added EtMgBr (1.40 mL, 0.80 M in THF, 1.12 mmol) slowly. After 40 min at 0 °C, CuBr·Me_2S (125 mg, 0.608 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1c** (90 mg, 0.367 mmol) in THF (1.5 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **11** (39 mg, 70%).

(1*s*,4*s*)-1-Isopropyl-4-methyl-1-vinylcyclohexane (12).

To an ice-cold solution of $ZnBr_2$ (275 mg, 1.22 mmol) in THF (6 mL) was added *i*-PrMgBr (1.13 mL, 0.81 M in THF, 0.904 mmol) slowly. After 30 min at 0 °C, CuBr·Me_2S (94 mg, 0.457 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1c** (75 mg, 0.306 mmol) in THF (1.5 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2.5 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **12** (40 mg, 79%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.78–1.62 (m, 7 H), 0.79 (d, *J* = 7 Hz, 6 H), 0.83 (d, *J* = 6 Hz, 3 H), 1.68–1.90 (m, 3 H), 4.90 (dd, *J* = 18, 2 Hz, 1 H), 5.20 (dd, *J* = 11, 2 Hz, 1 H), 5.47 (dd, *J* = 18, 11 Hz, 1 H).

(1*S,2*S**)-1,2-Dimethyl-1-vinylcyclohexane (13).**

To an ice-cold suspension of $CuBr·Me_2S$ (95 mg, 0.462 mmol) in THF (6 mL) was added MeMgBr (0.93 mL, 1.0 M in THF, 0.93 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –30 °C. A solution of **1d** (75 mg, 0.306 mmol) in THF (2 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **13** (26 mg, 61%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, *J* = 7 Hz, 3 H), 0.98 (s, 3 H), 0.70–2.15 (m, 9 H), 4.96 (dd, *J* = 18, 2 Hz, 1 H), 5.04 (dd, *J* = 11, 2 Hz, 1 H), 6.08 (dd, *J* = 18, 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 22.5, 26.6, 27.0, 31.1, 39.5, 39.8, 41.3, 112.8, 142.7.

(1*S,2*S**)-1-Butyl-2-methyl-1-vinylcyclohexane (14).**

To an ice-cold suspension of $CuBr·Me_2S$ (52 mg, 0.253 mmol) in THF (5 mL) was added *n*-BuMgBr (0.63 mL, 0.81 M in THF, 0.51 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –40 °C. A solution of **1d** (62.0 mg, 0.253 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **14** (31.5 mg, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–1.80 (m, 20 H), 1.92–2.05 (m, 3 H), 4.90 (dd, *J* = 18, 2 Hz, 1 H), 5.09 (dd, *J* = 11, 2 Hz, 1 H), 5.82 (dd, *J* = 18, 11 Hz, 1 H).

(1*R**,2*S**)-1-Isopropyl-2-methyl-1-vinylcyclohexane (15).

To an ice-cold solution of $ZnBr_2$ (220 mg, 0.977 mmol) in THF (6 mL) was added *i*-PrMgBr (0.80 mL, 0.90 M in THF, 0.72 mmol) slowly. After 30 min at 0 °C, $CuBr{\cdot}Me_2S$ (75 mg, 0.365 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1d** (60.0 mg, 0.245 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **15** (28 mg, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, *J* = 7 Hz, 3 H), 0.83 (d, *J* = 7 Hz, 3 H), 0.84 (d, *J* = 7 Hz, 3 H), 0.7–1.7 (m, 9 H), 1.76–1.92 (m, 1 H), 4.89 (dm, *J* = 18 Hz, 1 H), 5.19 (d, *J* = 11 Hz, 1 H), 5.66 (dd, *J* = 18, 11 Hz, 1 H).

(1*R**,2*S**)-1,2-Dimethylcyclohexanecarboxylic Acid (16).

To an ice-cold solution of **13** (25 mg, 0.181 mmol) in H_2O-CCl_4-MeCN (3 : 1 : 1, 1.8 mL) were added $NaIO_4$ (162 mg, 0.76 mmol) and $RuCl_3{\cdot}H_2O$ (1 mg, 0.005 mmol). After 5 h at 0 ^{0}C, the mixture was diluted with Et_2O and aqueous Na_2SO_3. The layers were separated and the aqueous layer was extracted with Et_2O twice. The combined extracts were dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **16** (21 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 084–1.74 (m, 8 H), 1.06 (d, *J* = 7 Hz, 3 H), 1.29 (s, 3 H), 1.96–2.06 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 22.8, 24.5, 25.2, 30.2, 35.2, 39.6, 45.7, 183.3.

The ^{13}C NMR spectrum of **16** was identical with that reported[5], and relative structure of **13** was determined as the above.

(1*S**,3*R**)-1-Ethyl-3-methyl-1-vinylcyclohexane (17).

Allylation using ZnI_2.

To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (46.3 mg, 0.225 mmol) and ZnI_2 (71.8 mg, 0.225 mmol) in THF (2 mL) was added EtMgBr (0.45 mL, 1.0 M in THF, 0.45 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –40 °C. A solution of **1e** (36.7 mg, 0.150 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 1 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **17** (14.2 mg, 62%): IR (neat) 3079, 1458, 1001, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68–0.94 (m, 3 H), 0.75 (t, *J* = 7 Hz, 3 H), 0.83 (d, *J* = 6 Hz, 3 H), 1.02 (dt, *J* = 5, 13 Hz, 1 H), 1.22 (q, *J* = 7 Hz, 2 H), 1.18–1.75 (m, 5 H), 4.88 (dd, *J* = 18, 2 Hz, 1 H), 5.11 (ddd, *J* = 11, 2, 1 Hz, 1 H), 5.52 (dd, *J* = 18, 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7 (–), 22.6 (+), 23.2 (–), 28.4 (–), 35.1 (+), 35.6 (+), 37.1 (+), 40.9 (+), 44.8 (+), 113.7 (+), 145.2 (–).

Allylation using $ZnBr_2$.

To an ice-cold solution of $ZnBr_2$ (200 mg, 0.888 mmol) in THF (7 mL) was added EtMgBr (0.91 mL, 0.81 M in THF, 0.737 mmol) slowly. After 30 min at 0 °C, $CuBr{\cdot}Me_2S$ (70 mg, 0.341 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for 20 min and cooled to –40 °C. A solution of **1e** (60.0 mg, 0.245 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **17** (31 mg, 84%).

(3*R*,10*S*,13*S*,17*S*)-17-(*tert*-Butyldimethylsilyloxy)-3-ethyl-10,13-dimethyl-3-vinylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene (23).

To an ice-cold suspension of $CuBr\cdot Me_2S$ (23.3 mg, 0.113 mmol) and ZnI_2 (36.4 mg, 0.114 mmol) in THF (1 mL) was added EtMgBr (0.23 mL, 1.0 M in THF, 0.230 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min and cooled to –40 °C. A solution of **22** (40.7 mg, 0.0757 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 1 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **23** (29.3 mg, 87%): $[\alpha]^{23}_{D}$ +23 (*c* 0.53, $CHCl_3$); IR (neat) 3078, 1472, 1255, 1119, 1094, 1081, 909, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.011 (s, 3 H), –0.004 (s, 3 H), 0.67 (s, 3 H), 0.745 (t, *J* = 8 Hz, 3 H), 0.754 (s, 3 H), 0.87 (s, 9 H), 1.20 (q, *J* = 8 Hz, 2 H), 0.54–1.91 (m, 22 H), 3.51 (t, *J* = 8 Hz, 1 H), 4.91 (dd, *J* = 18, 1 Hz, 1 H), 5.12 (dd, *J* = 11, 1 Hz, 1 H), 5.51 (dd, *J* = 18, 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7 (–), –4.4 (–), 7.8 (–), 11.5 (–), 12.1 (–), 18.2 (+), 20.7 (+), 23.6 (+), 26.0 (–), 28.9 (+), 30.4 (+), 31.0 (+), 31.7 (+), 34.9 (+), 35.7 (–), 36.4 (+), 36.9 (+), 37.3 (+), 39.0 (+), 40.6 (+), 42.1 (–), 43.4 (+), 50.8 (–), 54.9 (–), 82.0 (–), 113.5 (+), 145.6 (–).

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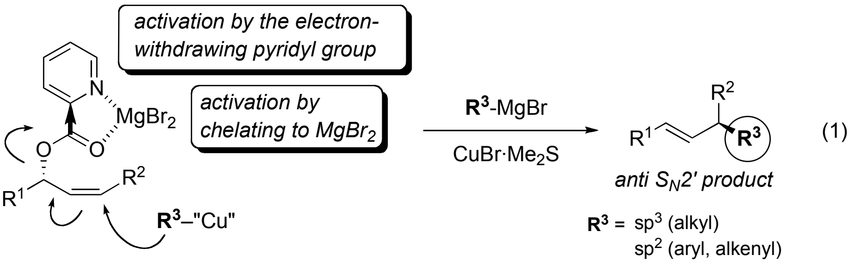
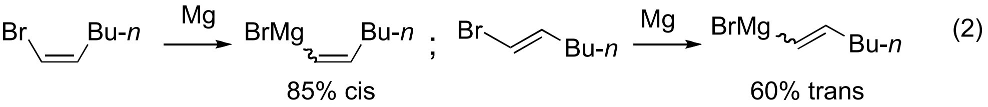
第５章「有機リチウム試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」

５−１．緒言

第２、第３章において、筆者はアリル化反応の脱離能に富むピコリン酸基を見出し、グリニャール試薬から調製したアリール又はアルケニル銅試薬を用いてアンチ S_N2' 生成物を得る事に成功した (eq 1)。

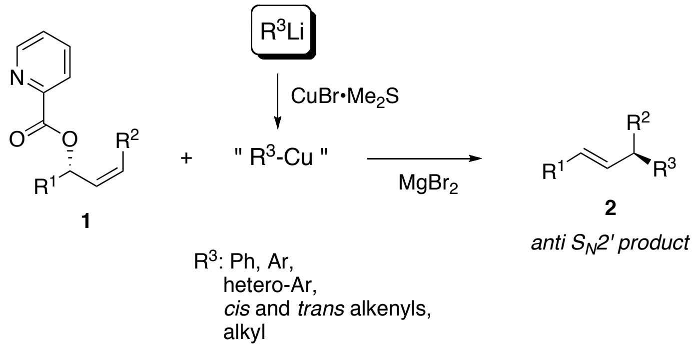


しかし、グリニャール試薬は調製しづらいものがある。例えば、アルケニルグリニャール試薬をアルケニルハライドと金属マグネシウムから調製すると、シス二重結合の異性化が起こることが知られている (eq 2)[1]。



そこで筆者は、有機銅の試薬源として有機リチウム (RLi) に注目した。有機リチウム試薬は、ハロゲン−リチウム交換、オルトリチエーションや水素−リチウム交換等、様々な方法で調製できるため、導入できる炭素団を拡張できると予想した。また一方、アルケニルハライドとのハロゲン−リチウム交換を用いれば二重結合の異性化の問題は解決できると考えた。本章では、こうした考えに沿って行った研究成果について述べる (Scheme 1)。

Scheme 1. Allylic substitution of picolinates.[a]



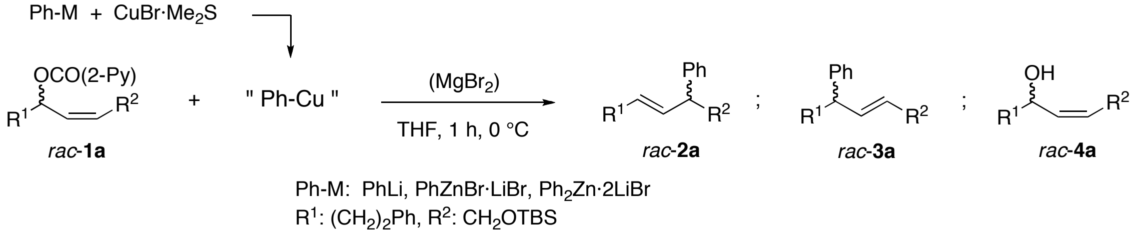
[a] Although the (*S*) chirality is drawn for **1**, (*R*) isomer is used in some cases.

５－２．ラセミ体を用いた条件検討

無機塩を含まない PhLi （基質に対し 2 当量）を異なる量の $CuBr{\cdot}Me_2S$（2, 1, 0.5 当量）に加え、氷冷下 20~30 分間撹拌し、3 種のフェニル銅試薬を調製した。これらの試薬は PhCu, Ph_2CuLi, Ph_2CuLi + 2PhLi の分子式で表され、この章では Ph/Cu (2/2), (2/1), (2/0.5) 試薬と定義する。これらのフェニル銅試薬を THF 中で、氷冷下 1 時間、ラセミ体の基質 *rac*-**1a** と反応させた (Table 1)。

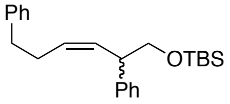
PhMgBr と $CuBr{\cdot}Me_2S$ から調製した銅試薬の結果と対照的に、PhLi 由来の銅試薬では、カルボニル炭素で反応したと考えられる副生物、アルコール体 *rac*-**4a** をかなりの割合で生じた (entries 1, 3, 7)。しかし、3 当量の $MgBr_2$ を添加すると、アリル化反応は加速され、1 時間以内に終了し、高収率かつほぼ完全な位置選択性で *rac*-**2a** を与えた (entries 2, 5, 8)。この生成物のオレフィンはトランスであった ($J_{CH=CH}$ = 15 Hz)。この他、位置異性体 *rac*-**3a** およびシス異性体 **5** と **6** が生成可能であったが、これらの異性体は検出されなかった（シス異性体の合成は第 2 章参照）。次に、反応温度をより低く (–60 ~ –50 °C) して反応を行った。しかし、反応速度は低下しなかった (footnote f in entries 2, 5, 8)。このような低温でも反応が進行する事は、0 °C で不安定な銅試薬を用いる時や、反応の選択性を向上させたい時に有用と考えられる (cf. Table 3, entries 4, 10)。なお、反応を銅塩無しで、PhLi (2 当量) と $MgBr_2$ (3 当量) で行うと、*rac*-**4a** と **-1a** の混合物を 21 : 79 の比で生成した。つまり、この反応において銅塩の存在が必須である。

Table 1. Preliminary study using *rac*-1a.[a]

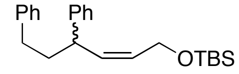


entry	Ph-M[b] (equiv)	CuBr·Me$_2$S, equiv	MgBr$_2$, equiv	ratio[c] of *rac*-**2a** : -**3a** : -**4a**: -**1a**	yield,[d,e] %
1	PhLi (2)	2	0	9 : 0 : 69 : 22	nd
2[f]	PhLi (2)	2	3	100 : 0 : 0 : 0	97
3	PhLi (2)	1	0	11 : 0 : 47 : 42	nd
4	PhLi (2)	1	2	84 : 0 : 15 : 1	nd
5[f]	PhLi (2)	1	3	100 : 0 : 0 : 0	94
6	PhLi (2)	1	4	98 : 0 : 2 : 0	92
7	PhLi (2)	0.5	0	48 : 0 : 44 : 8	nd
8[f]	PhLi (2)	0.5	3	98 : 2 : 0 : 0	95
9	PhZnBr·LiBr[g] (2)	0.5	0	17 : 0 : 47 : 36	nd
10	PhZnBr·LiBr[g] (2)	0.5	3	94 : 0 : 6 : 0	nd
11	Ph$_2$Zn·2LiBr[h] (3)	1.5	0	31 : 0 : 46 : 23	nd
12	Ph$_2$Zn·2LiBr[h] (3)	1.5	6	100 : 0 : 0 : 0	89

[a] Reactions were carried out at 0 °C unless otherwise noted. [b] Salt free PhLi was used. [c] Determined by ^{1}H NMR spectroscopy of the crude products. [d] Isolated combined yields of *rac*-**2a** and -**3a**. [e] nd: not determined. [f] Reaction at –60 ~ –50 °C afforded essentially the same result. [g] Prepared from PhLi (2 equiv per *rac*-**1a**) and ZnBr$_2$ (3 equiv). [h] Prepared from PhLi (6 equiv per *rac*-**1a**) and ZnBr$_2$ (3 equiv).



5 (*cis* isomer of *rac*-**2a**)

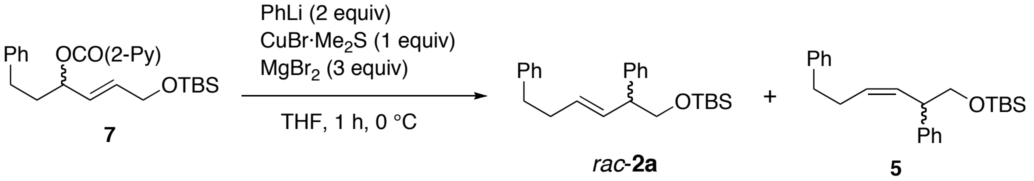


6 (*cis* isomer of *rac*-**3a**)

以上の実験では MgBr$_2$ を 3 当量用いたが、最適量を求めるため、2 または 4 当量の MgBr$_2$ を Ph/Cu (2/1) に添加した。まず、MgBr$_2$ を 2 当量加えた場合、*rac*-**2a** の生成比はかなり改善されたが、まだアルコール *rac*-**4a** の副生が見られた (entry 4)。一方、4 当量では *rac*-**2a** がほぼ完全な選択性で得られた (entry 6)。つまり、高い反応性と位置選択性を得るためには、Li$^+$ の当量より多く MgBr$_2$ を添加する事が必要である。著者は MgBr$_2$ > Li$^+$ の関係を *Requirement 1* と呼び、以下のアリル化反応にこの *Requirement 1* を適用することにした。

次に、上記の条件下でトランス体のピコリン酸アリル **7** を反応させた (Scheme 2)。反応は 0 °C で 1 時間以内に終了し、位置選択性は優れていたが (>95%)、S_N2' 生成物は *rac*-**2a** とシス異性体 **5** の 86 : 14 の比の混合物であった。よって、高い選択性のためにシス体である事が重要である。

Scheme 2. Substitution of *trans* picolinate 7.



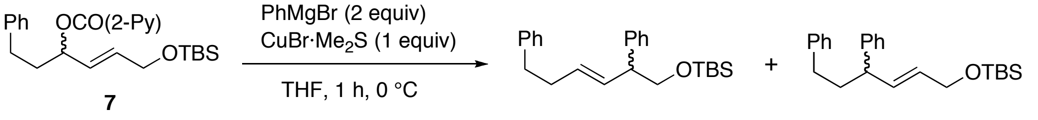
7

rac-**2a**

5

(86 : 14)

興味深い事に、この選択性は PhMgBr ベースの銅試薬 PhMgBr/CuBr·Me_2S (2/1) を用いた場合の傾向 (rac-**2a** と -**3a** を 60 : 40) と異なっていた (eq 3)。



(3)

7

rac-**2a**

rac-**3a**

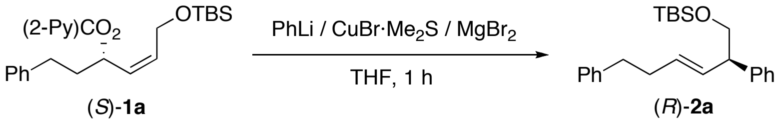
(60 : 40)

次に、亜鉛試薬 (PhZnBr, Ph_2Zn) から調製した Ph/Cu について調べた。亜鉛試薬は PhLi と $ZnBr_2$ から調製した。まず、PhZnBr (2 当量) と CuBr·Me_2S (0.5 当量) を氷冷下 30 分間撹拌し Ph/Cu (2/0.5) を調製した。次に、$MgBr_2$ (3 当量) の存在下または非存在下、*rac*-**1a** と 0 °C で 1 時間反応させた。この場合も、$MgBr_2$ を加えた系で反応の加速化と効率化が観測された (entry 10 vs entry 9)。同様な結果は、Ph_2Zn から調製した銅試薬でも得られた (entry 12 vs entry 11)。これらの結果は、亜鉛試薬が簡単に調製できたり市販品である場合に有用である事を示している[2]。

５−３．光学活性体を用いた検討

Entries 2, 5, 8 で示した３種類の銅試薬系を光学活性な基質 (*S*)-**1a** (95– 98% ee) に適用した (Table 2)。(*S*)-**1a** の合成は Scheme 4 で後述する。

Table 2. Allylic substitution of (*S*)-1a[a] with Ph copper reagents derived from PhLi.



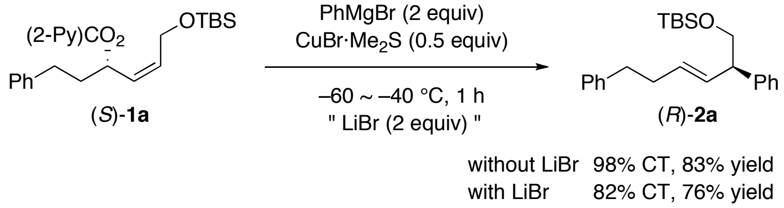
entry	source of PhLi (equiv)	CuBr·Me$_2$S, equiv	MgBr$_2$, equiv	temp, °C	(*R*)-**2a**[b]	
					CT,[c,d] %	yield, %
1	salt free PhLi[e] (2)	2	3	0	98	97
2	salt free PhLi[e] (2)	2	3	–60 ~ –50	98	92
3	salt free PhLi[e] (2)	1	3	0	98	92
4	salt free PhLi[e] (2)	1	3	–60 ~ –50	98	92
5	salt free PhLi[e] (2)	0.5	3	0	71	92
6	salt free PhLi[e] (2)	0.5	3	–60 ~ –50	84	90
7	PhBr (2) + *n*-BuLi (2)	1	3	0	–	0[f]
8	PhBr (2) + *t*-BuLi (4)	1	5	0	98	93
9	PhI (2) + *n*-BuLi (2)	1	3	0	–	0[f]
10	PhI (2) + *t*-BuLi (4)	1	5	0	98	90

[a] 95–98% ee. [b] The absolute configuration was determined by chiral HPLC analysis. [c] Chirality transfer (CT) defined by (% ee of (*R*)-**2a**/% ee of (*S*)-**1a**) x 100. [d] Determined by chiral HPLC analysis. [e] Obtained from a company. [f] Unidentified compounds were produced.

Table 2 の entries 1–6 に示す様に、３種類の銅試薬は全て (*R*)-**2a** を与えた。その絶対構造は既知の標品とキラル HPLC の保持時間を比較して決定した。この結果から反応はアンチ S_N2' 的に進行している事が判明した。さらに、反応の不斉転写率を求めてみたところ、優れた不斉転写が Ph/Cu (2/2) 及び Ph/Cu (2/1) で達成され、反応温度に依存しないことがわかった (entries 1–4)。ところが、Ph/Cu (2/0.5) の場合、いくぶん低い不斉転写率が観測され (entry 5)、反応温度を低くしても改善されなかった (entry 6)。この結果は PhMgBr ベースの銅試薬 PhMgBr/CuBr·Me$_2$S (2/0.5) が低温にすると不斉転写率をほぼ完全に改善できた事と異なっている (第２章参照)。以上の結果から、2 当量の RLi と 1~2 当量の CuBr·Me$_2$S が高い不斉転写率を得る為に必要な条件であり、著者はこの条件を *Requirement 2* と呼ぶ事にした。見方を変えると、この反応では、銅試薬調製の為の CuBr·Me$_2$S の正確な秤量は必要でなく、また、厳密な反応温度の制御も必要でないという操作上の長所を示している。

Entries 5 と 6 で観察された低い不斉転写率の原因を探るために、PhMgBr ベースの銅試薬 PhMgBr/CuBr·Me$_2$S (2/0.5) に 2 当量の LiBr を加えてみた。すると、LiBr を添加しない時の不斉転写率 (98%) から 82% まで低下した (Scheme 3)。ゆえに、PhLi と CuBr·Me$_2$S から Ph/Cu を調製するとき共に生成する LiBr の影響で低い不斉転写率を示したといえる (Table 2, entries 5, 6)。著者は、Ph/Cu (2/0.5) の反応系中に LiBr が存在すると、低温でもシン S$_N$2' 経路を抑える事ができず、不斉転写率が向上しなかったと考えている（第２章 Scheme 9 参照）。

Scheme 3. Influence of LiBr on CT.



次に、様々なハライドベンゼンを反応に適用する事を視野に入れ、ハロゲン–リチウム交換により系中で調製させた PhLi を用いた反応を調べた。最初に、*t*-BuLi (4 当量) を、Et$_2$O 中 0 °C で PhBr (2 当量) に加えた。30分後、LiBr, Me$_2$C=CH$_2$ と *t*-BuH （それぞれ 2 当量）と共に生成した PhLi (2 当量) を、CuBr·Me$_2$S (1 当量) に反応させて Ph/Cu (2/1) に変換した。そして、*Requirement 1* (MgBr$_2$ > Li$^+$) に従い、MgBr$_2$ を 5 当量添加した条件下で (*S*)-**1a** と置換反応を行うと、優れた生成物選択性と反応性で (*R*)-**2a** を与えた (entry 8)。Ph/Cu を *t*-BuLi と PhI から調製した場合も同様な結果を与えた (entry 10)。対照的に、ハロゲン–リチウム交換に *n*-BuLi (2 当量) と PhX (X = Br, I) を用いた場合、(*R*)-**2a** は得られなかった (entries 7, 9)。その原因は、ハロゲン–リチウム交換の際に副生する *n*-BuX の影響であると考えている (eq 4, X = Br, I)。

$$\underset{(2\ \text{equiv})}{\text{Ph–X}} \xrightarrow[\text{Et}_2\text{O, 0 °C}]{t\text{-BuLi (4 equiv)}} \underset{(2\ \text{equiv})}{\text{Ph–Li}} + \underset{(2\ \text{equiv})}{\text{Li–X}} + \underset{(2\ \text{equiv})}{\text{Me}_2\text{C=CH}_2} + \underset{(2\ \text{equiv})}{t\text{-BuH}}$$

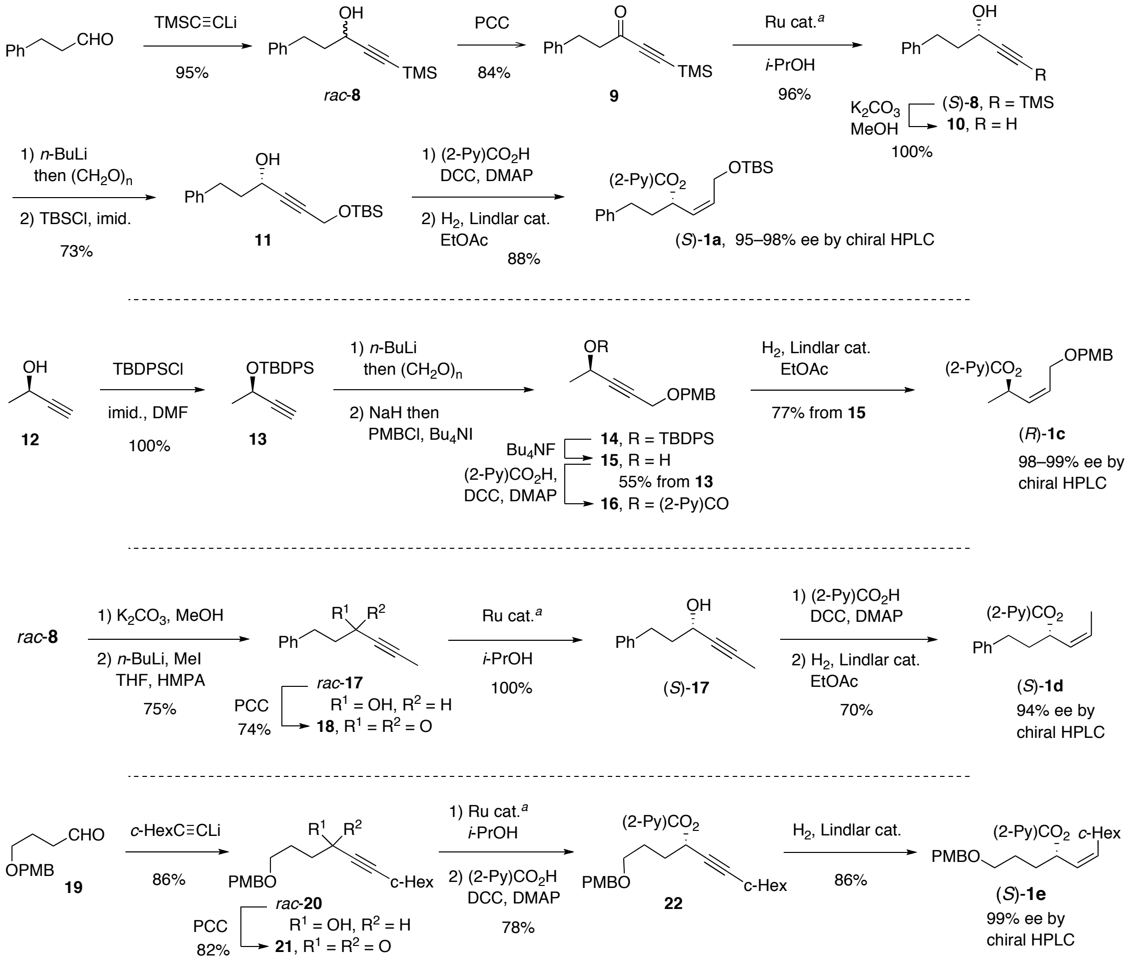
$$\underset{(2\ \text{equiv})}{\text{Ph–X}} \xrightarrow[\text{THF, 0 °C}]{n\text{-BuLi (2 equiv)}} \underset{(2\ \text{equiv})}{\text{Ph–Li}} + \underset{(2\ \text{equiv})}{n\text{-Bu–X}} \quad (4)$$

５−４．適応範囲の検討

5-4-1. 基質合成

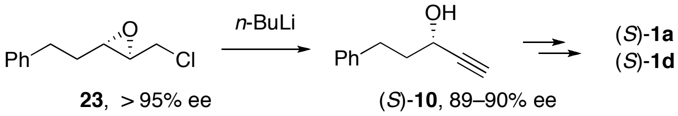
(*S*)-**1a** と Ph/Cu (2/1), Ph/Cu (2/2) で確立したアリル化反応の条件を、異なる置換基を持つ幾つかのピコリン酸アリルに適用した。後述の Table 3 に結果をまとめた。使用したピコリン酸アリルの合成のうち、(*S*)-**1a**, (*R*)-**1c**, (*S*)-**1d**,**e** は Scheme 4 に示す方法で合成した。第２章では、(*S*)-**1a**, -**1d** を Yadav[3] のプロトコルを利用し、89-90% ee のプロパルギルアルコール (*S*)-**10** を経て合成していた (Scheme 5)。今回の研究では、野依らが開発した Ru[(*S*,*S*)-TsDPEN](*p*-cymene) 触媒による不斉水素移動反応[4]を用いて、より高い光学純度の (*S*)-**1a**, -**1d**, -**1e** を合成した (94–99% ee)。

Scheme 4. Synthesis of optically active picolinates.



[a] Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene)

Scheme 5. Previous synthesis of (*S*)-1a and -1d in Chapter 2.



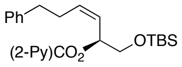
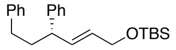
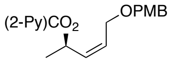
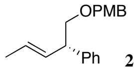
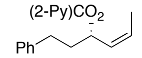
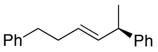
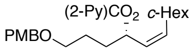
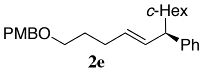
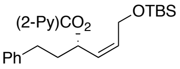
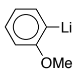
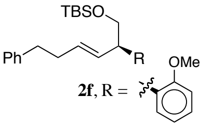
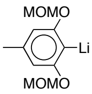
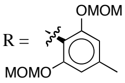
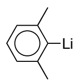
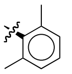
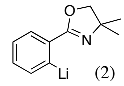
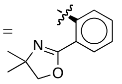
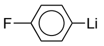
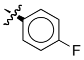
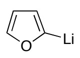
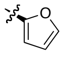
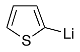
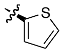
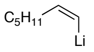
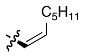
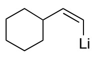
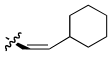
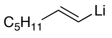
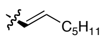
5-4-2. 基質の適応範囲の検討

まず、高選択的にアンチ S_N2' 生成物を得るために、*Requirement 1* ($MgBr_2$ > Li^+) と *Requirement 2* (Ph/Cu = 2:1–2) に従い、3 当量の $MgBr_2$ 存在下 Ph/Cu (2/1) を氷冷下 1 時間反応させた (Table 3, entries 1–5)。(*S*)-**1a** と反対の置換基配列を持つ (*S*)-**1b** の反応は、(*R*)-**2a** と同様、優れた効率で **2b**（すなわち **2a** の位置異性体）を生成した (Table 3, entry 1; cf. Table 2, entry 3)。この結果は、メチレン置換基の大きさ及び、酸素原子を含有する置換基が反応の効率に影響を及ぼさないことを示唆している。ピコリン酸アリル (*R*)-**1c** と (*S*)-**1d** も高選択的に **2c** と **2d** を生成した (entries 3, 4)。これらの結果も上述した一般性を支持する更なる例である。異なる銅試薬 Ph/Cu (2/2) を用いた (*R*)-**1c** との反応も同程度の効率であった (entry 2)。さらに、オレフィン炭素に嵩高いシクロヘキシル基が付いていても反応の効率には影響を及ぼさなかった (entry 5)。

5-4-3. 置換基を持つアリール基の導入

次に、(*S*)-**1a** に対して様々なアリール基を導入した。まず、立体的に反応性が低下している嵩高いアリール銅試薬を幾つか反応させた (entries 6–9)。最初に、*n*-BuLi を用いてアニソールのオルトリチエーション [5] を行い調製したリチウム試薬を、*Requirement 2* を参考に *o*-MeOPh/Cu (2/1) に変換した。この銅試薬を (*S*)-**1a** に反応させると、フェニル基の場合と同レベルの高い不斉転写率、および収率 85% で **2f** を生成した (entry 6)。

Table 3. Allylic substitution of optically active picolinates with copper reagents.[a]

entry	allylic picolinate (% ee)	RLi (equiv)	method giving RLi	CuBr·Me$_2$S, equiv	MgBr$_2$, equiv	anti S$_N$2' product[b,c]		
						structure	CT, %	yield, %
1	 (*S*)-**1b** (99% ee)	PhLi (2)	—	1	3	 **2b**	99	87
2	 (*R*)-**1c** (99% ee)	PhLi (2)	—	2	3	 **2c**	98	87
3	(*R*)-**1c** (99% ee)	PhLi (2)	—	1	3	**2c**	98	84
4	 (*S*)-**1d** (94% ee)	PhLi (2)	—	1	3	 **2d**	94 (97	82 92)[d]
5	 (*S*)-**1e** (99% ee)	PhLi (2)	—	1	3	 **2e**	98	94
6	 (*S*)-**1a** (95% ee)	 (2)	ortho lithiation using *n*-BuLi	1	3	 **2f**, R =	99	85
7	(*S*)-**1a** (98% ee)	 (2)	ortho lithiation using *n*-BuLi	1	3	**2g**, R = 	> 99	97
8	(*S*)-**1a** (97% ee)	 (2)	Li-Br exchange[e]	1	5	**2h**, R = 	97	88
9	(*S*)-**1a** (97% ee)	 (2)	ortho lithiation using *n*-BuLi	1	3	**2i**, R = 	> 99	98
10	(*S*)-**1a** (98% ee)	 (2)	Li-Br exchange[e]	1	5	**2j**, R = 	95 (97	92 92)[d]
11	(*S*)-**1a** (95% ee)	 (2)	direct lithiation using *n*-BuLi	1	3	**2k**, R = 	99	86
12	(*S*)-**1a** (97% ee)	 (2)	direct lithiation using *n*-BuLi	1	3	**2l**, R = 	99	83
13	(*S*)-**1a** (98% ee)	 (3)	Li-I exchange[e]	1.5	7	**2m**, R = 	98	75
14	(*S*)-**1a** (95% ee)	 (3)	Li-I exchange[e]	1.5	7	**2n**, R = 	99	82
15	(*S*)-**1a** (95% ee)	 (2)	Li-I exchange[e]	1	5	**2o**, R = 	98	93

[a] Reactions were carried out at 0 °C for 1 h unless otherwise noted. [b] Regioselectivities for all of the reactions were > 97% by ^{1}H NMR spectroscopy. [c] The absolute configuration of **2b** was confirmed by converting to known compound. Those of other products were determined by analogy of **2a**, **2b**, and **2d**. [d] At –60 °C (entry 4); –20 °C (entry 10). [e] Corresponding halide (3 or 2 equiv) and *t*-BuLi (6 or 4 equiv).

1,3-$(MOMO)_2$-5-MeC_6H_3 のオルトリチエーションにより調製した、さらに嵩高いアリール銅試薬も (*S*)-**1a** と反応し、不斉転写を損なうことなく **2g** を得た (entry 7)。次に、1-Br-2,6-$Me_2C_6H_3$ の Li–Br 交換を利用して調製した 2,6-$Me_2C_6H_3$/Cu (2/1) を、*Requirement 1* に従い 5 当量の $MgBr_2$ 存在下で (*S*)-**1a** と反応させると、収率 88%, 97% CT で **2h** を与えた (entry 8)。オルト位にカルボキシル基等価体を持つ嵩高いアリール銅試薬も、非常に効率的に生成物 **2i** を与えた (entry 9)。これらの例はこの反応系の長所を示すのに十分であるといえよう。

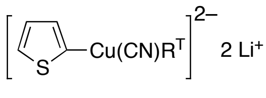
電子吸引基であるフッ素原子を持つ *p*-F-C_6H_4/Cu (2/1) は、収率 92%, 95% CT で生成物 **2j** を与えた (entry 10)。氷冷下の反応では不斉転写率は若干低かったが、–20 °C で反応を行うことで容易に改善できた (entry 10, in a parenthesis)。

以上、様々な方法で調製したアリールリチウム試薬がアリル化反応に適用できる事がわかった。しかも、ベンゼン環上の電子的及び立体的な要因に関わらず良好な位置・立体選択性が得られた事は期待していた以上の成果であった。

5-4-4. フラン、チオフェン環の導入

上記の反応条件を、芳香族複素環であるフランとチオフェンに由来する銅試薬に適用した。これらの複素環の銅試薬は反応性が低い事が知られている。フランの銅試薬は TMSBr や BF_3 等のルイス酸を添加しないと 1,4–付加反応が進行しない [6]。チオフェンは更に反応性が低いため、1,4–付加反応において Lipshutz 試薬のダミーリガンドとして使われている (Figure 1)[7]。しかし、これらの銅試薬を用いて (*S*)-**1a** のアリル反応を行ってみると、驚くほど反応性が良く、高い収率及び不斉転写率で **2k** と **2l** を得る事ができた (entries 11, 12)。

Figure 1. Lipshutz reagents for 1,4-addition.



5-4-5. アルケニル基の導入

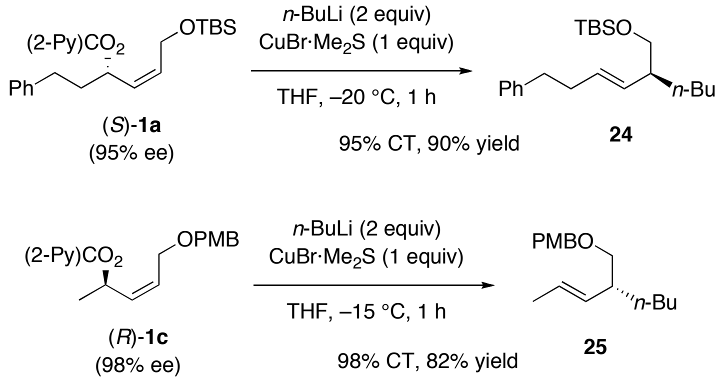
次に、アルケニル基の導入を行った。緒言でも述べた様に、アルケニルハライドと金属マグネシウムからのアルケニルグリニャール試薬の調製では、一部

二重結合の異性化が起こることが知られている。グリニャール試薬とは対照的に、*t*-BuLi と (*Z*)-1-ヨードアルケンの Li–I 交換で調製したアルケニルリチウムと $CuBr\cdot Me_2S$ から調製した銅試薬を (*S*)-**1a** と反応させるとは、シス型を損なう事なく、高い不斉転写率と良好な収率で **2m** と **2n** を与えた。トランス型の、(*E*)-1-ヘプテニル銅試薬によるアリル化もオレフィンの立体を損なうことなく進行し、**2o** を効率的に与えた。

5-4-6. アルキル基の導入

前節までに明らかにした反応条件を、アルキルリチウムの典型例である *n*-BuLi に適用した。Scheme 6 で示すように、銅試薬 *n*-$Bu_2CuLi\cdot LiBr$ は、sp^3-C 炭素の反応性が高い為か、$MgBr_2$ がない場合でさえ非常に反応性良くアンチ S_N2' 生成物 **24** と **25** を与えた。

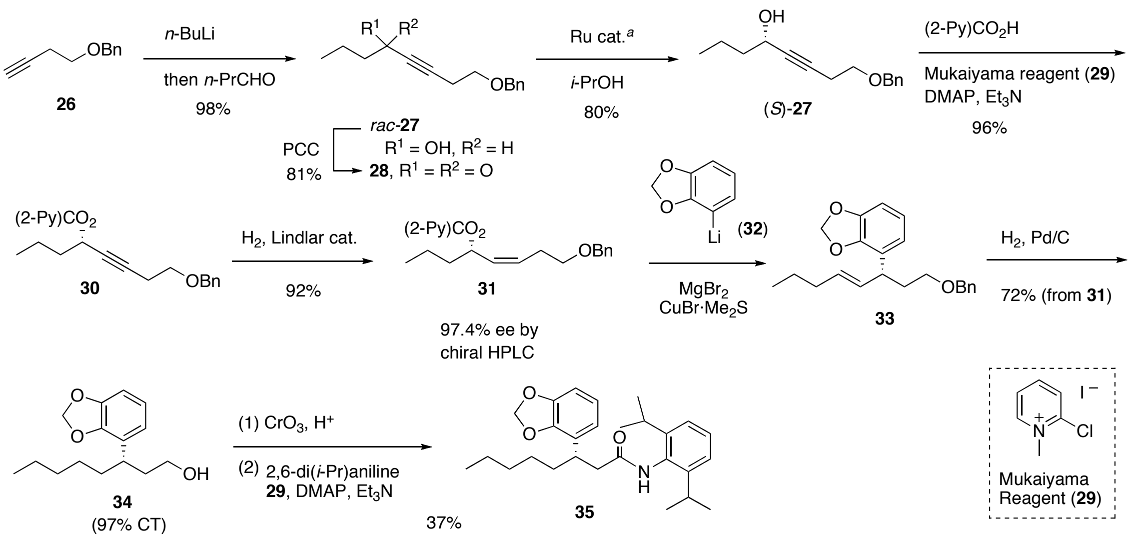
Scheme 6. Reaction with the *n*-BuLi/$CuBr\cdot Me_2S$ reagent.



５－５．応用研究（ACAT 阻害活性化合物の合成）

この章で見出した反応の応用研究として、強力なアシル CoA コレステロールアシルトランスフェラーゼ (ACAT) 阻害活性を持つ化合物 **35** [8] の合成を行うことにした。**35** はラセミ体での活性値 (0.01 μM) が報告されているのみであるが、不斉中心の立体化学が生理活性等に影響を及ぼす事が予想されるため、簡便な光学活性体の合成法の確立は重要と考えた。合成結果を Scheme 7 に示す。

Scheme 7. Synthesis of ACAT inhibitor 35.



[a] Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene)

出発物のアセチレン **26** をリチオ化し、*n*–ブタナールに付加させて *rac*-**27** とした。ラセミ体のアルコールを酸化し、Ru 触媒による不斉還元で光学活性なアルコール (*S*)-**27** とした。更に、向山試薬 **29** を用いてピコリン酸を縮合し、Lindlar 触媒を用いた部分還元でピコリン酸アリル **31** を 97.4% ee の光学純度で調製した。Li–Br 交換により調製したリチウム試薬 **32** を用いた **31** のアリル化は円滑に進行し、位置選択性良く **33** を生成した。しかし、試薬の残査との分離が困難であったため、水素雰囲気下、Pd/C を用いて二重結合の還元とベンジル基の脱保護を行いアルコール **34** に変換し、この段階で単離・精製した。その不斉転写を測定したところ、97% CT と高い立体選択性を示した。最後に、カルボン酸への酸化と続くアミド化により、**35** の合成を達成できた。

以上、全９行程、全収率 15% と、工程数・収率共に従来法を改善でき、アリル化反応を鍵とした光学活性体の合成の利点を示す事が出来た。さらに、ピコリン酸基を用いたアリル化反応は、基質の一般性が高く、種々の芳香環を円滑に導入できるので、このような骨格を持つ化合物の合成に適していると考える事ができる。

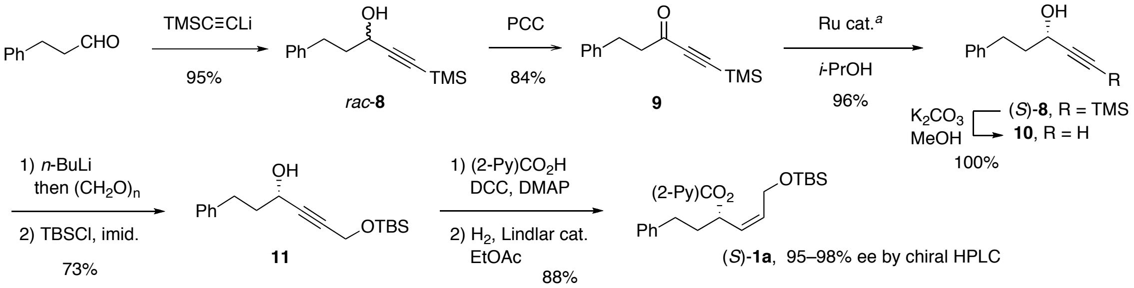
５−６．結論

有機リチウムと $CuBr{\cdot}Me_2S$ から調製した有機銅試薬によるピコリン酸アリルエステルのアリル化反応は、$MgBr_2$ の添加によって効果的に加速され、位置選択的にアンチ S_N2' 生成物が得られる事を明らかにした。この時、良好な結果を達成するための 2 つの条件：*Requirement 1* ($MgBr_2$ > Li^+) 及び *Requirement 2* (Ph/Cu = 2:1–2) を確立した。Table 3 に示すように、基質ピコリン酸アリルの一般性も良く、また、立体的・電子的な要因に依らずに様々なアリール銅試薬からアンチ S_N2' 生成物を高選択的に生成した。さらに、ハロゲン–リチウム交換やオルトリチエーションのような、アリールリチウムの様々な調製法がこのアリル化反応に適応可能な事も示せた。他にも、シス及びトランスアルケニル基、フリル、チエニル、アルキル基も円滑に導入できた。

Experimental section

Synthesis of Picolinates.

Synthesis of Picolinate (*S*)-1a.



5-Phenyl-1-(trimethylsilyl)-1-pentyn-3-one (9).

To an ice-cold solution of trimethylsilylacetylene (2.30 mL, 16.3 mmol) in THF (25 mL) was added *n*-BuLi (9.30 mL, 1.60 M in hexane, 14.9 mmol). The mixture was stirred at 0 °C for 30 min and cooled to –78 °C. $Ph(CH_2)_2CHO$ (1.66 mL, 12.4 mmol) was added to it dropwise and the resulting mixture was allowed to warm to 0 °C over 1 h. Saturated NH_4Cl and EtOAc were added to the mixture. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol *rac*-**8**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9 H), 1.79 (d, $J = 6$ Hz, 1 H), 1.96–2.07 (m, 2 H), 2.80 (t, $J = 8$ Hz, 2 H), 4.36 (q, $J = 6$ Hz, 1 H), 7.16–7.33 (m, 5 H).

To an ice-cold solution of *rac*-**8** (1.42 g, 6.11 mmol) in CH_2Cl_2 (20 mL) were added Celite (2.9 g) and PCC (1.45 g, 6.73 mmol). The mixture was stirred at rt overnight, diluted with hexane, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **9** (1.18 g, 84%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9 H), 2.86–2.94 (m, 2 H), 2.94–3.04 (m, 2 H), 7.16–7.24 (m, 3 H), 7.25–7.33 (m, 2 H).

The ^1H NMR spectra of *rac*-**8** and **9** were identical with that reported.[9]

(*S*)-5-Phenylpent-1-yn-3-ol (10).

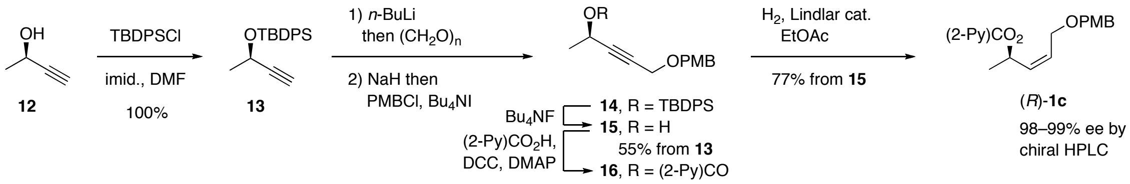
To a solution of **9** (1.18 g, 5.12 mmol) in *i*-PrOH (50 mL) was added Ru[(1*S*,2*S*)-TsDPEN](*p*-cymene) (61 mg, 0.102 mmol). The mixture was stirred at 30 °C overnight and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the (*S*)-**8** (1.14 g, 96%). The ^{1}H NMR spectrum of the alcohol was identical with that of *rac*-**8**.

To an ice-cold solution of (*S*)-**8** (1.99 g, 8.57 mmol) in MeOH (17 mL) was added K_2CO_3 (355 mg, 2.57 mmol). The mixture was stirred at rt overnight and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **10** (1.37 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (dd, J = 6, 1 Hz, 1 H), 1.95–2.13 (m, 2 H), 2.51 (dd, J = 2, 1 Hz, 1 H), 2.81 (t, J = 8 Hz, 2 H), 4.37 (dddd, J = 7, 7, 6, 2 Hz, 1 H), 7.16–7.33 (m, 5 H). The ^{1}H NMR spectrum of **10** was identical with that reported.[9]

Picolinate (*S*)-1a.

Alcohol **10** was transformed to (*S*)-**1a** according to the procedure in Chapter 2: (1) BuLi then $(CH_2O)_n$; (2) TBSCl, imidazole; (3) H_2, Lindlar cat.; (4) picolinic acid, DCC, DMAP. Enantiomeric excess (98% ee) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.5 mL/min, rt; t_R (min) = 19.4 (*S*), 84.9 (*R*). The ^{1}H NMR spectrum of (*S*)-**1a** was identical with that reported in Chapter 2.

Synthesis of Picolinate (*R*)-1c.



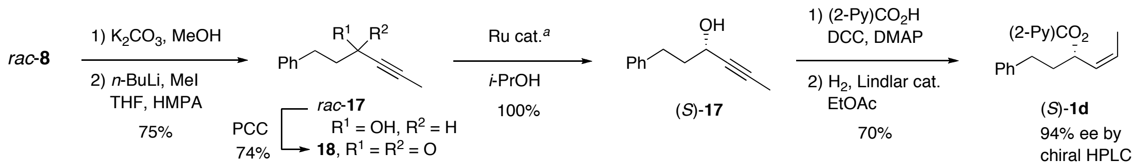
(*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-butyne (13).

To an ice-cold solution of (*R*)-3-butyne-2-ol (**12**) (1.00 mL, 12.8 mmol) and imidazole (1.74 g, 25.6 mmol) in CH_2Cl_2 (25 mL) was added TBDPSCl (4.90 mL, 19.1 mmol). After being stirred overnight at rt, the solution was diluted with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **13** (3.95 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.39 (d, J = 7 Hz, 3 H), 2.33 (d, J = 2 Hz, 1 H), 4.45 (dq, J = 2, 7 Hz, 1 H), 7.33–7.47 (m, 6 H), 7.66–7.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (+), 25.2 (–), 26.9 (–), 59.8 (–), 71.6 (+), 86.2 (+), 127.6 (–), 127.7 (–), 129.78 (–), 129.83 (–), 133.5 (+), 133.7 (+), 135.8 (–), 136.0 (–); HRMS (EI) calcd for $C_{20}H_{24}OSi$ (M^+) 308.1596, found 308.1597.

Picolinate (*R*)-1c.

The title compound was synthesized from **13** according to the procedure in Chapter 2. The ^{1}H and ^{13}C NMR spectra of the product were identical with those reported in Chapter 2. Enantiomeric excess (98% ee) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 96/4, 0.4 mL/min, rt; t_R (min) = 75.6 (*S*), 85.9 (*R*).

Synthesis of Picolinate (*S*)-1d.



1-Phenylhex-4-yn-3-ol (*rac*-17).

To a solution of racemic alcohol of **10** (502 mg, 3.13 mmol) in THF (6 mL) was added *n*-BuLi (4.30 mL, 1.60 M in hexane, 6.88 mmol) at –78 °C. After 30 min at –78 °C, HMPA (1.6 mL, 9.20 mmol) and MeI (0.25 mL, 4.07 mmol) were added to the solution dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by addition of saturated NH_4Cl. The product was extracted with hexane three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford methyl acetylene *rac*-**17** (407 mg, 75%): IR (neat) 3369, 2246, 1496, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, *J* = 2 Hz, 3 H), 1.93–2.11 (m, 3 H), 2.77 (t, *J* = 8 Hz, 2 H), 4.33 (tq, *J* = 7, 2 Hz, 1 H), 7.13–7.31 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6 (–), 31.5 (+), 39.5 (+), 62.0 (–), 80.2 (+), 81.4 (+), 125.9 (–), 128.4 (–), 128.5 (–), 141.5 (+); HRMS (EI) calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1043.

1-Phenylhex-4-yn-3-one (18).

To an ice-cold solution of *rac*-**17** (357 mg, 2.05 mmol) in CH_2Cl_2 (7 mL) were added Celite (1.0 g) and PCC (486 mg, 2.25 mmol). The mixture was stirred at rt overnight, diluted with hexane, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **18** (261 mg, 74%): IR (neat) 2222, 1674, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3 H), 2.82–2.89 (m, 2 H), 2.94–3.01 (m, 2 H), 7.16–7.23 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.2 (–), 29.9 (+), 46.9 (+), 80.2 (+), 90.6 (+), 126.3 (–), 128.4 (–), 128.6 (–), 140.4 (+), 187.1 (+); HRMS (EI) calcd for $C_{12}H_{12}O$ (M^+) 172.0888, found 172.0888.

(*S*)-1-Phenylhex-4-yn-3-ol ((*S*)-17).

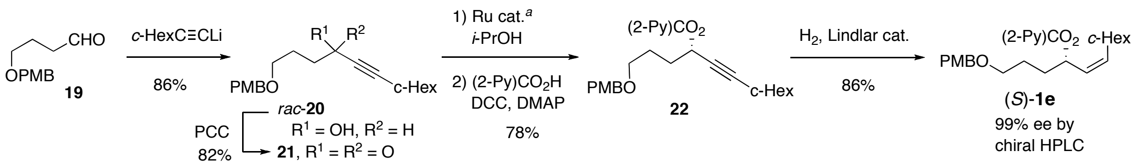
To a solution of **18** (503 mg, 2.92 mmol) in *i*-PrOH (15 mL) was added Ru[(1*S*,2*S*)-TsDPEN](*p*-cymene) (18 mg, 0.0300 mmol). The mixture was stirred at 30 °C overnight, and the catalyst (36 mg, 0.0600 mmol) was added again. The mixture was stirred at 30 °C overnight, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**17** (508 mg, 100%). The ^{1}H NMR spectrum of the product was identical with that of *rac*-**17**.

Picolinate (*S*)-1d.

To an ice-cold solution of (*S*)-**17** (508 mg, 2.92 mmol) in CH_2Cl_2 (11 mL) were added picolinic acid (431 mg, 3.50 mmol), DMAP (107 mg, 0.876 mmol), and DCC (783 mg, 3.79 mmol). The mixture was stirred at rt for 2 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish the corresponding ester (664 mg, 81%).

To a solution of the above ester (664 mg, 2.38 mmol) in EtOAc (12 mL) was added Lindlar catalyst (Aldrich, 240 mg). The mixture was stirred at rt overnight under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**1d** (582 mg, 87%): 94% ee by HPLC analysis (Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, t_R (min) = 93.6 (*S*), 109.8 (*R*)). The ^{1}H NMR spectrum of (*S*)-**1d** was identical with that reported in Chepter 2.

Synthesis of Picolinate (*S*)-1e.



1-Cyclohexyl-6-[(4-methoxybenzyl)oxy]-1-hexyn-3-one (21).

To a solution of (2,2-dibromovinyl)cyclohexane[10] (1.99 g, 7.43 mmol) in THF (8 mL) was added *n*-BuLi (9.30 mL, 1.60 M in hexane, 14.9 mmol) dropwise at –78 °C. After 30 min at –78 °C, a solution of aldehyde **19**[11] (1.03 g, 4.95 mmol) in THF (2 mL) was added to it. The reaction was carried out at –78 °C for 1 h, and quenched by addition of saturated NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford *rac*-**20** (1.34 g, 86%).

To an ice-cold solution of *rac*-**20** (320 mg, 1.01 mmol) in CH_2Cl_2 (4 mL) were added Celite (0.5 g) and PCC (262 mg, 1.22 mmol). The mixture was stirred at rt overnight, diluted with hexane, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **21** (260 mg, 82%). IR (neat) 2206, 1673, 1513, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.59 (m, 6 H), 1.63–1.88 (m, 4 H), 1.95 (tt, *J* = 7, 6 Hz, 2 H), 2.45–2.60 (m, 1 H), 2.65 (t, *J* = 7 Hz, 2 H), 3.47 (t, *J* = 6 Hz, 2 H), 3.80 (s, 3 H), 4.42 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (+), 24.7 (+), 25.6 (+), 29.1 (–), 31.6 (+), 42.4 (+), 55.3 (–), 68.8 (+), 72.6 (+), 80.8 (+), 98.0 (+), 113.8 (–), 129.3 (–), 130.5 (+), 159.2, (+) 188.1 (+); HRMS (FAB) calcd for $C_{20}H_{27}O_3$ [(M + H)$^+$] 315.1960, found 315.1960.

(*S*)-1-Cyclohexyl-6-[(4-methoxybenzyl)oxy]-1-hexyn-3-ol ((*S*)-20).

To a solution of **21** (260 mg, 0.827 mmol) in *i*-PrOH (8 mL) was added Ru[(1*S*,2*S*)-TsDPEN](*p*-cymene) (25 mg, 0.417 mmol). The mixture was stirred at 30 °C overnight and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**20** (229 mg, 87%): IR (neat) 3406, 2207, 1612, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.54 (m, 6 H), 1.62–1.90 (m, 8 H), 2.32–2.43 (m, 1 H), 2.57 (d, *J* = 6 Hz, 1 H), 3.50 (t, *J* = 5 Hz, 2 H), 3.80 (s, 3 H), 4.37–4.48 (m, 1 H), 4.45 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9 (+), 25.6 (+), 25.9 (+), 29.1 (–), 32.7 (+), 35.7 (+), 55.3 (–), 62.4 (–), 69.9 (+), 72.6 (+), 81.1 (+), 89.6 (+), 113.9 (–), 129.4 (–), 130.3 (+), 159.2 (+); HRMS (FAB) calcd for $C_{20}H_{28}O_3Na$ [(M + Na)$^+$] 339.1936, found 339.1929.

(*S*)-1-Cyclohexyl-6-[(4-methoxybenzyl)oxy]-1-hexyn-3-yl Pyridine-2-carboxylate (22).

To an ice-cold suspension of picolinic acid (107 mg, 0.869 mmol) in CH_2Cl_2 (1 mL) were added DMAP (88 mg, 0.720 mmol) and DCC (194 mg, 0.940 mmol). After 20 min at rt, (*S*)-**20** (229 mg, 0.723 mmol) in CH_2Cl_2 (2 mL) was added to the mixture at 0 °C. The mixture was stirred at rt for 1.5 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **22** (274 mg, 90%): IR (neat)

2236, 1719, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18–1.54 (m, 6 H), 1.60–1.89 (m, 6 H), 1.96–2.08 (m, 2 H), 2.32–2.44 (m, 1 H), 3.51 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 5.73 (dt, *J* = 2, 7 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H), 7.47 (ddd, *J* = 8, 5, 2 Hz, 1 H), 7.83 (dd, *J* = 8, 8 Hz, 1 H), 8.13 (dd, *J* = 8, 2 Hz, 1 H), 8.78 (dm, *J* = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8 (+), 25.6 (+), 25.9 (+), 29.0 (–), 32.2 (+), 32.4 (+), 55.3 (–), 66.0 (–), 69.4 (+), 72.6 (+), 91.1 (+), 109.1 (+), 113.8 (–), 125.4 (–), 126.9 (–), 129.3 (–), 130.6 (+), 137.0 (–), 148.1 (+), 150.0 (–), 159.2 (+), 164.2 (+); HRMS (FAB) calcd for $C_{26}H_{32}NO_4$ (M^+) 422.2331, found 422.2336.

Picolinate (*S*)-1e.

To a solution of **22** (264 mg, 0.626 mmol) in EtOAc (3 mL) was added Lindlar catalyst (Aldrich, 110 mg). The mixture was stirred at rt for 2 days under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**1e** (228 mg, 86%): IR (neat) 1717, 1513, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95–1.50 (m, 6 H), 1.52–2.03 (m, 8 H), 2.43–2.58 (m, 1 H), 3.48 (t, *J* = 6 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.37 (dd, *J* = 11, 8 Hz, 1 H), 5.43 (dd, *J* = 11, 9 Hz, 1 H), 5.90 (dt, *J* = 8, 7 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H), 7.45 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.81 (ddd, *J* = 8, 8, 2 Hz, 1 H), 8.10 (d, *J* = 8 Hz, 1 H), 8.67 (dm, *J* = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (+), 25.8 (+), 26.0 (+), 31.7 (+), 33.0 (+), 33.3 (+), 37.1 (–), 55.3 (–), 69.7 (+), 72.2 (–), 72.6 (+), 113.8 (–), 125.1 (–), 125.4 (–), 126.7 (–), 129.3 (–), 130.6 (+), 136.9 (–), 140.8 (–), 148.6 (+), 150.0 (–), 159.2 (+), 164.5 (+); HRMS (FAB) calcd for $C_{26}H_{33}NO_4Na$ [$(M + Na)^+$] 446.2307, found 446.2308. Enantiomeric excess (99% ee) was determined by chiral HPLC analysis: Chiralcel AD-H; hexane/*i*-PrOH = 95/5, 0.5 mL/min, rt; t_R (min) = 23.0 (*S*), 46.5 (*R*).

Allylic Substitution.

The reactions of (*S*)-**1a** with Ph coppers prepared by various ways are described below as the general methods.

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,6-diphenyl-3-hexene ((*R*)-2a).

Table 2, entry 1: To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (39.5 mg, 0.192 mmol) in THF (1.6 mL) were added PhLi (0.180 mL, 1.08 M in cyclohexane-Et_2O, 0.194 mmol) and $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol). After 30 min at 0 °C, a solution of (*S*)-**1a** (39.5 mg, 0.0960 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**2a** (34.0 mg, 97%, 96% ee, 98% CT). The ^1H NMR spectrum and retention time of (*R*)-**2a** on chiral HPLC were identical with those reported in Chapter 2.

Table 2, entry 3: To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (22.0 mg, 0.107 mmol) in THF (1.4 mL) were added PhLi (0.200 mL, 1.08 M in cyclohexane-Et_2O, 0.216 mmol) and $MgBr_2$ (1.60 mL, 0.20 M in THF, 0.320 mmol). After 30 min at 0 °C, a solution of (*S*)-**1a** (44.1 mg, 0.107 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford (*R*)-**2a** (36.2 mg, 92%, 96% ee, 98% CT by chiral HPLC analysis).

Table 2, entry 8: To an ice-cold solution of PhBr (0.022 mL, 0.209 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.250 mL, 1.57 M in pentane, 0.393 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (2.40 mL, 0.20 M in THF, 0.480 mmol) and $CuBr{\cdot}Me_2S$ (19.9 mg, 0.0968 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (39.8 mg, 0.0967 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, to afford (*R*)-**2a** (33.0 mg, 93%, 93% ee, 98% CT by chiral HPLC analysis).

Table 2, entry 10: To an ice-cold solution of PhI (0.024 mL, 0.214 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.250 mL, 1.57 M in pentane, 0.393 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (2.40 mL, 0.20 M in THF, 0.480 mmol) and $CuBr{\cdot}Me_2S$ (19.7 mg, 0.0958 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (39.5 mg, 0.0960 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford (*R*)-**2a** (31.8 mg, 90%, 93% ee, 98% CT by chiral HPLC analysis).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4,6-diphenyl-2-hexene (2b).

Table 3, entry 1: To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (19.5 mg, 0.0949 mmol) in THF (1.6 mL) were added PhLi (0.180 mL, 1.08 M in cyclohexane-Et_2O, 0.194 mmol) and $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol). After 30 min at 0 °C, a solution of (*S*)-**1b** (39.0 mg, 0.0947 mmol, 99% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2b** (30.1 mg, 87%, 98% ee, 99% CT). The ^{1}H NMR spectrum and retention time of **2b** were identical with those reported in Chapter 2.

(*S*,*E*)-5-((4-Methoxybenzyl)oxy)-4-phenyl-2-hexene (2c).

Table 3, entry 2: To an ice-cold suspension of CuBr·Me$_2$S (23.6 mg, 0.115 mmol) in THF (1.3 mL) were added PhLi (0.210 mL, 1.08 M in cyclohexane-Et$_2$O, 0.227 mmol) and MgBr$_2$ (1.70 mL, 0.20 M in THF, 0.340 mmol). After 30 min at 0 °C, a solution of (*R*)-**1c** (37.4 mg, 0.115 mmol, 99% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2c** (27.1 mg, 84%, 97% ee, 98% CT). The ^{1}H NMR spectrum of **2c** was identical with that reported in Chapter 2.

(*R*,*E*)-1,5-Diphenyl-3-hexene (2d).

Table 3, entry 4: To an ice-cold suspension of CuBr·Me$_2$S (16.8 mg, 0.0817 mmol) in THF (1.6 mL) were added PhLi (0.15 mL, 1.08 M in cyclohexane-Et$_2$O, 0.162 mmol) and MgBr$_2$ (1.30 mL, 0.20 M in THF, 0.260 mmol). After 30 min at 0 °C, a solution of (*S*)-**1d** (23.0 mg, 0.0817 mmol, 94% ee) in THF (1 mL) was added to it dropwise at –60 °C. The resulting mixture was stirred at –60 °C for 1 h to afford **2d** (17.8 mg, 92%, 91% ee, 97% CT). The ^{1}H and ^{13}C NMR spectra of **2d** and its retention time were identical with that reported in Chapter 2.

(*R*,*E*)-1-Cyclohexyl-6-((4-methoxybenzyl)oxy)-1-phenyl-2-hexene (2e).

Table 3, entry 5: To an ice-cold suspension of CuBr·Me$_2$S (18.3 mg, 0.0890 mmol) in THF (1.5 mL) were added PhLi (0.170 mL, 1.08 M in cyclohexane-Et$_2$O, 0.184 mmol) and MgBr$_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol). After 30 min at 0 °C, a solution of (*S*)-**1e** (37.8 mg, 0.0892 mmol, 99% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2e** (31.9 mg, 94%): IR (neat) 1612, 1513, 1248 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.70–0.96 (m, 2 H), 1.04–1.28 (m, 3 H), 1.32–1.90 (m, 8 H), 2.07 (dt, *J* = 7, 7 Hz, 2 H), 2.86 (dd, *J* = 9, 9 Hz, 1 H), 3.40 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.39 (s, 2 H), 5.38 (dt, *J* = 15, 7 Hz, 1 H), 5.57 (dd, *J* = 15, 9 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.06–7.30 (m, 7 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.47 (+), 26.49 (+), 26.6 (+), 29.2 (+), 29.6 (+), 31.4 (+), 31.5 (+), 42.6 (–), 55.3 (–), 56.4 (–), 69.5 (+), 72.6 (+), 113.8 (–), 125.8 (–), 127.9 (–), 128.3 (–), 129.3 (–), 130.2 (–), 130.8 (+), 133.3 (–), 145.0 (+), 159.2 (+); HRMS (FAB) calcd for $C_{26}H_{34}O_2Na$ [(M + Na)$^+$] 401.2457, found 401.2447. The enantiomeric information

(97% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 41.9 (*R*), 47.9 (*S*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methoxyphenyl)-6-phenyl-3-hexene (2f).

Table 3, entry 6: To an ice-cold solution of anisole (0.025 mL, 0.23 mmol) in THF (1.4 mL) was added *n*-BuLi (0.13 mL, 1.60 M in hexane, 0.208 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.60 mL, 0.20 M in THF, 0.32 mmol) and $CuBr{\cdot}Me_2S$ (21.2 mg, 0.103 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (42.4 mg, 0.103 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2f** (34.6 mg, 85%, 94% ee, 99% CT). The ^{1}H NMR spectrum of **2f** was identical with that reported in Chapter 2.

(*R*,*E*)-2-[(2,6-Bis(methoxymethoxy)-4-methyl)phenyl]-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-3-hexene (2g).

Table 3, entry 7: To an ice-cold solution of 1,3-bis(methoxymethoxy)-5-methylbenzene (43.9 mg, 0.207 mmol) in THF (1.6 mL) was added *n*-BuLi (0.120 mL, 1.60 M in hexane, 0.192 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and $CuBr{\cdot}Me_2S$ (19.3 mg, 0.0939 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (38.7 mg, 0.0940 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford a mixture of **2g** and $(2,6\text{-}(MOMO)_2\text{-}4\text{-}MeC_6H_2)_2$ in a 84 : 16 ratio by ^{1}H NMR analysis (54.1 mg in total, 97% yield of **2g**): ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.08 (s, 3 H), –0.07 (s, 3 H), 0.78 (s, 9 H), 2.21 (s, 3 H), 2.15–2.28 (m, 2 H), 2.57 (t, *J* = 8 Hz, 1 H), 3.39 (s, 6 H), 3.72 (dd, *J* = 10, 6 Hz, 1 H), 3.96 (dd, *J* = 10, 9 Hz, 1 H), 4.08 (ddd, *J* = 9, 7, 6 Hz, 1 H), 5.06 (s, 4 H), 5.46 (dt, *J* = 15, 7 Hz, 1 H), 5.86 (dd, *J* = 15, 8 Hz, 1 H), 6.52 (s, 2 H), 7.03–7.12 (m, 3 H), 7.13–7.22 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.1, 18.5, 21.8, 26.0, 34.8, 36.1, 42.5, 56.2, 65.3, 94.6, 109.2, 117.2, 125.7, 128.3, 128.5, 130.6, 130.7, 137.7, 142.4, 156.0.

Transformation of **2g** *to alcohol for determination of the structure*: To a solution of the above mixture of **2g** and $(2,6\text{-}(MOMO)_2\text{-}4\text{-}MeC_6H_2)_2$ in THF (1 mL) was added Bu_4NF (0.14 mL, 1.0 M in THF, 0.14 mmol). The reaction was carried out at rt overnight to furnish the corresponding alcohol (34.1 mg, 94% from (*S*)-**1a**): IR (neat) 3430, 1610, 1583, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (br s, 1 H), 2.29 (s, 3

H), 2.32 (ddd, *J* = 8, 7, 7 Hz, 2 H), 2.63 (dt, *J* = 14, 8 Hz, 1 H), 2.71 (dt, *J* = 14, 7 Hz, 1 H), 3.46 (s, 6 H), 3.70–3.81 (m, 1 H), 3.85–3.95 (m, 1 H), 4.18 (dt, *J* = 8, 8 Hz, 1 H), 5.14 (s, 4 H), 5.62 (dt, *J* = 15, 7 Hz, 1 H), 5.87 (dd, *J* = 15, 8 Hz, 1 H), 6.61 (s, 2 H), 7.11–7.20 (m, 3 H), 7.22–7.28 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (–), 34.6 (+), 35.9 (+), 42.8 (–), 56.2 (–), 64.5 (+), 94.5 (+), 109.3 (–), 116.1 (+), 125.9 (–), 128.3 (–), 128.5 (–), 129.9 (–), 132.2 (–), 138.3 (+), 142.0 (+), 155.9 (+); HRMS (FAB) calcd for $C_{23}H_{30}O_5Na$ [(M + Na)$^+$] 409.1991, found 409.1988. The enantiomeric information (98% ee, > 99% CT) was determined by chiral HPLC analysis: Chiralcel AD-H; hexane/*i*-PrOH = 98/2, 0.3 mL/min, rt; t_R (min) = 108.2 (*S*), 112.5 (*R*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2,6-dimethylphenyl)-6-phenyl-3-hexene (2h).

Table 3, entry 8: To an ice-cold solution of 2-bromo-1,3-dimethylbenzene (0.026 mL, 0.195 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.280 mL, 1.57 M in pentane, 0.361 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (2.30 mL, 0.20 M in THF, 0.460 mmol) and CuBr·Me_2S (18.8 mg, 0.0914 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (37.6 mg, 0.0913 mmol, 97% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2h** (31.7 mg, 88%): IR (neat) 1255, 1099, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.06 (s, 3 H), –0.02 (s, 3 H), 0.84 (s, 9 H), 2.25–2.38 (m, 8 H), 2.65 (t, *J* = 8 Hz, 2 H), 3.72–3.84 (m, 1 H), 3.96–4.07 (m, 2 H), 5.39 (dt, *J* = 16, 7 Hz, 1 H), 5.81 (dm, *J* = 16 Hz, 1 H), 6.93–7.04 (m, 3 H), 7.11–7.19 (m, 3 H), 7.21–7.28 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), 18.3 (+), 21.8 (–), 26.0 (–), 34.9 (+), 36.0 (+), 46.4 (–), 65.2 (+), 125.8 (–), 126.2 (–), 128.3 (–), 128.5 (–), 130.0 (–), 130.3 (–), 138.8 (+), 142.2 (+); HRMS (FAB) calcd for $C_{26}H_{38}OSiNa$ [(M + Na)$^+$] 417.2590, found 417.2592. The enantiomeric information (94% ee, 97% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.4 mL/min, rt; t_R (min) = 50.1 (*S*), 71.9 (*R*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-6-phenyl-3-hexene (2i).

Table 3, entry 9: To an ice-cold solution of 4,4-dimethyl-2-phenyl-2-oxazoline (0.035 mL, 0.205 mmol) in THF (1.6 mL) was added *n*-BuLi (0.12 mL, 1.60 M in hexane, 0.192 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and CuBr·Me_2S (19.1 mg, 0.0929 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a**

(38.3 mg, 0.0930 mmol, 97% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford a mixture of **2i** and Ar_2 in a 82 : 18 ratio by ^{1}H NMR analysis (48.8 mg in total, 98% yield of **2i**): IR (neat) 1645, 1102, 1038, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.06 (s, 3 H), –0.04 (s, 3 H), 0.84 (s, 9 H), 1.38 (s, 6 H), 2.39 (ddd, *J* = 8, 7, 7 Hz, 2 H), 2.67 (dd, *J* = 8, 7 Hz, 2 H), 3.75 (dd, *J* = 10, 7 Hz, 1 H), 3.81 (dd, *J* = 10, 6 Hz, 1 H), 4.06 (s, 3 H), 4.40 (ddd, *J* = 7, 7, 6 Hz, 1 H), 5.56 (dt, *J* = 16, 7 Hz, 1 H), 5.70 (dd, *J* = 16, 7 Hz, 1 H), 7.13–7.29 (m, 7 H), 7.34 (ddd, *J* = 8, 8, 1 Hz, 1 H), 7.66 (dd, *J* = 8, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3 (–), 18.3 (+), 26.0 (–), 28.4 (–), 34.8 (+), 36.0 (+), 46.3 (–), 67.1 (+), 67.9 (+), 78.9 (+), 125.7 (–), 125.9 (–), 128.2 (+), 128.3 (–), 128.6 (–), 128.7 (–), 130.0 (–), 130.2 (–), 131.1 (–), 131.4 (–), 142.2 (+), 142.4 (+), 162.9 (+); HRMS (FAB) calcd for $C_{29}H_{41}NO_2SiNa$ [(M + Na)$^+$] 486.2804, found 486.2799.

*Transformation of **2i** to alcohol for determination of the structure*: To a solution of the above mixture of **2i** and Ar_2 in THF (1 mL) was added Bu_4NF (0.14 mL, 1.0 M in THF, 0.14 mmol). The reaction was carried out at rt overnight to furnish the corresponding alcohol (30.6 mg, 94% from (*S*)-**1a**): IR (neat) 3292, 1739, 1642, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 1.41 (s, 3 H), 2.31–2.44 (m, 2 H), 2.67 (dt, *J* = 14, 8 Hz, 1 H), 2.72 (dt, *J* = 14, 8 Hz, 1 H), 3.61 (dd, *J* = 10, 10 Hz, 1 H), 4.07 (dd, *J* = 10, 5 Hz, 1 H), 4.10 (d, *J* = 8 Hz, 1 H), 4.14 (d, *J* = 8 Hz, 1 H), 4.48 (ddd, *J* = 10, 10, 5 Hz, 1 H), 5.43 (br s, 1 H), 5.48–5.62 (m, 2 H), 7.14–7.32 (m, 7 H), 7.40 (ddd, *J* = 8, 8, 1 Hz, 1 H), 7.67 (dm, *J* = 8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (–), 28.8 (–), 34.7 (+), 35.8 (+), 45.1 (–), 68.1 (+), 68.5 (+), 79.2 (+), 125.9 (–), 126.1 (–), 127.6 (+), 128.2 (–), 128.4 (–), 128.6 (–), 129.1 (–), 130.9 (–), 131.1 (–), 131.2 (–), 141.8 (+), 143.8 (+), 163.0 (+); HRMS (EI) calcd for $C_{23}H_{27}NO_2$ [M$^+$] 349.2042, found 349.2046. The enantiomeric information (97% ee, > 99% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 97/3, 0.5 mL/min, rt; t_R (min) = 33.7 (*R*), 41.3 (*S*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(4-fluorophenyl)-6-phenyl-3-hexene (2j).

Table 3, entry 10: To an ice-cold solution of 1-bromo-4-fluorobenzene (0.020 mL, 0.182 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.220 mL, 1.57 M in pentane, 0.345 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (2.20 mL, 0.20 M in THF, 0.440 mmol) and $CuBr{\cdot}Me_2S$ (17.8 mg, 0.0866 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, cooled to –20 °C. A solution of (*S*)-**1a** (39.8 mg, 0.0967 mmol, 97% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at –20 °C for 1 h to afford **2j** (30.6 mg, 92%): IR (neat) 1509, 1099, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.07 (s, 3 H), –0.06 (s, 3 H), 0.83 (s, 9 H), 2.34 (ddd, *J* = 8, 6, 6 Hz, 2 H), 2.68 (dd, *J* = 8, 6 Hz, 2 H), 3.40 (ddd, *J* = 7, 7, 7 Hz, 1 H), 3.68 (dd, *J* = 10, 7 Hz, 1 H), 3.74 (dd, *J* = 10, 7 Hz, 1 H), 5.51 (dt, *J* = 16, 6 Hz, 1 H), 5.61 (dd, *J* = 16, 7 Hz, 1 H), 6.95 (ddt, *J* = 9, 9, 2 Hz, 2 H), 7.07–7.21 (m, 5 H), 7.22–7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.4 (–), 18.3 (+), 25.9 (–), 34.7 (+), 35.9 (+), 50.5 (–), 67.5 (+), 114.9 (d, *J* = 21 Hz) (–), 125.8 (–), 128.3 (–), 128.6 (–), 129.7 (d, *J* = 7 Hz) (–), 131.0 (–), 131.3 (–), 138.3 (d, *J* = 3 Hz) (+), 142.0 (+), 161.6 (d, *J* = 242 Hz) (+); HRMS (FAB$^+$) calcd for $C_{24}H_{33}FOSiNa$ [(M + Na)]$^+$ 407.2194, found 407.2182. The enantiomeric information (94% ee, 97% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.5 mL/min, rt; t_R (min) = 64.3 (*R*), 75.2 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(furan-2-yl)-6-phenyl-3-hexene (2k).

Table 3, entry 11: To an ice-cold solution of furan (0.015 mL, 0.206 mmol) in THF (1.6 mL) was added *n*-BuLi (0.120 mL, 1.60 M in hexane, 0.192 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and CuBr·Me_2S (19.2 mg, 0.0934 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (38.4 mg, 0.0933 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2k** (28.5 mg, 86%): IR (neat) 1471, 1255, 1105, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.88 (s, 9 H), 2.32–2.44 (m, 2 H), 2.70 (t, *J* = 8 Hz, 2 H), 3.44 (ddd, *J* = 7, 7, 7 Hz, 1 H), 3.75 (dd, *J* = 10, 7 Hz, 1 H), 3.86 (dd, *J* = 10, 7 Hz, 1 H), 5.53–5.68 (m, 2 H), 6.03 (dd, *J* = 3, 1 Hz, 1 H), 6.31 (dd, *J* = 3, 2 Hz, 1 H), 7.17–7.23 (m, 3 H), 7.26–7.33 (m, 2 H), 7.34 (dd, *J* = 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.39 (–), –5.36 (–), 18.4 (+), 25.9 (–), 34.6 (+), 35.8 (+), 45.5 (–), 65.5 (+), 105.8 (–), 110.1 (–), 125.8 (–), 128.3 (–), 128.4 (–), 128.5 (–), 132.3 (–), 141.1 (–), 142.0 (+), 155.7 (+); HRMS (FAB) calcd for $C_{22}H_{32}O_2SiNa$ [(M + Na)$^+$] 379.2069, found 379.2071. The enantiomeric information (94% ee, 99% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 93.5 (*S*), 110.0 (*R*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenyl-2-(thiophen-2-yl)-3-hexene (2l).

Table 3, entry 12: To an ice-cold solution of thiophene (0.016 mL, 0.200 mmol) in THF (1.6 mL) was added *n*-BuLi (0.12 mL, 1.60 M in hexane, 0.192 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and

CuBr·Me$_2$S (18.9 mg, 0.0919 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (37.8 mg, 0.0918 mmol, 97% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2l** (28.5 mg, 83%): IR (neat) 1255, 1107, 837 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.06 (s, 6 H), 0.93 (s, 9 H), 2.37–2.48 (m, 2 H), 2.75 (dd, *J* = 9, 7 Hz, 2 H), 3.70–3.86 (m, 3 H), 5.60–5.74 (m, 2 H), 6.85 (dt, *J* = 4, 1 Hz, 1 H), 6.99 (dd, *J* = 5, 4 Hz, 1 H), 7.21 (dd, *J* = 5, 1 Hz, 1 H), 7.22–7.27 (m, 3 H), 7.29–7.37 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ –5.3 (–), 18.4 (+), 26.0 (–), 34.5 (+), 35.9 (+), 46.8 (–), 67.8 (+), 123.5 (–), 124.1 (–), 125.9 (–), 126.4 (–), 128.4 (–), 128.6 (–), 130.8 (–), 131.9 (–), 142.0 (+), 145.7 (+); HRMS (FAB) calcd for $C_{22}H_{32}OSSiNa$ [(M + Na)$^+$] 395.1841, found 395.1842. The enantiomeric information (96% ee, 99% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OB-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 62.1 (*R*), 64.9 (*S*).

(*S*,*1'E*,*3Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(4'-phenyl-1'-butenyl)-3-nonene (2m).

Table 3, entry 13: To an ice-cold solution of (*Z*)-1-iodo-1-heptene (58.1 mg, 0.259 mmol) in Et$_2$O (1 mL) was added *t*-BuLi (0.320 mL, 1.57 M in pentane, 0.502 mmol) slowly. After 30 min at 0 °C, a solution of MgBr$_2$ (2.90 mL, 0.20 M in THF, 0.580 mmol) and CuBr·Me$_2$S (25.8 mg, 0.125 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (34.4 mg, 0.0836 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2m** (24.1 mg, 75%): IR (neat) 1255, 1103, 836 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.03 (s, 6 H), 0.85–0.94 (m, 3 H), 0.89 (s, 9 H), 1.23–1.38 (m, 6 H), 2.03 (dt, *J* = 8, 6 Hz, 2 H), 2.31 (dt, *J* = 7, 8 Hz, 2 H), 2.66 (t, *J* = 8 Hz, 2 H), 3.16 (ddt, *J* = 9, 7, 7 Hz, 1 H), 3.47 (d, *J* = 7 Hz, 2 H), 5.20 (dd, *J* = 11, 9 Hz, 1 H), 5.39 (dd, *J* = 16, 7 Hz, 1 H), 5.39–5.57 (m, 2 H), 7.14–7.23 (m, 3 H), 7.24–7.32 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ –5.2 (–), 14.2 (–), 18.5 (+), 22.7 (+), 26.0 (–), 27.7 (+), 29.5 (+), 31.7 (+), 34.8 (+), 36.1 (+), 43.7 (–), 67.0 (+), 125.8 (–), 128.3 (–), 128.5 (–), 129.3 (–), 130.2 (–), 130.9 (–), 131.4 (–), 142.2 (+); HRMS (FAB) calcd for $C_{25}H_{42}OSiNa$ [(M + Na)$^+$] 409.2903, found 409.2899. The enantiomeric information (96% ee, 98% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 99/1, 0.2 mL/min, 40 °C; t_R (min) = 69.2 (*R*), 76.2 (*S*).

(*R*,*1Z*,*4E*)-3-[(*tert*-Butyldimethylsilyl)oxymethyl]-1-cyclohexyl-7-phenylhepta-1,4-diene (2n).

Table 3, entry 14: To an ice-cold solution of (*Z*)-(2-iodovinyl)cyclohexane (61.7 mg, 0.261 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.32 mL, 1.57 M in pentane, 0.502 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (3.00 mL, 0.20 M in THF, 0.600 mmol) and $CuBr{\cdot}Me_2S$ (26.0 mg, 0.126 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (34.7 mg, 0.0843 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2n** (27.5 mg, 82%): IR (neat) 1255, 1105, 837, 775, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 0.96–1.35 (m, 6 H), 1.53–1.76 (m, 4 H), 2.18–2.36 (m, 3 H), 2.66 (dd, *J* = 8, 6 Hz, 2 H), 3.18 (ddt, *J* = 10, 6, 7 Hz, 1 H), 3.47 (d, *J* = 7 Hz, 2 H), 5.09 (dd, *J* = 11, 10 Hz, 1 H), 5.30 (dd, *J* = 11, 10 Hz, 1 H), 5.40 (dd, *J* = 16, 6 Hz, 1 H), 5.52 (dd, *J* = 16, 7 Hz, 1 H), 7.13–7.21 (m, 3 H), 7.23–7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2 (–), –5.1 (–), 18.5 (+), 25.99 (+), 26.04 (+), 26.07 (–), 26.13 (+), 33.3 (+), 33.6 (+), 34.8 (+), 36.1 (+), 36.8 (–), 43.9 (–), 67.2 (+), 125.8 (–), 127.5 (–), 128.3 (–), 128.5 (–), 130.1 (–), 131.2 (–), 137.3 (–), 142.2 (+); HRMS (FAB) calcd for $C_{26}H_{42}OSiNa$ [(M + Na)$^+$] 421.2903, found 421.2902. The enantiomeric information (94% ee, 99% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 52.5 (*R*), 55.5 (*S*).

(*S,1'E,3E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(4'-phenyl-1'-butenyl)-3-nonene (2o).

Table 3, entry 15: To an ice-cold solution of (*E*)-1-iodo-1-heptene (49.8 mg, 0.222 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.260 mL, 1.57 M in pentane, 0.404 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (2.50 mL, 0.20 M in THF, 0.500 mmol) and $CuBr{\cdot}Me_2S$ (20.8 mg, 0.101 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1a** (41.6 mg, 0.101 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h to afford **2o** (36.4 mg, 93%): IR (neat) 1255, 1104, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.85–0.94 (m, 3 H), 0.89 (s, 9 H), 1.23–1.41 (m, 6 H), 1.99 (dt, *J* = 7, 7 Hz, 2 H), 2.32 (dt, *J* = 8, 6 Hz, 2 H), 2.68 (t, *J* = 8 Hz, 2 H), 2.81 (ddt, *J* = 7, 7, 7 Hz, 1 H), 3.49 (d, *J* = 7 Hz, 2 H), 5.32 (dd, *J* = 16, 7 Hz, 1 H), 5.32–5.43 (m, 1 H), 5.43 (dd, *J* = 16, 7 Hz, 1 H), 5.51 (dt, *J* = 16, 6 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.24–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2 (–), 14.2 (–), 18.5 (+), 22.6 (+), 26.0 (–), 29.2 (+), 31.5 (+), 32.8 (+), 34.8 (+), 36.1 (+), 48.5 (–), 67.0 (+), 125.8 (–), 128.3 (–), 128.6 (–), 130.0 (–), 130.6 (–), 131.1 (–), 131.9 (–), 142.2 (+); HRMS (FAB) calcd for $C_{25}H_{42}OSiNa$ [(M + Na)$^+$] 409.2903, found 409.2897. The enantiomeric information (93% ee, 98% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 51.2 (*R*), 57.8 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-butyl-6-phenyl-3-hexene (24).

To a suspension of CuBr·Me_2S (18.8 mg, 0.116 mmol) in THF (2 mL) was added *n*-BuLi (0.12 mL, 1.55 M in hexane, 0.186 mmol) slowly at –20 °C. The resulting mixture was stirred at –20 °C for 30 min, and a solution of (*S*)-**1a** (37.6 mg, 0.0913 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The mixture was allowed to warm to –20 °C for 1 h to afford **24** (28.6 mg, 90%, 90% ee, 95% CT). The ^1H NMR spectrum of **24** was identical with that reported in Chapter 3.

(*R*,*E*)-1-[(2-Butylpent-3-enyloxy)methyl]-4-methoxybenzene (25).

To a suspension of CuBr·Me_2S (22.4 mg, 0.109 mmol) in THF (2 mL) was added *n*-BuLi (0.13 mL, 1.66 M in hexane, 0.216 mmol) slowly at –15 °C. The resulting mixture was stirred at –15 °C for 30 min, and a solution of (*R*)-**1c** (35.4 mg, 0.109 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was allowed to warm to 0 °C for 1 h to afford **25** (23.5 mg, 82%): IR (neat) 1612, 1513, 1248, 1092, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.11–1.36 (m, 5 H), 1.40–1.52 (m, 1 H), 1.67 (dd, *J* = 6, 1 Hz, 3 H), 2.20–2.32 (m, 1 H), 3.30 (d, *J* = 9 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.23 (ddq, *J* = 16, 8, 1 Hz, 1 H), 5.47 (dq, *J* = 16, 6 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (–), 18.2 (–), 22.9 (+), 29.3 (+), 31.5 (+), 43.0 (–), 55.3 (–), 72.6 (+), 74.1 (+), 113.8 (–), 125.9 (–), 129.2 (–), 130.9 (+), 133.1 (–), 159.1 (+); HRMS (FAB) calcd for $C_{17}H_{26}O_2$ [M^+] 262.1933, found 262.1939. The enantiomeric information (96% ee, 98% CT) was determined by chiral HPLC: Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 61.8 (*R*), 72.9 (*S*).

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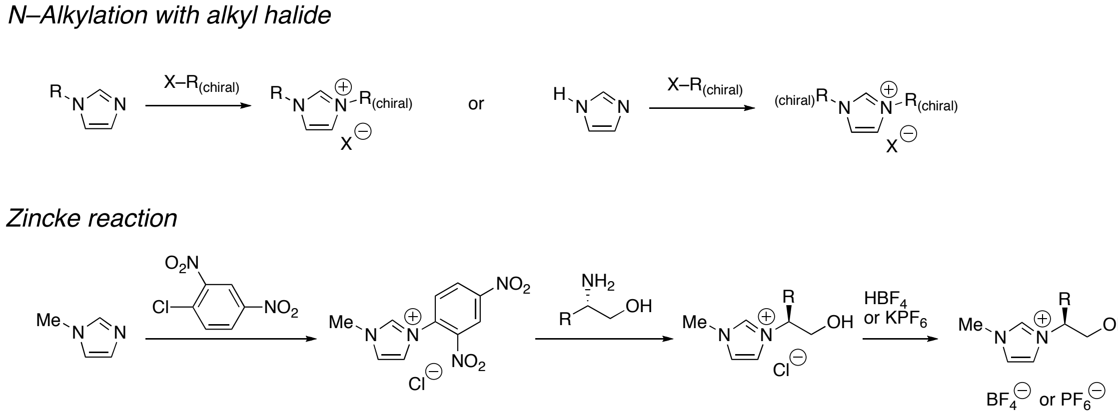
第６章「ピコリン酸アリルのアリル化反応を活用した, 光学活性なイミダゾリウム塩とピリジニウム塩の合成」

６−１．緒言

光学活性な側鎖を持つイミダゾリウム塩は不斉触媒や新しい有機材料として大変注目されている[1]。従来、それらは不斉中心を持つアルキルハライド等の求電子剤とイミダゾールの *N*–ジアルキル化、又は、*N*–アルキルイミダゾールの *N*–アルキル化によって合成されてきた (Scheme 1)[2]。しかし、光学活性な側鎖の不斉中心は、イミダゾールの窒素原子から２つまたはそれ以上の炭素数で離れている事が多い。一方、Zincke 反応は *N*–2,4–ジニトロフェニル基で活性化したイミダゾール環に第１級アミン (RNH_2) を付加脱離させる反応であり、第１級アミン由来の窒素原子がイミダゾール環に組み込まれ、隣接する炭素に不斉中心を持つイミダゾリウム塩が合成できる[3]。

Scheme 1. Previous syntheses of chiral imidazolium salts.

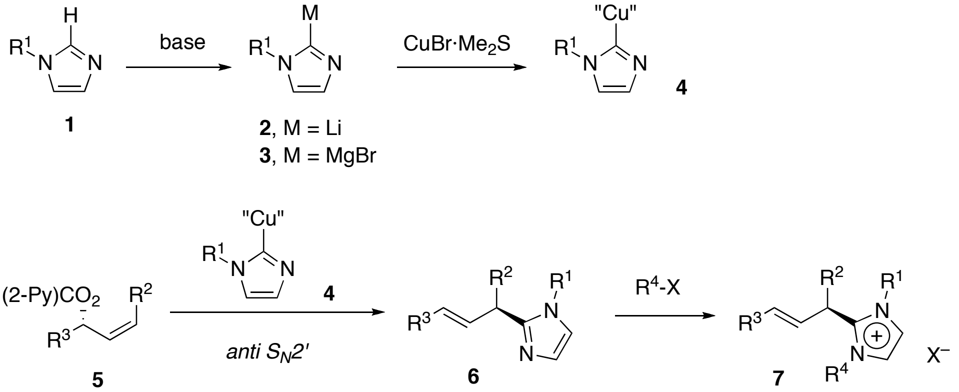


こうして合成した光学活性なイミダゾリウム塩は主として、触媒として使用されてきたが、”光学活性” という特徴を活かした新しい材料の開発に使用することも可能である。しかし、前述の方法だけでは合成できるイミダゾリウム塩の構造が限られてしまう。そこで、著者はイミダゾール C2 位の水素原子が容

易に脱プロトン化されることに着目し、C2 位にアニオンをもつイミダゾールアニオンとのアルキル化の可能性について考えた。文献を調査したところ、C2 位でのアルキル化反応について報告があるが、第１級のハロゲン化アルキルに限られ、第２級の(すなわちキラルな)ハロゲン化アルキルとの反応は見あたらなかった。一般に、第２級ハロゲン化アルキルの求核置換反応は立体障害が影響して、効率的に進行しない。イミダゾールアニオンとの反応も例外ではないと思われる。

著者は前章までに、グリニャール試薬または有機リチウム試薬由来の有機銅試薬をピコリン酸アリル化合物に反応させると、高い選択性でアンチ S_N2' 生成物が得られる事を見出している。さらに、有機リチウム試薬に関しては、様々な調製法が可能である事も分かっている。これらの結果を基に、著者は、（*N*–アルキルイミダゾール-2–イル）銅試薬 **4** をピコリン酸アリル **5** に反応させてイミダゾール **6** とし、更に *N*–アルキル化することで、光学活性な側鎖を持つイミダゾリウム塩 **7** を得る事ができると考えた (Scheme 2)。以下にこれらの検討結果について述べる。

Scheme 2. Synthesis of chiral imidazoles and imidazolium salts through allylic substitution.



６−２．アリル化反応を活用したイミダゾール環への側鎖導入

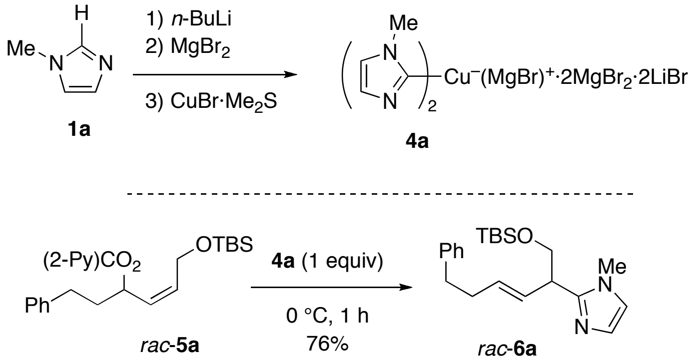
前章までに良好な結果をもたらした有機銅試薬の量関係、「RMgBr : CuBr·Me$_2$S = 2:1」をベースに、*N*–メチルイミダゾール (**1a**, R^1 = Me) のアニオン種 **2a** または **3a** から R$_2$Cu$^-$(MgBr)$^+$ 型の銅試薬を調製する事を試みた。アニオン **2a** または **3a** を得る際の方法として、(1) **1a** の 2 位のプロトンを引き抜く、(2) 2–ブロモイミダゾール体 **8a** の Br–メタル交換 [4] が考えられる。しかし、Figure 1 に例を示す様に、2–ブロモイミダゾール誘導体 **8** は対応するイミダゾール **1** に比べて高価であるか入手性が悪い。そこで、(1) の方法でイミダゾールのアニオン **2a** または **3a** を調製する事を試みた。

Figure 1. Prices of some imidazoles.

1a	**8a** (bromide of **1a**)	**1b**	**8b** (bromide of **1b**)
$ 400 / 3 kg (Aldrich)	$ 458 / 5 g (Aldrich)	$ 100 / 25 g (Aldrich)	not available (Aldrich)

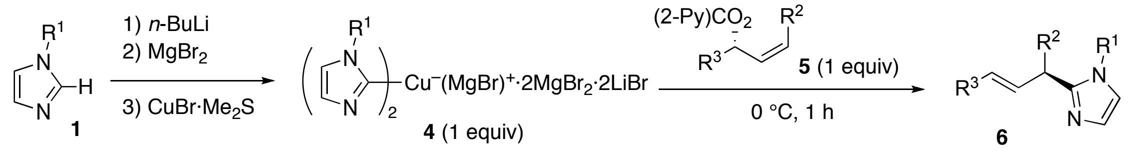
まずはじめに、グリニャール試薬 (EtMgBr または *t*-BuMgCl) を用いて *N*–アルキルイミダゾールの C2 位をマグネシオ化してアリル化を試みたが、生成物は得られなかった。そこで、より強い塩基である *n*-BuLi を用いて **1a** をリチオ化すると、リチウムアニオン **2a** と思われる赤色溶液が生じた。さらに CuBr·Me$_2$S を加え、銅試薬 **2a**/Cu (2/1) へ変換した。第５章の結果 (*Requirement 1*: MgBr$_2$ > Li$^+$) に従い 3 当量の MgBr$_2$ を添加し、**4a** を *rac*-**5a** と 0 °C で 1 時間反応させると、反応は完結しており、収率 76%, 位置選択性 >98 : 2 と高い S$_N$2’ 選択性で *rac*-**6a** を得る事が出来た (Scheme 3)。オレフィンの立体はトランス型であった($J_{CH=CH}$ = 15 Hz)。つまり、イミダゾール **1** と *n*-BuLi から調製したリチウム塩 **2** を経由して合成した銅試薬 **4** が、ピコリン酸アリルのアリル化に有効である事を明らかにできた。

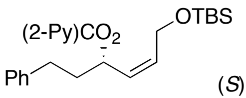
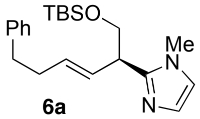
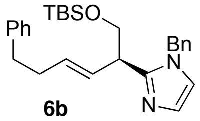
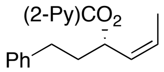
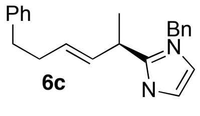
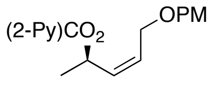
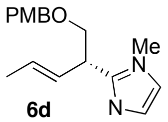
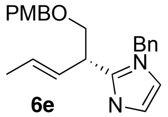
Scheme 3. Prelininary result.



そこで、ラセミ体の結果を基に、光学活性なピコリン酸アリル (*S*)-**5a**,**b** と (*R*)-**5c** に対してイミダゾール環の導入を行った。その結果を Table 1 に示す。

Table 1. Allylation of picolinates with imidazol-2-yl copper reagents 4.[a]



entry	allyl picolinate (% ee)	imidazole **1**	anti S_N2' product		
			structure	CT, %	yield, %
1	 (*S*)-**5a** (97% ee)	**1a** (R^1 = Me)	 **6a**	98	81
2	(*S*)-**5a** (95% ee)	**1b** (R^1 = Bn)	 **6b**	99	89
3	 (*S*)-**5b** (94% ee)	**1b**	 **6c**	98	81
4	 (*R*)-**5c** (98% ee)	**1a**	 **6d**	95	82
5	(*R*)-**5c** (98% ee)	**1b**	 **6e**	96	86

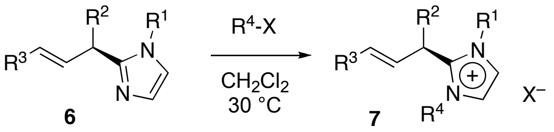
[a] Regioselectivities for all of the reactions were > 98% by ^{1}H NMR spectroscopy.

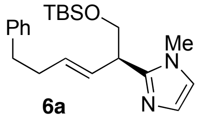
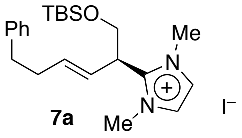
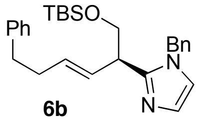
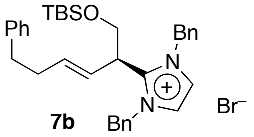
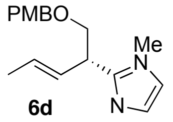
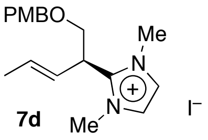
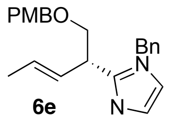
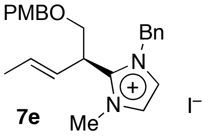
ピコリン酸アリル (*S*)-**5a** (97% ee) を **4a** でアリル化すると **6a** (95% ee) が得られ、不斉転写率は 98% CT と良好であった (Table 1, entry 1)。置換基 R^1 にメチル基より大きいベンジル基を持つイミダゾール **1b** についても、反応の収率や位置・立体選択性に影響は見られなかった (entry 2)。さらに、ピコリン酸アリルの置換基 R^2, R^3 についても、反応効率に影響を及ぼさず良好な結果を与えた (entries 3–5)。なお、行った全ての反応の不斉転写は良好であり (> 95%)、前章までの結果からアンチ S_N2' 生成物の立体化学であると類推している。

６−３．イミダゾリウム塩への変換

前セクションで得られた光学活性なイミダゾール誘導体 **6** を *N*–アルキル化して、イミダゾリウム塩 **7** を合成する検討を行った。その際、得られた誘導体の性状に関しても留意した。まず、**6** に対してアルキルハライドを作用させた。イミダゾールの反応点隣の C2 位に嵩高い置換基がある為に反応が進行しない恐れはあったが、過剰量の R^4-X 存在下、CH_2Cl_2 溶媒中 30 °C で一昼夜から数日の間に原料は消失し、良好な収率で **7** を得る事が出来た (Table 2)。Table 2 に示すように、２つのイミダゾール環窒素原子には同一または異なるアルキル基を持つものを選んで合成可能であり、**7d** と **7e** の比較から、２つの窒素原子には同一置換基を有している方が結晶性が良いと考えられる (entries 3, 4)。

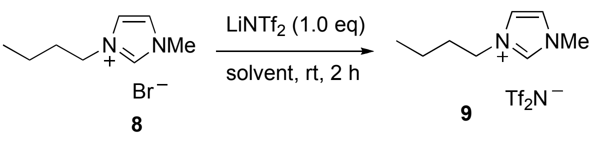
Table 2. *N*-Alkylation of imidazoles 6.



			product		
entry	substrate	R^4-X	structure	yield, %	
1	 **6a**	MeI	 **7a**	85	pale-yellow solid mp 97-98 °C
2	 **6b**	BnBr	 **7b**	100	white amorphous
3	 **6d**	MeI	 **7d**	87	yellow solid mp 99-100 °C
4	 **6e**	MeI	 **7e**	84	yellow syrup

次に、得られたイミダゾールのハロゲン塩 **7** の塩交換について検討し、塩交換が可能かどうか、また物性に変化があるかを見ることにした。塩交換反応については様々な条件での反応が報告されているが、**7** のような複雑で大きな分子を効率的に変換できる反応の速い条件を見出すべきと考えた。そこで、共に市販品である **8**, **9** をモデル化合物として、塩交換反応を検討した (Scheme 4)。

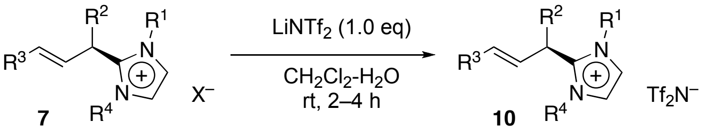
Scheme 4. Reaction to 9 from 8.

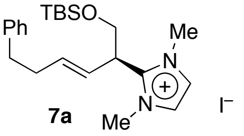
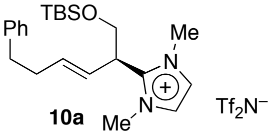
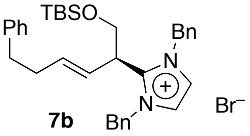
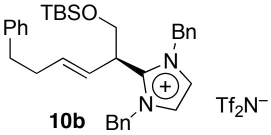
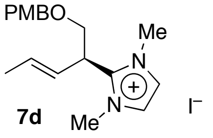
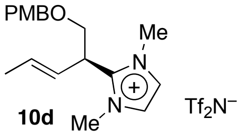
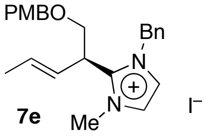
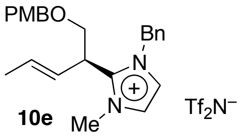


solvent
CH_2Cl_2-H_2O (1:1) : complete
acetone-H_2O (1:1) : not complete
acetone : too slow

3 種類の溶媒系を用いて、臭化物塩 **8** に 1 当量の $LiNTf_2$ を作用させ、室温で 2 時間撹拌した。反応は TLC を用いてモニタリングした。溶媒がアセトンのみ、またはアセトン–水 (1 : 1) の時は反応は完結しなかったが、二層系である塩化メチレン–水 (1 : 1) 溶媒の時、反応は完結し **9** が生成した。よって、塩化メチレン–水 (1 : 1) 溶媒を用いて **7** の塩交換を行う事にした。その結果、室温で数時間撹拌すると、イミダゾール誘導体 **7** の塩交換は円滑に進行した (Table 3)。また、ビストリフルオロメタンスルフォニルイミド塩 **10** は、ハロゲン塩 **7** の性状に関わらずオイル状の物質として得られた (entries 1–4)。

Table 3. Transformation of 7 to 10.



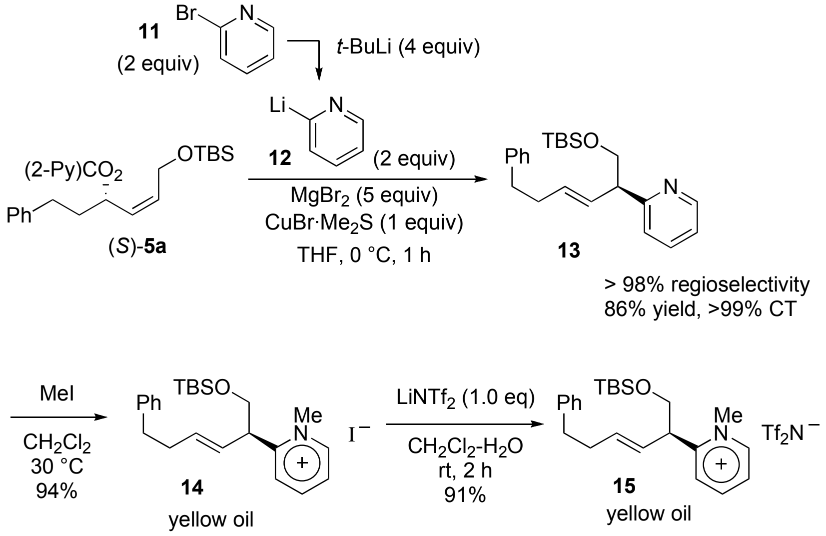
			product		
entry	substrate		structure	yield, %	
1	 **7a**	pale-yellow solid mp 97-98 °C	 **10a**	86	yellow oil
2	 **7b**	white amorphous	 **10b**	88	yellow oil
3	 **7d**	yellow solid mp 99-100 °C	 **10d**	100	yellow oil
4	 **7e**	yellow syrup	 **10e**	78	yellow oil

６−４．光学活性な側鎖を持つピリジニウム塩の合成

前セクションまでに、著者はイミダゾールの４級塩を得る方法を確立した。

そこで、その知見を生かして、光学活性な側鎖を有するピリジニウム塩の合成を検討する事にした (Scheme 5)。

Scheme 5. Synthesis of pyridinium salt 15.



第５章の知見を基に、2–ブロモピリジン **11** と *t*-BuLi から得られる **12** (2 当量) に 1 当量の CuBr·Me$_2$S と 5 当量の MgBr$_2$ を加え銅試薬を調製し、(*S*)-**5a** と 0 °C で 1 時間反応させた。反応は完結しており、収率 86%、高い位置及び立体選択性で **13** を得る事が出来た。さらに、MeI による４級化と塩交換も高い収率で進行し、高効率的にピリジニウム塩 **15** を合成できる事を示せた。

６−５．結論

本章では、これまで例が知られていない反応形式により、新規なイミダゾリウム塩およびピリジニウム塩の構築法を確立した。これらの塩は対アニオンを Tf$_2$N$^-$ にすることで室温でも液体として存在し、新しいイオン液体と考えられる。さらに、得られたイミダゾール誘導体の側鎖には二重結合の他にも官能基を有する事ができ、更なる誘導体に変換するなど、新規４級塩の合成とその応用展開が期待できる。

Experimental section

Allylic Substitution.

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(1-methyl-1*H*-imidazol-2-yl)-6-phenyl-3-hexene (6a).

(Table 1, entry 1) To an ice-cold solution of 1-methylimidazole (0.017 mL, 0.210 mmol) in THF (1.5 mL) was added *n*-BuLi (0.13 mL, 1.60 M in hexane, 0.21 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and $CuBr·Me_2S$ (20.6 mg, 0.100 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**5a** (41.2 mg, 0.100 mmol, 97% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6a** (30.1 mg, 81%): IR (neat) 1492, 1471, 1255, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.05 (s, 3 H), –0.01 (s, 3 H), 0.84 (s, 9 H), 2.35 (dt, *J* = 7, 8 Hz, 2 H), 2.68 (t, *J* = 8 Hz, 2 H), 3.53 (s, 3 H), 3.58 (ddd, *J* = 8, 8, 7 Hz, 1 H), 3.87 (dd, *J* = 10, 7 Hz, 1 H), 3.93 (dd, *J* = 10, 8 Hz, 1 H), 5.51 (dt, *J* = 15, 7 Hz, 1 H), 5.68 (dd, *J* = 15, 8 Hz, 1 H), 6.75 (d, *J* = 1 Hz, 1 H), 6.96 (d, *J* = 1 Hz, 1 H), 7.12–7.21 (m, 3 H), 7.22–7.31 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.4 (–), 18.3 (+), 25.9 (–), 32.6 (–), 34.4 (+), 35.7 (+), 43.5 (–), 66.7 (+), 120.3 (–), 125.9 (–), 127.3 (–), 128.3 (–), 128.4 (–), 128.5 (–), 132.4 (–), 141.9 (+), 148.2 (+); HRMS (FAB) calcd for $C_{22}H_{35}N_2OSi$ (M^+) 370.2519, found 371.2516. The enantiomeric information (95% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 98/2, 0.5 mL/min, rt; t_R (min) = 28.1 (*R*), 49.5 (*S*).

(*R*,*E*)-2-(1-Benzyl-1*H*-imidazol-2-yl)-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-3-hexene (6b).

(Table 1, entry 2) To an ice-cold solution of 1-benzyl-1*H*-imidazole (31.6 mg, 0.200 mmol) in THF (1.5 mL) was added *n*-BuLi (0.110 mL, 1.60 M in hexane, 0.176 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol) and $CuBr·Me_2S$ (18.7 mg, 0.0910 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**5a** (37.4 mg, 0.0909 mmol, 95% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6b** (36.1 mg, 89%): IR (neat) 1256, 1101, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.06 (s, 3 H), –0.02 (s, 3 H), 0.83 (s, 9 H), 2.27 (dt, *J* = 7, 8 Hz, 2 H), 2.60 (t, *J* = 8 Hz, 2 H), 3.52 (ddd, *J* = 8, 8, 8 Hz, 1 H), 3.85 (dd, *J* = 10, 8 Hz, 1 H), 3.95 (dd, *J* = 10, 8 Hz, 1 H), 5.00 (d, *J* = 16 Hz, 1 H), 5.12 (d, *J* = 16 Hz, 1 H), 5.36 (dt, *J* = 16, 7 Hz, 1 H), 5.62 (dd, *J* = 16, 8 Hz, 1 H), 6.79 (d, *J* = 1 Hz, 1 H), 6.99–7.06 (m, 3 H), 7.09–7.20 (m, 3 H), 7.22–7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.4 (–), 18.3 (+), 25.9 (–), 34.3 (+), 35.6 (+), 43.8 (–), 49.2 (+), 66.5 (+), 119.7 (–), 125.8 (–), 126.7 (–), 127.7 (–), 127.8 (–), 128.3 (–), 128.4 (–), 128.5 (–), 128.9 (–), 132.5 (–), 136.9 (+), 141.9 (+), 148.3 (+); HRMS (FAB) calcd for $C_{28}H_{38}N_2OSiNa$ [$(M + Na)^+$] 469.2651, found 469.2649. The enantiomeric information (94% ee, 99% CT) was determined by chiral HPLC analysis of the corresponding alcohol: Chiralcel OJ-H; hexane/*i*-PrOH = 97/3, 0.5 mL/min, 40 °C; t_R (min) = 85.3 (*R*), 100.8 (*S*).

(*R*,*E*)-5-(1-Benzyl-1*H*-imidazol-2-yl)-1-phenyl-3-hexene (6c).

(Table 1, entry 3) To an ice-cold solution of 1-benzyl-1*H*-imidazole (42.8 mg, 0.271 mmol) in THF (1.2 mL) was added *n*-BuLi (0.15 mL, 1.60 M in hexane, 0.24 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.80 mL, 0.20 M in THF, 0.360 mmol) and $CuBr·Me_2S$ (25.3 mg, 0.123 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**5b** (34.6 mg, 0.123 mmol, 94% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6c** (31.5 mg, 81%): IR (neat) 1735, 1496, 1453, 1243, 730, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, *J* = 7 Hz, 3 H), 2.26 (dt, *J* = 7, 7 Hz, 2 H), 2.60 (t, *J* = 7 Hz, 2 H), 3.42 (dq, *J* = 7, 7 Hz, 1 H), 4.99 (s, 2 H), 5.35 (dt, *J* = 15, 7 Hz, 1 H), 5.54 (dd, *J* = 15, 7 Hz, 1 H), 6.79 (d, *J* = 1 Hz, 1 H), 6.96–7.04 (m, 3 H), 7.09–7.21 (m, 3 H), 7.22–7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8 (–), 33.9 (+), 35.2 (–), 35.6 (+), 49.1 (+), 120.1 (–), 125.9 (–), 126.6 (–), 127.4 (–), 127.9 (–), 128.3 (–), 128.5 (–), 128.9

(–), 129.8 (–), 132.9 (–), 136.8 (+), 141.8 (+), 150.5 (+); HRMS (FAB) calcd for $C_{22}H_{25}N_2$ [(M + H)$^+$] 317.2018, found 317.2017. The enantiomeric information (92% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 90/10, 0.4 mL/min, rt; t_R (min) = 41.5 (*S*), 45.0 (*R*).

(*S*,*E*)-5-[(4-Methoxybenzyl)oxy]-4-(1-methyl-1*H*-imidazol-2-yl)-2-pentene (6d).

(Table 1, entry 4) To an ice-cold solution of 1-methylimidazole (0.014 mL, 0.176 mmol) in THF (0.8 mL) was added *n*-BuLi (0.10 mL, 1.60 M in hexane, 0.16 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.20 mL, 0.20 M in THF, 0.24 mmol) and CuBr·Me_2S (16.7 mg, 0.0812 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**5c** (26.5 mg, 0.0814 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6d** (19.2 mg, 82%): IR (neat) 1512, 1248, 1097, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6 Hz, 3 H), 3.54 (s, 3 H), 3.68 (ddd, *J* = 8, 7, 7 Hz, 1 H), 3.73–3.90 (m, 2 H), 3.79 (s, 3 H), 4.40 (s, 2 H), 5.46 (dq, *J* = 15, 6 Hz, 1 H), 5.63 (dd, *J* = 15, 8 Hz, 1 H), 6.77 (br s, 1 H), 6.85 (d, *J* = 9 Hz, 2 H), 6.97 (br s, 1 H), 7.19 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (–), 32.6 (–), 41.3 (–), 55.3 (–), 72.7 (+), 73.0 (+), 109.1 (+), 113.8 (–), 120.5 (–), 127.2 (–), 127.9 (–), 128.7 (–), 129.3 (–), 130.5 (+), 159.2 (+); HRMS (FAB) calcd for $C_{17}H_{23}N_2O_2$ [(M + H)$^+$] 287.1760, found 287.1757. The enantiomeric information (93% ee, 95% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 90/10, 0.5 mL/min, rt; t_R (min) = 22.9 (*R*), 26.9 (*S*).

(*S*,*E*)-4-(1-Benzyl-1*H*-imidazol-2-yl)-5-[(4-methoxybenzyl)oxy]-2-pentene (6e).

(Table 1, entry 5) To an ice-cold solution of 1-benzyl-1*H*-imidazole (27.6 mg, 0.160 mmol) in THF (0.8 mL) was added *n*-BuLi (0.10 mL, 1.60 M in hexane, 0.16 mmol) slowly. After 30 min at 0 °C, a solution of $MgBr_2$ (1.20 mL, 0.20 M in THF, 0.24 mmol) and CuBr·Me_2S (16.3 mg, 0.0793 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**5c** (25.8 mg, 0.0793 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **6e** (24.6 mg, 86%): IR (neat) 1513, 1248, 1096, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (dd, *J* = 7, 1 Hz, 3 H), 3.65 (ddd, *J* = 8, 7, 7 Hz, 1 H), 3.75 (dd, *J* = 9, 7 Hz, 1 H), 3.79 (s, 3 H), 3.83 (dd, *J* = 9, 8 Hz, 1 H), 4.40 (s, 2 H), 5.04 (d, *J* = 16 Hz, 1 H), 5.11 (d, *J* = 16 Hz, 1 H), 5.34 (dq, *J* = 15, 7 Hz, 1 H), 5.59 (ddq, *J* = 15, 7, 1 Hz, 1 H), 6.78 (br s, 1 H), 6.84 (d, *J* = 9 Hz, 2 H), 7.00–7.06 (m, 3 H), 7.16 (d, *J* = 9 Hz, 2 H), 7.25–7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (–), 41.4 (–), 49.3 (+), 55.3 (–), 72.8 (+), 72.9 (+), 113.7 (–), 119.8 (–), 126.9 (–), 127.7 (–), 127.9 (–), 128.0 (–), 128.4 (–), 128.9 (–), 129.3 (–), 130.5 (+), 136.7 (+), 148.3 (+), 159.2 (+); HRMS (FAB) calcd for $C_{23}H_{27}N_2O_2$ [(M + H)$^+$] 363.2073, found 363.2063. The enantiomeric information (94% ee, 96% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, 40 °C; t_R (min) = 38.0 (*R*), 40.4 (*S*).

Synthesis of imidazolium salt 7.

(*R*,*E*)-2-[1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-1,3-dimethyl-1*H*-imidazol-3-ium Iodide (7a).

(Table 2, entry 1) A solution of **6a** (24.4 mg, 0.0658 mmol) and methyl iodide (0.008 mL, 0.13 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 30 °C overnight and concentrated. The residue was washed with hexane-Et_2O (3 : 1, 5 mL) three times and dried under vacuum to afford **7a** (28.7 mg, 85%): mp. 97–98 °C; $[\alpha]^{24}_D$ +19 (*c* 0.43, $CHCl_3$); IR (nujor) 3083, 1111, 838, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.02 (s, 3 H), 0.01 (s, 3 H), 0.77 (s, 9 H), 2.46 (dt, *J* = 7, 7 Hz, 2 H), 2.74 (t, *J* = 7 Hz, 2 H), 3.88 (s, 6 H), 3.93 (dd, *J* = 10, 9 Hz, 1 H), 4.01 (dd, *J* = 10, 5 Hz, 1 H), 4.26–4.39 (m, 1 H), 5.60 (dd, *J* = 16, 8 Hz, 1 H), 5.77 (dt, *J* = 16, 7 Hz, 1 H), 7.11–7.32 (m, 5 H), 7.74 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.6 (–), –5.5 (–), 18.0 (+), 25.6 (–), 34.1 (+), 34.7 (+), 37.0 (–), 41.1 (–), 63.1 (+), 121.4 (–), 123.7 (–), 126.2 (–), 128.48 (–), 128.52 (–), 136.7 (–), 140.1 (+), 145.6 (+).

(*R*,*E*)-1,3-Bibenzyl-2-[1-[(*tert*-butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-1*H*-imidazol-3-ium Bromide (7b).

(Table 2, entry 2) A solution of **6b** (19.0 mg, 0.0425 mmol) and benzyl bromide (0.020 mL, 0.168 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 30 °C for 2 days and concentrated. The residue was washed with hexane-Et_2O (1 : 1, 5 mL) three times and dried under vacuum to afford **7b** (26.3 mg, 100%): $[\alpha]^{27}_{D}$ +15 (*c* 0.54, $CHCl_3$); IR (neat) 1254, 1101, 838, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.07 (s, 3 H), –0.04 (s, 3 H), 0.81 (s, 9 H), 2.26 (dt, *J* = 8, 7 Hz, 2 H), 2.55 (t, *J* = 7 Hz, 2 H), 3.76 (d, *J* = 7 Hz, 2 H), 4.40 (dt, *J* = 6, 7 Hz, 1 H), 5.35–5.47 (m, 1 H), 5.45–5.60 (m, 1 H), 5.48 (d, *J* = 16 Hz, 1 H), 5.58 (d, *J* = 16 Hz, 1 H), 7.05 (d, *J* = 7 Hz, 2 H), 7.12–7.29 (m, 7 H), 7.34–7.44 (m, 6 H), 7.70 (s, 2 H);^{13}C NMR (75 MHz, $CDCl_3$) δ –5.5 (–), 18.2 (+), 25.8 (–), 33.9 (+), 34.6 (+), 41.4 (–), 52.8 (+), 63.6 (+), 121.6 (–), 123.3 (–), 126.1 (–), 127.8 (–), 128.40 (–), 128.44 (–), 129.2 (–), 129.5 (–), 133.4 (+), 136.8 (–), 141.0 (+), 146.2 (+).

(*S*,*E*)-1,3-Dimethyl-2-[1-[(4-methoxybenzyl)oxy]pent-3-en-2-yl]-1*H*-imidazol-3-ium Iodide (7d).

(Table 2, entry 3) A solution of **6d** (14.4 mg, 0.0503 mmol) and methyl iodide (0.010 mL, 0.16 mmol) in CH_2Cl_2 (1 mL) was stirred at 30 °C for 2 days and concentrated. The residue was washed with hexane-Et_2O (1 : 1, 5 mL) three times and dried under vacuum to afford **7d** (18.7 mg, 87%): mp. 99–100 °C; $[\alpha]^{27}_{D}$ –20 (*c* 0.37, $CHCl_3$); IR (nujol) 1513, 1242, 1089, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6 Hz, 3 H), 3.80–3.98 (m, 2 H), 3.82 (s, 3 H), 3.93 (s, 6 H), 4.36–4.46 (m, 1 H), 4.38 (d, *J* = 12 Hz, 1 H), 4.47 (d, *J* = 12 Hz, 1 H), 5.60 (dd, *J* = 16, 5 Hz, 1 H), 5.68 (dq, *J* = 16, 6 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.10 (d, *J* = 8 Hz, 2 H), 7.74 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (–), 37.2 (–), 39.1 (–), 55.4 (–), 68.2 (+), 73.0 (+), 114.0 (–), 121.5 (–), 123.7 (–), 128.8 (+), 129.6 (–), 132.6 (–), 145.4 (+), 159.6 (+).

(*S*,*E*)-1-Benzyl-2-[1-[(4-methoxybenzyl)oxy]pent-3-en-2-yl]-3-methyl-1*H*-imidazol-3-ium Iodide (7e).

(Table 2, entry 4) A solution of **6e** (14.6 mg, 0.0403 mmol) and methyl iodide (0.005

mL, 0.0803 mmol) in CH_2Cl_2 (1 mL) was stirred at 30 °C overnight and concentrated. The residue was washed with hexane-Et_2O (1 : 1, 5 mL) three times and dried under vacuum to afford **7e** (17.1 mg, 84%): $[\alpha]^{25}_{D}$ –21 (*c* 0.342, $CHCl_3$); IR (neat) 1611, 1513, 1457, 1248, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63–1.68 (m, 3 H), 3.72–3.84 (m, 2 H), 3.82 (s, 3 H), 3.96 (s, 3 H), 4.33 (d, *J* = 12 Hz, 1 H), 4.41 (d, *J* = 12 Hz, 1 H), 4.34–4.46 (m, 1 H), 5.41 (d, *J* = 15 Hz, 1 H), 5.48–5.62 (m, 2 H), 5.54 (d, *J* = 15 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.10 (d, *J* = 9 Hz, 2 H), 7.14–7.22 (m, 2 H), 7.31–7.40 (m, 3 H), 7.46 (d, *J* = 2 Hz, 1 H), 7.84 (d, *J* = 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (–), 37.6 (–), 39.2 (–), 52.8 (+), 55.4 (–), 68.5 (+), 73.1 (+), 114.1 (–), 121.6 (–), 122.4 (–), 124.4 (–), 127.9 (–), 128.9 (+), 129.2 (–), 129.4 (–), 129.7 (–), 132.7 (–), 133.0 (+), 145.8 (+), 159.6 (+). HRMS (FAB) calcd for $C_{24}H_{29}N_2O_2$ (M^+) 377.2229, found 377.2219.

Synthesis of imidazol-3-ium bis(trifluoromethylsulfonyl)imides 10.

(*R*,*E*)-2-[1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-1,3-dimethyl-1*H*-imidazol-3-ium Bis(trifluoromethylsulfonyl)imide (10a).

(Table 3, entry 1) A solution of **7a** (28.7 mg, 0.056 mmol) and $LiNTf_2$ (16.4 mg, 0.0571 mmol) in CH_2Cl_2-H_2O (1 : 1, 2 mL) was stirred at rt for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give **10a** (32.2 mg, 86%): $[\alpha]^{26}_{D}$ +17 (*c* 0.64, $CHCl_3$); IR (neat) 1353, 1194, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.02 (s, 3 H), 0.003 (s, 3 H), 0.76 (s, 9 H), 2.45 (dt, *J* = 7, 7 Hz, 2 H), 2.73 (t, *J* = 7 Hz, 2 H), 3.69 (s, 6 H), 3.89 (dd, *J* = 10, 9 Hz, 1 H), 3.99 (dd, *J* = 10, 6 Hz, 1 H), 4.14–4.24 (m, 1 H), 5.49 (dd, *J* = 16, 5 Hz, 1 H), 5.69 (ddt, *J* = 16, 2, 7 Hz, 1 H), 7.11–7.30 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.8 (–), –5.7 (–), 17.9 (+), 25.6 (–), 34.1 (+), 34.7 (+), 36.3 (–), 41.1 (–), 62.9 (+), 120.0 (+, q, $J_{C\text{–}F}$ = 320 Hz), 121.0 (–), 123.3 (–), 126.2 (–), 128.5 (–), 128.6 (–), 136.8 (–), 141.1 (+), 145.9 (+).

(*R*,*E*)-1,3-Bibenzyl-2-[1-[(*tert*-butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-1*H*-

imidazol-3-ium Bis(trifluoromethylsulfonyl)imide (10b).

(Table 3, entry 2) A solution of **7b** (26.5 mg, 0.0429 mmol) and $LiNTf_2$ (13 mg, 0.045 mmol) in CH_2Cl_2-H_2O (1 : 1, 2 mL) was stirred at rt for 4 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$, and concentrated to give **10b** (30.7 mg, 87%): $[\alpha]^{21}_{D}$ +7 (*c* 0.61, $CHCl_3$); IR (neat) 1353, 1196, 1137, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.06 (s, 3 H), –0.02 (s, 3 H), 0.81 (s, 9 H), 2.28 (dt, *J* = 6, 7 Hz, 2 H), 2.56 (t, *J* = 7 Hz, 2 H), 3.72–3.84 (m, 2 H), 4.24 (dt, *J* = 7, 6 Hz, 1 H), 5.28 (s, 4 H), 5.38 (dt, *J* = 16, 6 Hz, 1 H), 5.46 (dd, *J* = 16, 7 Hz, 1 H), 7.06 (d, *J* = 7 Hz, 2 H), 7.11–7.28 (m, 7 H), 7.34–7.45 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.6 (–), 18.2 (+), 25.8 (–), 33.9 (+), 34.5 (+), 41.4 (–), 52.8 (+), 63.4 (+), 119.9 (+, q, J_{C-F} = 320 Hz), 121.1 (–), 122.8 (–), 126.1 (–), 127.6 (–), 128.46 (–), 128.48 (–), 129.5 (–), 129.6 (–), 132.8 (+), 137.0 (–), 141.0 (+), 146.3 (+).

(*S*,*E*)-1,3-Dimethyl-2-[1-[(4-methoxybenzyl)oxy]pent-3-en-2-yl]-1*H*-imidazol-3-ium Bis(trifluoromethylsulfonyl)imide (10d).

(Table 3, entry 3) A solution of **7d** (18.4 mg, 0.0430 mmol) and $LiNTf_2$ (12.6 mg, 0.044 mmol) in CH_2Cl_2-H_2O (1 : 1, 2 mL) was stirred at rt for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give **10d** (25.0 mg, 100%): $[\alpha]^{25}_{D}$ –21 (*c* 0.48, $CHCl_3$); IR (neat) 1514, 1354, 1196, 1138, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (ddd, *J* = 6, 2, 1 Hz, 3 H), 3.75 (s, 6 H), 3.74–3.86 (m, 2 H), 3.80 (s, 3 H), 4.19–4.30 (m, 1 H), 4.34 (d, *J* = 12 Hz, 1 H), 4.44 (d, *J* = 12 Hz, 1 H), 5.52 (ddq, *J* = 16, 5, 2 Hz, 1 H), 5.67 (ddq, *J* = 16, 2, 6 Hz, 1 H), 6.86 (d, *J* = 9 Hz, 2 H), 7.07 (d, *J* = 9 Hz, 2 H), 7.23 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (–), 36.4 (–), 39.2 (–), 55.4 (–), 68.0 (+), 73.0 (+), 114.0 (–), 119.9 (+, q, J_{C-F} = 320 Hz), 121.1 (–), 123.4 (–), 128.9 (+), 129.7 (–), 132.8 (–), 145.6 (+), 159.7 (+).

(*S*,*E*)-1-Benzyl-2-[1-[(4-methoxybenzyl)oxy]pent-3-en-2-yl]-3-methyl-1*H*-imidazol-3-ium Bis(trifluoromethylsulfonyl)imide (10e).

(Table 3, entry 4) A solution of **7e** (17.6 mg, 0.0349 mmol) and $LiNTf_2$ (10.2 mg, 0.036 mmol) in CH_2Cl_2-H_2O (1 : 1, 2 mL) was stirred at rt for 4 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give **10e** (17.9 mg, 78%): $[\alpha]^{24}_D$ –19 (*c* 0.38, $CHCl_3$); IR (neat) 1515, 1354, 1194, 1137, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–1.69 (m, 3 H), 3.71 (dd, J = 9, 9 Hz, 1 H), 3.77 (dd, J = 9, 5 Hz, 1 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.24–4.33 (m, 1 H), 4.30 (d, J = 12 Hz, 1 H), 4.39 (d, J = 12 Hz, 1 H), 5.21 (d, J = 15 Hz, 1 H), 5.31 (d, J = 15 Hz, 1 H), 5.42–5.60 (m, 2 H), 6.86 (d, J = 8 Hz, 2 H), 7.04–7.13 (m, 5 H), 7.26–7.40 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (–), 36.7 (–), 39.2 (–), 52.6 (+), 55.4 (–), 68.2 (+), 73.1 (+), 114.1 (–), 119.9 (+, q, J_{C-F} = 320 Hz), 121.2 (–), 122.1 (–), 124.0 (–), 127.7 (–), 128.8 (+), 129.4 (–), 129.5 (–), 129.8 (–), 132.7 (+), 132.8 (–), 145.8 (+), 159.7 (+).

Synthesis of Pyridinium salt. (Scheme 5)

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenyl-2-(pyridine-2-yl)-3-hexene (13).

To a solution of 2-bromopyridine (0.020 mL, 0.210 mmol) in Et_2O (1 mL) was added *t*-BuLi (0.24 mL, 1.57 M in pentane, 0.377 mmol) slowly at –78 °C. After 30 min at –78 °C, a solution of $MgBr_2$ (2.40 mL, 0.20 M in THF, 0.480 mmol) and $CuBr{\cdot}Me_2S$ (19.5 mg, 0.0949 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**5a** (39.0 mg, 0.0947 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **13** (29.8 mg, 86%): IR (neat) 1590, 1255, 1097, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.11 (s, 3 H), –0.08 (s, 3 H), 0.79 (s, 9 H), 2.35 (dt, J = 7, 8 Hz, 2 H), 2.68 (t, J = 8 Hz, 2 H), 3.60 (ddd, J = 8, 8, 7 Hz, 1 H), 3.84 (dd, J = 10, 7 Hz, 1 H), 3.95 (dd, J = 10, 8 Hz, 1 H), 5.61 (dt, J = 16, 7 Hz, 1 H), 5.75 (dd, J = 16, 8 Hz, 1 H), 7.06–7.30 (m, 7 H), 7.57 (ddd,

J = 8, 8, 2 Hz, 1 H), 8.55 (d, J = 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.5 (–), –5.4 (–), 18.3 (+), 25.9 (–), 34.7 (+), 35.9 (+), 53.9 (–), 66.9 (+), 121.4 (–), 123.7 (–), 125.8 (–), 128.3 (–), 128.5 (–), 130.0 (–), 132.1 (–), 136.1 (–), 142.1 (+), 149.3 (–), 162.2 (+); HRMS (FAB) calcd for 390.2229 $C_{23}H_{33}NOSiNa$ [(M + Na)$^+$], found 390.2231. The enantiomeric information (98% ee, > 99% CT) was determined by chiral HPLC analysis: Chiralcel AD-H; hexane/*i*-PrOH = 99/1, 0.1 mL/min, rt; t_R (min) = 52.1 (*R*), 60.9 (*S*).

(*R*,*E*)-[1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-2-pyridinium Iodide (14).

A solution of **13** (26.5 mg, 0.0722 mmol) and methyl iodide (0.020 mL, 0.32 mmol) in CH_2Cl_2 (1 mL) was stirred at 30 °C for 2 days and concentrated. The residue was washed with hexane-Et_2O (3 : 1, 5 mL) three times and dried under vacuum to afford **14** (34.7 mg, 94%): $[\alpha]^{23}_D$ +6 (*c* 0.68, $CHCl_3$); IR (neat) 1629, 1254, 1104, 839 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.05 (s, 3 H), –0.01 (s, 3 H), 0.77 (s, 9 H), 2.40 (ddd, J = 7, 7 Hz, 2 H), 2.68 (dt, J = 14, 7 Hz, 1 H), 2.73 (dt, J = 14, 7 Hz, 1 H), 3.84 (dd, J = 10, 8 Hz, 1 H), 4.08 (dd, J = 10, 4 Hz, 1 H), 4.23 (ddd, J = 8, 7, 4 Hz, 1 H), 4.55 (s, 3 H), 5.49 (dd, J = 16, 7 Hz, 1 H), 5.68 (dt, J = 16, 7 Hz, 1 H), 7.07–7.32 (m, 5 H), 7.84 (d, J = 8 Hz, 1 H), 7.99 (dd, J = 8, 6 Hz, 1 H), 8.41 (dd, J = 8, 8 Hz, 1 H), 9.61 (d, J = 6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.6 (–), –5.5 (–), 18.0 (+), 25.7 (–), 34.2 (+), 34.9 (+), 46.2 (–), 47.3 (–), 65.7 (+), 124.6 (–), 126.1 (–), 126.2 (–), 127.4 (–), 128.4 (–), 128.5 (–), 136.6 (–), 140.1 (+), 145.0 (–), 147.4 (–), 159.4 (+).

(*R*,*E*)-[1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenylhex-3-en-2-yl]-2-pyridinium Bis(trifluoromethylsulfonyl)imide (15).

A solution of **14** (34.0 mg, 0.0667 mmol) and $LiNTf_2$ (19.5 mg, 0.0679 mmol) in CH_2Cl_2-H_2O (1 : 1, 2 mL) was stirred at rt for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give **15** (40.2 mg, 91%): $[\alpha]^{24}_D$ +4 (*c* 0.77, $CHCl_3$); IR (neat) 1354, 1197, 1137, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.07 (s, 3 H), –0.01

(s, 3 H), 0.76 (s, 9 H), 2.41 (dt, *J* = 7, 7 Hz, 2 H), 2.70 (t, *J* = 7 Hz, 2 H), 3.81 (dd, *J* = 10, 8 Hz, 1 H), 4.03 (dd, *J* = 10, 5 Hz, 1 H), 4.04–4.15 (m, 1 H), 4.28 (s, 3 H), 5.43 (dd, *J* = 16, 7 Hz, 1 H), 5.64 (dt, *J* = 16, 7 Hz, 1 H), 7.09–7.30 (m, 5 H), 7.78 (dd, *J* = 8, 2 Hz, 1 H), 7.82 (ddd, *J* = 8, 6, 2 Hz, 1 H), 8.33 (dd, *J* = 8, 8 Hz, 1 H), 8.71 (d, *J* = 6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.8 (–), –5.7 (–), 18.0 (+), 25.6 (–), 34.1 (+), 34.8 (+), 46.5 (–), 46.6 (–), 65.8 (+), 119.8 (+, q, $J_{C–F}$ = 320 Hz), 124.3 (–), 126.0 (–), 126.1 (–), 127.6 (–), 128.5 (–), 128.6 (–), 136.8 (–), 141.1 (+), 145.2 (–), 146.7 (–), 159.7 (+).

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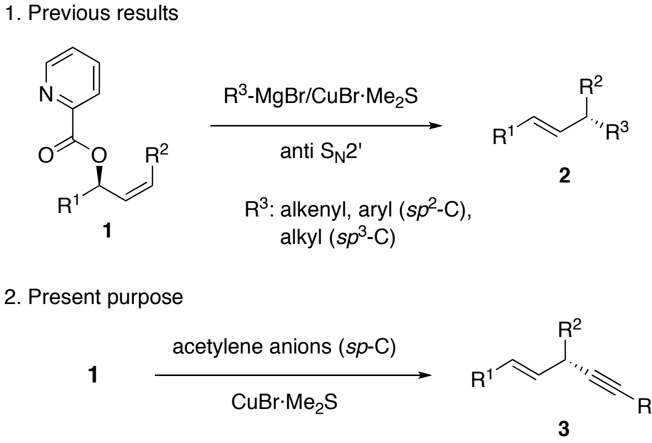
第７章「アルキニル銅試薬を用いたピコリン酸アリルのアリル化反応の開発」

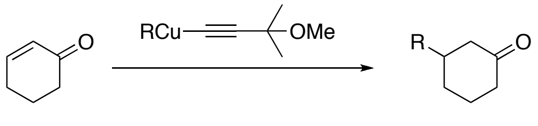
７−１．緒言

これまで著者はピコリン酸基を脱離基としたアリル化反応を見出し、様々なアリール・アルケニル (sp^2-C) 及びアルキル (sp^3-C) 銅試薬が広範囲な基質に適応可能である事を示してきた (Scheme 1)。

Scheme 1. Allylic substitution: previous results and the present purpose.


1. Previous results
2. Present purpose

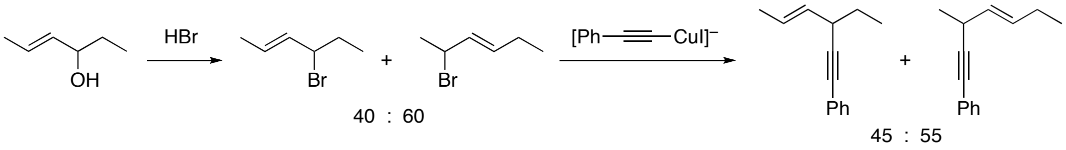
ところで、sp-C であるアルキニル銅試薬はかなり求核性に乏しく，mixed cuprate のダミーリガンドとして使われており(eq 1)[1]、また、一般的にエノンへの 1,4–付加の反応性に乏しい求核剤である。（しかし、近年、1,4–付加反応は報告される様になってきた。）[2]



(1)

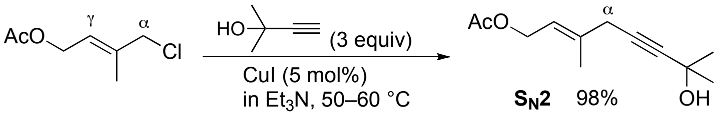
R = *n*-Bu (100%), *i*-C_3H_5 (95%), *t*-Bu (95%)

おそらく同様の理由によると思われるが、アルキニル銅試薬のアリル置換反応は２級アリルアルコール誘導体では前例がなく、より反応性に富む２級のアリル臭素化合物で報告されているだけである (eq 2)[3]。しかしながら、アリル臭化物の調製においてさえ位置選択性が低いため、アリル化自体の位置選択性は不確かなものである。この事から、光学活性体への適応は難しいと思われる。

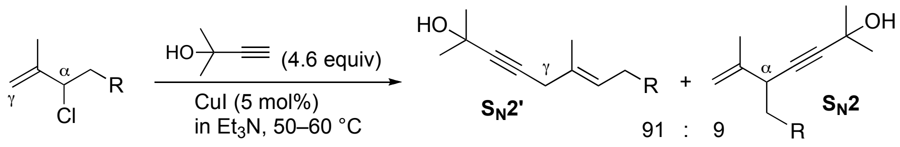


(2)

一方、1–ハロ–2–アルケンや、3–ハロ–1–アルケンの置換反応では、立体的に空いている１級炭素側で反応が起こる (eqs 3, 4)[3,4]。



(3)

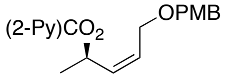


(4)

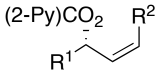
つまり、アルキニル銅試薬を第２級アリルアルコール誘導体に反応させてキラルな炭素–アセチレン結合を構築する実用的な反応条件は開発されていなかった。このような背景から、著者は、炭素求核種の中でも最も求核性に乏しい sp-C アニオンとのアリル化反応を可能にするため，この研究を行った。その足掛りとして，今まで困難だった sp^2-C や求核性の低いチオフェンで成功したピコリン酸脱離基で検討し，その他の脱離基についても検討した。

この研究では、Figure 1 に示すアリルアルコール誘導体を用いて初期検討を行なうことにした。(*R*)-**1a** とそのラセミ体 *rac*-**1a** は高反応性を示すピコリン酸基を有している。一方、ピコリン酸基がベストであるとは言えないため、化合物 **4–9** についても調べることにした。

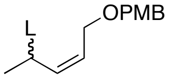
Figure 1. Substrates for the present investigation.



(*R*)-**1a**



(*S*)-**1b**, $R^1 = Ph(CH_2)_2$; $R^2 = CH_2OTBS$
(*S*)-**1c**, $R^1 = Ph(CH_2)_2$; $R^2 = Me$
(*S*)-**1d**, $R^1 = PMBO(CH_2)_3$; $R^2 = C_5H_{11}$
(*S*)-**1e**, $R^1 = PMBO(CH_2)_3$; $R^2 = c\text{-}C_6H_{11}$



(racemic)

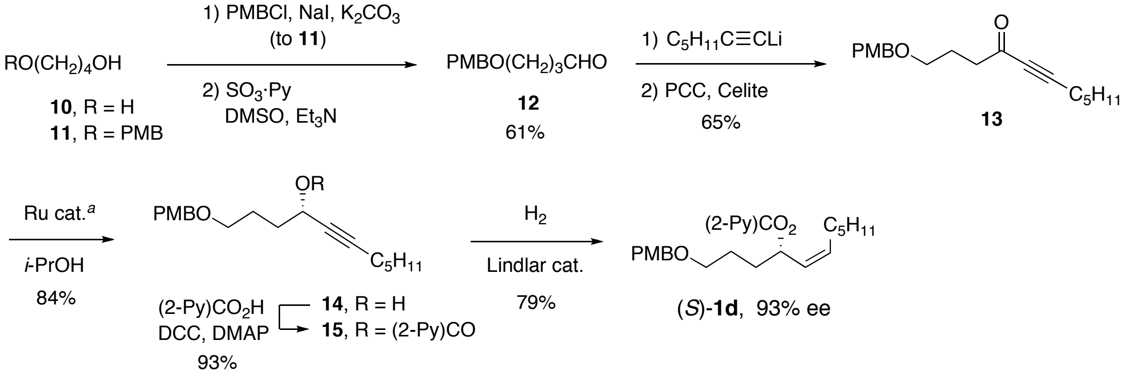
rac-**1a**, L = (2-pyridine)CO_2
4, L = (2-pyrazine)CO_2
5, L = $(EtO)_2P(O)O$
6, L = $C_6F_5CO_2$
7, L = *o*-$(Ph_2P)C_6H_4CO_2$
8, L = $MeOCO_2$
9, L = AcO

７−２．ラセミ体を用いた初期検討

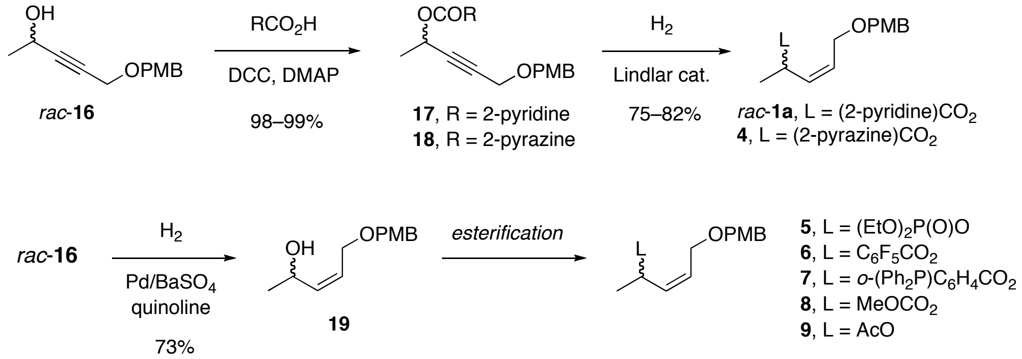
基質のうち、(*R*)-**1a**, *rac*-**1a**, (*S*)-**1b**, **-1c**, **-1e** は第５章で合成したものを用いた。その他の基質も同様の方法で合成し，その結果を Scheme 2 に示した。この中で、ラセミ体のアルコール *rac*-**16** はピコリン酸もしくはピラジンカルボン酸と縮合してエステル **17**, **18** に変換し、続いて、これらを Lindlar 還元して *rac*-**1a** と **4** を得た。一方、**5–9** についても、同様の手法を試してみたが、Lindlar 還元の際、ホスフェート体ではリン酸基の脱離が起こり、アセテート体では飽和体が得られてしまった。そこで、アルコール *rac*-**16** をオレフィン **19** に部分還元した後にエステル化して **5–9** を調製した。

Scheme 2. Synthesis of allylic esters.

Preparation of (S)-1d



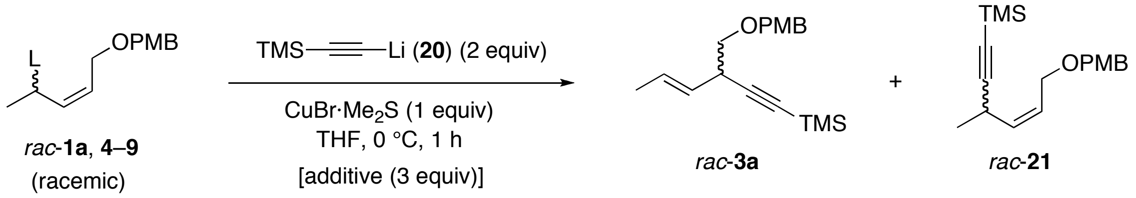
Synthesis of racemic allylic esters



[a] Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene)

はじめに、 sp^3-C または sp^2-C 銅試薬でのアリル化に適している脱離基を持つラセミ体の基質 *rac*-**1a**, **4–9** に対して反応を試した (Table 1)。まず、TMSC≡CLi (**20**) (2 当量) と CuBr·Me_2S (1 当量) から $(TMSC≡C)_2CuLi·LiBr$ (1 当量) を調製し、THF 中、0 °C で基質 *rac*-**1a**, **4–9** に作用させた。しかし、*rac*-**1a** と **4** ではカルボニル基への求核攻撃が起こり (entries 1, 4)、**7** では対応するホスフィンオキサイドが得られた [5] (entry 12)。その他では原料を回収するのみであった (entries 6, 15, 17)。

Table 1. Preliminary study using racemic substrates.

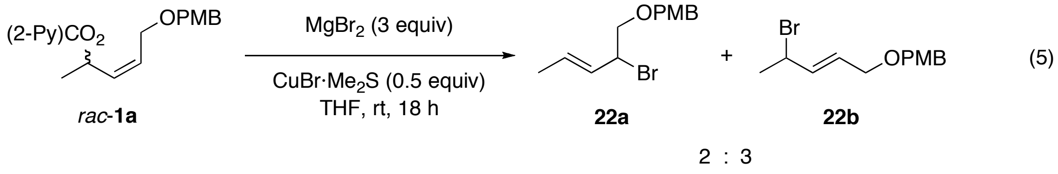


entry	substrate	L	additive^{a}	yield, %	*rac*-**3a**:*rac*-**21**^{b}
1	*rac*-**1a**	(2-Py)CO$_2$	–	0^{c}	–
2	*rac*-**1a**	(2-Py)CO$_2$	MgBr$_2$	88	94:6
3	*rac*-**1a**	(2-Py)CO$_2$	ZnBr$_2$	0^{c}	–
4	**4**	(2-pyrazine)CO$_2$	–	0^{c}	–
5	**4**	(2-pyrazine)CO$_2$	MgBr$_2$	51^{d}	92:8
6	**5**	(EtO)$_2$P(O)O	–	nr^{e}	–
7	**5**	(EtO)$_2$P(O)O	MgBr$_2$	12^{f}	nd^{g}
8	**5**	(EtO)$_2$P(O)O	ZnBr$_2$	nr^{e}	–
9	**6**	C$_6$F$_5$CO$_2$	–	nr^{e}	–
10	**6**	C$_6$F$_5$CO$_2$	MgBr$_2$	nr^{e}	–
11	**6**	C$_6$F$_5$CO$_2$	ZnBr$_2$	nr^{e}	–
12	**7**	*o*-(Ph$_2$P)C$_6$H$_4$CO$_2$	–	0^{h}	–
13	**7**	*o*-(Ph$_2$P)C$_6$H$_4$CO$_2$	MgBr$_2$	0^{h}	–
14	**7**	*o*-(Ph$_2$P)C$_6$H$_4$CO$_2$	ZnBr$_2$	0^{h}	–
15	**8**	MeOCO$_2$	–	nr^{e}	–
16	**8**	MeOCO$_2$	MgBr$_2$	nr^{e}	–
17	**9**	AcO	–	nr^{e}	–
18	**9**	AcO	MgBr$_2$	nr^{e}	–

[a] Three (3) equiv. [b] Determined by ^{1}H NMR spectroscopy. [c] Alcohol **19** was obtained. [d] Unidentified products were co-produced. [e] No reaction after 18 h at rt. [f] Allylic bromides **22a** and **22b** were produced in 88% NMR yield ($J_{CH=CH}$ = 15 Hz). [g] Not determined. [h] The corresponding phosphine oxide was produced.

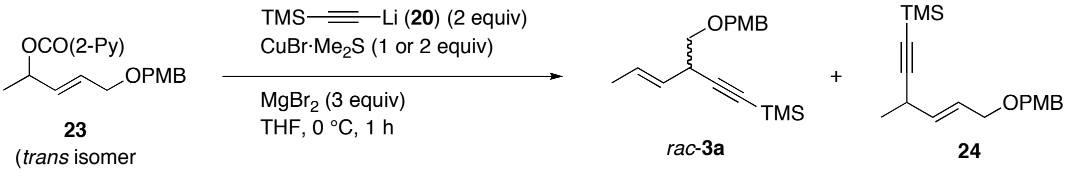
そこで、反応性を改善すべく、ルイス酸の添加を考えた。こうする事で、(1) 脱離基を活性化させる、(2) 銅試薬自体の反応性を上げる事を狙った。sp^3- と sp^2-C 銅試薬による置換反応で [R$_2$Cu]$^-$Li$^+$ より反応性が高いとされる [R$_2$Cu]$^-$MBr$^+$ (M = Mg, Zn) を形成させる目的で MgBr$_2$ と ZnBr$_2$ をルイス酸として選択した。実際、MgBr$_2$ (3 当量) を (TMSC≡C)$_2$CuLi·LiBr (1 当量) に加えると、狙い通り、ピコリン酸アリル *rac*-**1a** とのアリル化反応が進行する様になり、0 °C、1 時間で反応は完結した。その結果、収率 88%、位置異性体 *rac*-**21** に対し 94% の位置選択性で *rac*-**3a** を与えた (entry 2)。なお、位置異性体 *rac*-**21** のオレフィンはシス型 ($J_{CH=CH}$ = 11 Hz) であり、*rac*-**1a** のオレフィンの立体化学が保たれていた。興味深い事に、Ph$_2$CuMgBr (sp^2-C 銅試薬) でのアリル化反応の S$_N$2 型生成物がトランス型であったのと異なっている (第 2 章)。

上で出した 94% の位置選択性のさらなる向上を図り、反応温度を –20 °C または –60 °C に下げたが、位置選択性は改善されず、単に反応を遅らせるだけだった。また、銅塩非存在下、TMSC≡CLi (**20**) (2 当量) と MgBr$_2$ (3 当量) を作用させても、アルコール **19** が得られるのみであり、反応に銅塩が必要である事を確認した。ピラジンカルボン酸アリル **4** も MgBr$_2$ によって活性化されアリル化が進行したが、臭化物 **22a**/**22b** が生成し、生成物選択性は低かった (entry 5)。リン酸エステル **5** の場合、MgBr$_2$ を添加しても反応は 0 °C、1 時間では終了せず、室温で 18 時間さらに反応させると *rac*-**3a** を生じたが、主生成物はアリル臭化物 **22a**/**22b** (1 : 1) であった (entry 7)。なお、*rac*-**1a** に CuBr·Me$_2$S (0.5 当量) 及び MgBr$_2$ (3 当量) を作用させるとゆっくりと臭素化が進行し、室温で１８時間後に、トランス体の臭化物 **22a**/**22b** を NMR 比 2 : 3 で生成した (eq 5)。(^{1}H NMR で $J_{\mathrm{CH=CH}}$ = 15 Hz が観測された事からトランス体と決定した。) 他の基質 **6**–**9** は MgBr$_2$ によって活性化されなかった (entries 10, 13, 16, 18)。



次に、ZnBr$_2$ (3 当量) の効果を検討した。しかし、上記の結果と対照的に、ピコリン酸アリル *rac*-**1a** は 0 °C、1 時間では反応せず、更に室温で反応させたところアルコール **19** を副生するのみだった (entry 3)。リン酸エステル **5** は 0 °C から室温まで反応させても原料を回収するのみだった (entry 8)。その他、C$_6$F$_5$CO$_2$ 基も *o*-(Ph$_2$P)C$_6$H$_4$CO$_2$ 基も活性化されなかった (entries 11, 14)。

続いて、基質のオレフィンの立体を比較した。シスオレフィンをもつ *rac*-**1a** と対照的に、トランス体のピコリン酸アリル **23** の置換反応を、MgBr$_2$ 存在下 (TMSC≡C)$_2$CuLi·LiBr を用いて行うと、*rac*-**3a** とその位置異性体 (S$_\mathrm{N}$2 生成物) **24** の混合物を与えた (eq 6)。アセチレンアニオン **20** と Cu の割合が 1 : 1 の試薬でも位置異性体の混合物を与えた。よって、sp-C 銅試薬においても、基質のオレフィンの立体はシス型が適していることを確認できた。なお、シスオレフィンはアルキルイリドを使った Wittig 反応や三重結合の Lindlar 還元を行って立体選択的に合成できるため、合成上のデメリットはない。また、トランス体と比較しても、トランス体より合成しにくいこともない。



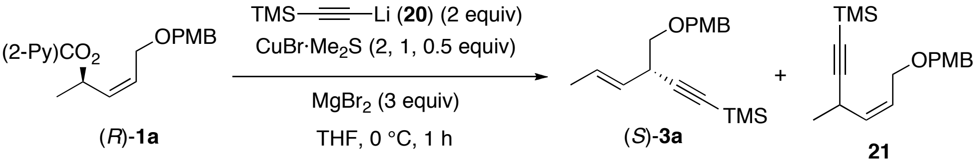
(6)

20/Cu (2/1) *rac*-**3a** / **24** = 64 : 36
20/Cu (2/2) *rac*-**3a** / **24** = 64 : 36

７−３．光学活性体を用いた反応条件の検討

Table 1, entry 2 の反応条件（$(TMSC{\equiv}C)_2CuLi{\cdot}LiBr$ from **20**/Cu = 2/1, $MgBr_2$, 0 °C, 1 h）を (*R*)-**1a** (98% ee) に適用した (Table 2)。

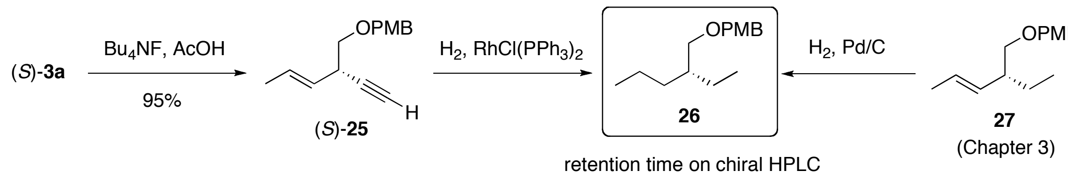
Table 2. Reaction of (*R*)-1a and 20/CuBr·Me$_2$S/MgBr$_2$.[a]



entry	**20**/CuBr·Me$_2$S/MgBr$_2$, equiv	ratio[b] of (*S*)-**3a** : **21** : **19** : (*R*)-**1a**	yield,[c] %	CT,[d] %
1	2 / 2 / 3	93 : 7 : 0 : 0	86	99
2	2 / 1 / 3	94 : 6 : 0 : 0	93	99
3	2 / 0.5 / 3	91 : 5 : 4 : 0	81	nd[e]

[a] In the absence of $MgBr_2$, reactions in entries 1–3 gave alcohol **19** in 13, 23, 45% yields, respectively. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield of (*S*)-**3a** and **21**. [d] Determined by chiral HPLC analysis. [e] Not determined.

entry 2 に示すように、(*S*)-**3a** の光学純度をキラル HPLC 分析で決定したところ 97% ee であり、ほとんど完全な不斉転写 (99% CT) が達成された。(*S*)-**3a** の絶対構造は既知化合物へ変換して決定し、反応がアンチ S_N2' 経由である事を明らかにした (eq 7)。なお、(*S*)-**25** を酢酸エチル溶媒中、10% Pd/C 触媒で接触還元すると一部ラセミ化が進行した。そこで、Wilkinson 触媒を用いて不飽和結合の還元を行ったところ、ラセミ化を抑えることができた。



(7)

retention time on chiral HPLC
was identical each other

続いて、アセチレンアニオン **20** と $CuBr\cdot Me_2S$ の比率を変えた銅試薬で反応を行った。**20**/Cu (2/2) では、**20**/Cu (2/1) に相当する選択性・反応性を示した (entry 1)。一方、**20**/Cu (2/0.5) では、選択性・反応性は良好であったが、アルコール **19** も 4% 生成した (entry 3)。つまり、良好な結果を得る為の試薬量は **20**/Cu (2/2~1) であり、厳密な秤量を要しない事は実験操作上有用である。

2 : 1 の比率で **20** と他の銅塩 (CuCl, CuBr, CuI, CuCN) から調製したアルキニル銅試薬を用いて反応を行った。どの銅塩を用いても (*S*)-**3a** を生成したが、その生成比や収率、不斉転写は **20**/$CuBr\cdot Me_2S$ に劣るものであった。(Table 3)。

Table 3. Effect of CuX on the reaction.[a]

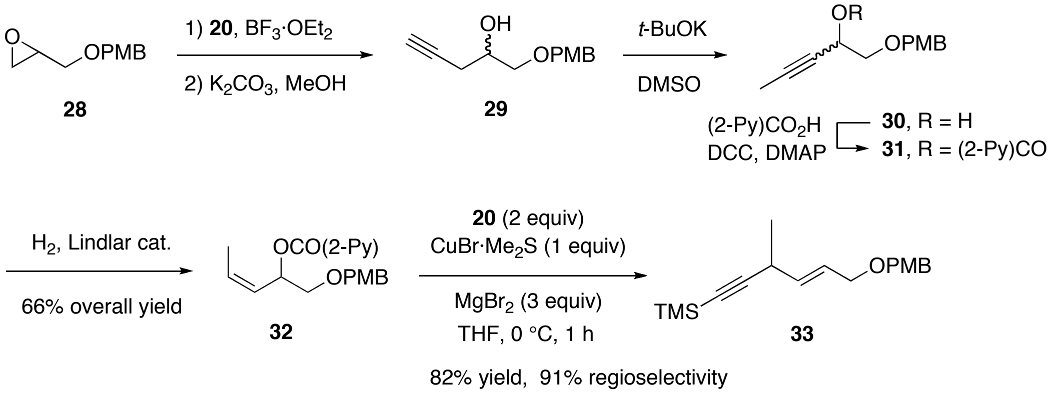
entry	CuX	ratio of (*S*)-**3a** : **21** : **19** : (*R*)-**1a**	yield,[b] %	CT,[c] %
1	CuBr	93 : 7 : 0 : 0	74[d]	96
2	CuCl	86 : 6 : 0 : 8	57[d]	95
3	CuI	94 : 6 : 0 : 0	83	91
4	CuCN	81 : 6 : 6 : 7	nd[e]	nd[e]

[a] Reactions of (*R*)-**1a** with copper reagents derived from **20** (2 equiv) and CuX (1 equiv) were examined in the presence of $MgBr_2$ (3 equiv) at 0 °C for 1 h. [b] Isolated yield of (*S*)-**3a** and **21**. [c] Determined by chiral HPLC analysis. [d] Allylic bromides **22a** and **22b** were co-produced. [e] Not determined.

７−４．種々の基質・アセチレンについての検討

このアリル化反応の適応範囲を調べる為に、種々のピコリン酸アリル及びアルキニル銅試薬を用いて反応を行う事にした。まず、*rac*-**1a** と R^1, R^2 の配置が逆になっているラセミ体 **32** を合成し、アリル化反応を行ったところ、*rac*-**3a** の位置異性体である **33** を良好な選択性及び収率で生成した (Scheme 3)。つまり、このアリル化はアリル部位の置換基によらず S_N2' 選択的であった。

Scheme 3. Synthesis and allylation of picolinate 32.



さらに様々な置換基を持つ基質について検討した (Table 4)。アリル基に隣接する色々なメチレン基や CH_2OR （アルコキシメチル）基は、$(TMSC{\equiv}C)_2CuLi{\cdot}MgBr_2$ の反応に影響を及ぼさず、アンチ S_N2'生成物 (*R*)-**3b-d** を与えた (entries 1‐3)。それと対照的に、オレフィン炭素により嵩高いシクロヘキシル基を持つ基質 (*S*)-**1e** では選択性と収率が低下した (entry 4)。なお、(*R*)-**3b** の絶対構造は、(*S*)-**3a** と同様に既知化合物 **36** へ変換して決定した (eq 8)。

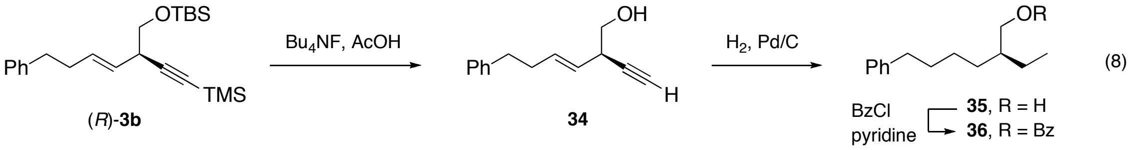
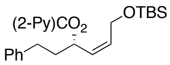
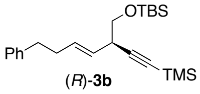
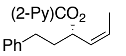
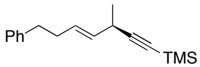
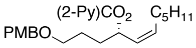
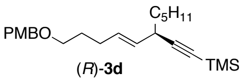
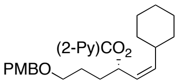
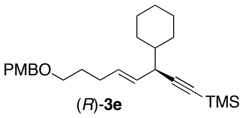
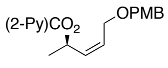
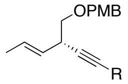


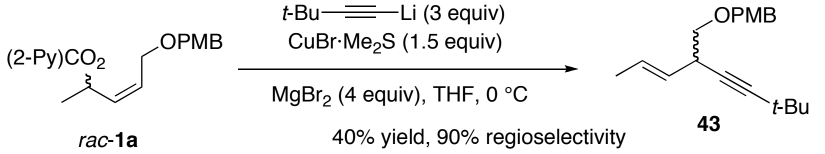
Table 4. Substitution of picolinates with alkynyl copper reagents.

entry	picolinate	ArC≡CLi (equiv)	CuBr·Me$_2$S, equiv	MgBr$_2$, equiv	product	isolated yield[b,c]	regio-selec-tivity[b,d]	CT[b,e]
1	 (*S*)-**1b** (98% ee)	TMSC≡CLi (**20**) (2)	1	3	 (*R*)-**3b**	83	97	98
2	 (*S*)-**1c** (94% ee)	**20** (2)	1	3	 (*R*)-**3c**	80	98	98
3	 (*S*)-**1d** (93% ee)	**20** (2)	1	3	 (*R*)-**3d**	89	94	98
4	 (*S*)-**1e** (99% ee)	**20** (2)	1	3	 (*R*)-**3e**	66	86	nd[f]
5	 (*R*)-**1a** (98% ee)	PhC≡CLi (**37**) (3)	1.5	4	 (*S*)-**3f** (R = Ph)	70	95	96
6	(*R*)-**1a** (98% ee)	*p*-TBSOC$_6$H$_4$C≡CLi (**38**) (3)	1.5	4	(*S*)-**3g** (R = *p*-TBSOC$_6$H$_4$)	61	93	95
7	(*R*)-**1a** (98% ee)	*p*-MeOC$_6$H$_4$C≡CLi (**39**) (3)	1.5	4	(*S*)-**3h** (R = *p*-MeOC$_6$H$_4$)	67	92	97
8	(*R*)-**1a** (98% ee)	*o*-MeOC$_6$H$_4$C≡CLi (**40**) (3)	1.5	4	(*S*)-**3i** (R = *o*-MeOC$_6$H$_4$)	89	97	97
9	(*R*)-**1a** (98% ee)	*p*-MeC$_6$H$_4$C≡CLi (**41**) (3)	1.5	4	(*S*)-**3j** (R = *p*-MeC$_6$H$_4$)	84	94	97
10	(*R*)-**1a** (98% ee)	*p*-FC$_6$H$_4$C≡CLi (**42**) (3)	1.5	4	(*S*)-**3k** (R = *p*-FC$_6$H$_4$)	88	95	98

[a] Reactions in entries 1–4 were carried out with **20** (2 equiv), CuBr·Me$_2$S (1 equiv), and MgBr$_2$ (3 equiv) in THF at 0 °C for 1 h. Reactions in entries 5–9 were carried out with Ar-C≡CLi (3 equiv), CuBr·Me$_2$S (1.5 equiv), and MgBr$_2$ (4 equiv) in THF at 0 °C for 1 h. [b] In %. [c] Combined yield of the regioisomers. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by chiral HPLC analysis. [f] HPLC signals on several chiral columns were separated incompletely.

続いて、他のアセチレンを検討した。2 当量の Ph-C≡CLi (**37**) と 1 当量の CuBr·Me$_2$S から調製した､2-フェニルアルキニル銅試薬 (Ph-C≡C)$_2$CuLi·LiBr は、(TMSC≡C)$_2$CuLi·LiBr より反応性が低く、 0 °C, 1 時間で 18% の基質 (*R*)-**1a** を回収した。反応を完結させるため､1.5 倍量の **37**/Cu を用いると原料は消失し、(*S*)-**3f** が収率 70%で得られた (entry 5)。その選択性は (TMSC≡C)$_2$CuLi·LiBr に相当する選択性であった。同様に、**38–42** から調製した種々の (ArC≡C)$_2$CuLi·LiBr (Ar : *p*-TBSOC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *p*-MeC$_6$H$_4$, *p*-FC$_6$H$_4$) を用いた反応では、高い選択性及び収率で (*S*)-**3g–k** を生成した。芳香環上の置換基の電子的効果 (電子供与性・電子吸引性置換基) は、反応性及び選択性にあまり影響を及ぼさなかった。なお、アルキル置換アセチレンとして、

$(t\text{-BuC}\equiv\text{C})_2\text{CuLi}\cdot\text{LiBr}$ をラセミ体の *rac*-**1a** と反応させたが、反応性が低く $\text{S}_\text{N}2'$ 生成物 **43** を 40% の収率で得るのみであった (eq 9)。

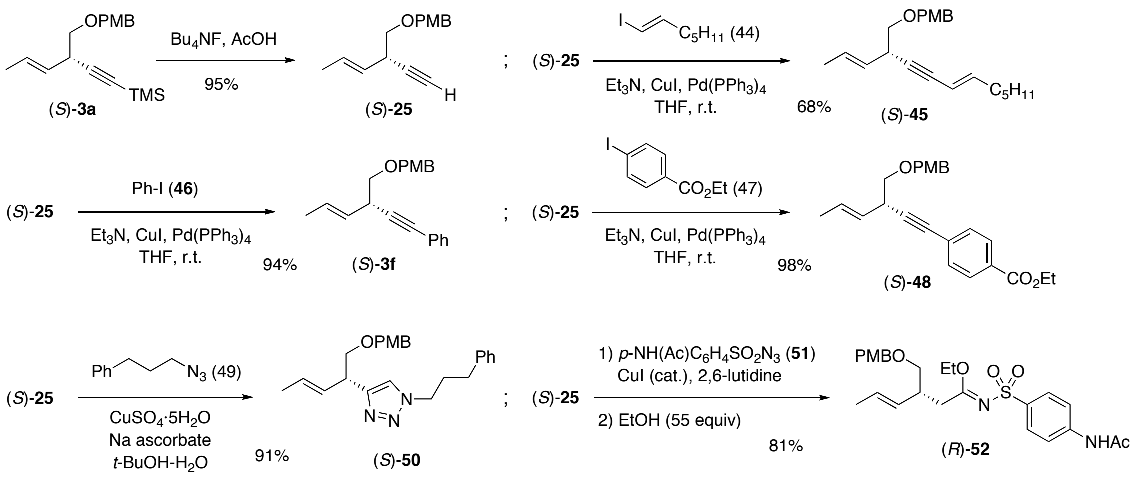


(9)

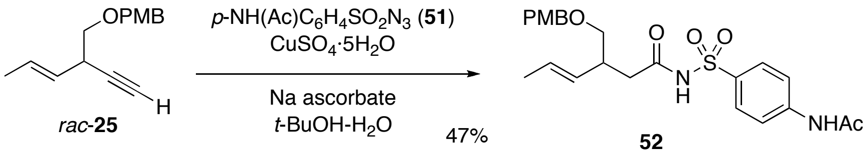
７－５．応用展開：1, 4−エンインの変換

ここではアリル化生成物である 1,4-エンインの変換について検討した結果について述べる (Scheme 4)。数ページ前に述べた様に、(*S*)-**3a** を THF 中、$\text{Bu}_4\text{NF-AcOH}$ (1 : 1) で処理することにより容易に TMS 基を除去でき、(*S*)-**25** を得た (eq 7)。同様に (*R*)-**3b** からはアセチレンアルコール **34** へと誘導できた (eq 8)。なお、 (*R*)-**3b** を TBAF のみで処理した場合、望みの生成物 **34** とアレン体との混合物を与えてしまった。(*E*)-I-CH=$\text{CHC}_5\text{H}_{11}$ (**44**), PhI (**46**) 及び *p*-I-$\text{C}_6\text{H}_4\text{CO}_2\text{Et}$ (**47**) と (*S*)-**25** の薗頭反応は標準的な条件で進行し、それぞれ良好な収率で (*S*)-**45**, **3f**, **48** を生成した。(*S*)-**48** のようなエステル基を持つアセチレンは、*p*-$(\text{EtO}_2\text{C})\text{C}\equiv\text{CLi}$ の調製が困難でアリル化で合成できないが、薗頭反応を利用する事で合成できる事が示せた。

Scheme 4. Transformations of (*S*)-3a.



続いて、アジドとの反応を検討した。銅触媒を用いた Ph(CH$_2$)$_3$N$_3$ (**49**) と (*S*)-**25** の 1,3-双極子付加反応[6]では、高収率でトリアゾール (*S*)-**50** を与えた。また、銅触媒下 *p*-NH(Ac)C$_6$H$_4$SO$_2$N$_3$ (**51**) と (*S*)-**25** を反応させ、過剰量の EtOH で処理[7]すると 収率 81% でイミデート (*R*)-**52** へと変換することも可能であった。一方、 *rac*-**25** と **51** を *t*-BuOH 水溶液中で反応させると、**53** が中程度の収率で得られた (eq 10)。



(10)

７−６．結論

本章では、これまで全く報告がなかった、アルキニル銅試薬を用いた第２級アリルアルコール誘導体へのアリル化反応について検討した。その結果、ピコリン酸基を脱離基とする事が非常に重要であり、高い位置・立体選択性でアンチ S$_N$2’ 生成物を得ることが出来る反応系を初めて見出した。さらに、光学活性な 1,4-エンインは従来合成が難しかったタイプの化合物であり、Scheme 4 に示した他にも様々な応用展開が期待できると考えている。

Experimental section

Synthesis of Picolinate (*S*)-1d. (Scheme 2)

4-[(4-Methoxybenzyl)oxy]-1-butanol (11).

To a suspension of K_2CO_3 (8.76 g, 63.4 mmol) and NaI (8.63 g, 57.6 mmol) in acetone (20 mL) were added 1,4-butanediol (**10**) (6.80 mL, 76.7 mmol) and PMBCl (2.60 mL, 19.2 mmol). The mixture was refluxed overnight, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **11** (3.35 g, 83%): IR (neat) 3391, 1612, 1512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60–1.76 (m, 4 H), 2.36–2.48 (m, 1 H), 3.49 (t, *J* = 6 Hz, 2 H), 3.63 (dt, *J* = 5, 5 Hz, 2 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8 (+), 30.3 (+), 55.3 (–), 62.8 (+), 70.1 (+), 72.8 (+), 113.9 (–), 129.4 (–), 130.2 (+), 159.3 (+); HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1251. The ^{1}H NMR spectrum of **11** was identical with that reported.[8]

4-(4-Methoxybenzyloxy)-1-butanal (12).

To an ice-cold solution of **11** (1.62 g, 7.70 mmol) in CH_2Cl_2 and DMSO (1 : 1, 32 mL) were added SO_3·Py (4.90 g, 30.8 mmol) and Et_3N (5.40 mL, 38.5 mmol). The reaction mixture was stirred at 0 °C for 3 h, and diluted with EtOAc and H_2O. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **12** (1.18 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (tt, *J* = 7, 6 Hz, 2 H), 2.54 (dt, *J* = 2, 7 Hz, 2 H), 3.48 (t, *J* = 8 Hz, 2 H), 3.81 (s, 3 H), 4.42 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.24 (d, *J* = 9 Hz, 2 H), 9.78 (t, *J* = 2 Hz, 1 H). The ^{1}H NMR spectrum of **12** was identical with that reported.[8]

1-(4-Methoxybenzyloxy)undec-5-yn-4-one (13).

To an ice-cold solution of 1-heptyne (1.20 mL, 9.15 mmol) in THF (9 mL) was added BuLi (5.50 mL, 1.55 M in hexane, 8.53 mmol) dropwise. The mixture was stirred at 0 °C for 30 min and cooled to –78 °C. A solution of **12** (1.18 g, 5.67 mmol) in THF (3 mL) was added to it dropwise and the resulting mixture was allowed to warm to –20 °C over 2 h. Saturated NH_4Cl and EtOAc were added to the mixture, and the product was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$

and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding alcohol (1.48 g, 86%).

To an ice-cold solution of the above alcohol (519 mg, 1.70 mmol) in CH_2Cl_2 (6 mL) were added Celite (1.0 g) and PCC (441 mg, 2.05 mmol). The mixture was stirred at rt overnight, and PCC (147 mg, 0.682 mmol) was added again. The mixture was stirred at rt overnight, diluted with hexane, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **13** (388 mg, 75%): IR (neat) 2210, 1675, 1513, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7 Hz, 3 H), 1.24–1.45 (m, 4 H), 1.49–1.65 (m, 2 H), 1.95 (tt, *J* = 7, 6 Hz, 2 H), 2.35 (t, *J* = 7 Hz, 2 H), 2.65 (t, *J* = 7 Hz, 2 H), 3.47 (t, *J* = 6 Hz, 2 H), 3.81 (s, 3 H), 4.42 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (–), 18.9 (+), 22.1 (+), 24.2 (+), 27.4 (+), 31.0 (+), 42.3 (+), 55.3 (–), 68.8 (+), 72.6 (+), 80.9 (+), 94.5 (+), 113.8 (–), 129.2 (–), 130.5 (+), 159.2 (+), 187.9 (+); HRMS (FAB) calcd for $C_{19}H_{27}O_3$ [$(M + H)^+$] 303.1960, found 303.1967.

(*S*)-1-(4-Methoxybenzyloxy)undec-5-yn-4-ol (14).

To a solution of **13** (388 mg, 1.28 mmol) in *i*-PrOH (10 mL) was added Ru[(1*S*,2*S*)-TsDPEN](*p*-cymene) (23 mg, 0.383 mmol). The mixture was stirred at 30 °C overnight and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **14** (330 mg, 84%): IR (neat) 3410, 1612, 1513, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.23–1.42 (m, 4 H), 1.43–1.56 (m, 2 H), 1.69–1.90 (m, 4 H), 2.19 (dt, *J* = 2, 7 Hz, 2 H), 2.64 (d, *J* = 6 Hz, 1 H), 3.45–3.54 (m, 2 H), 3.81 (s, 3 H), 4.34–4.45 (m, 1 H), 4.45 (s, 2 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (–), 18.7 (+), 22.2 (+), 25.6 (+), 28.4 (+), 31.1 (+), 35.6 (+), 55.3 (–), 62.4 (–), 69.9 (+), 72.6 (+), 81.2 (+), 85.5 (+), 113.8 (–), 129.4 (–), 130.3 (+), 159.2 (+); HRMS (FAB) calcd for $C_{19}H_{28}O_3Na$ [$(M + Na)^+$] 327.1936, found 327.1938.

(*S*)-1-(4-Methoxybenzyloxy)undec-5-yn-4-yl Pyridine-2-carboxylate (15).

To an ice-cold solution of **14** (330 mg, 1.08 mmol) in CH_2Cl_2 (4 mL) were added picolinic acid (160 mg, 1.30 mmol), DMAP (40 mg, 0.327 mmol), and DCC (290 mg, 1.41 mmol). The mixture was stirred at rt for 2 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **15** (410 mg, 93%): IR (neat) 2241, 1718, 1513, 1247, 1128 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* =

7 Hz, 3 H), 1.22–1.40 (m, 4 H), 1.43–1.62 (m, 2 H), 1.78–1.90 (m, 2 H), 1.98–2.08 (m, 2 H), 2.19 (dt, J = 2, 7 Hz, 2 H), 3.51 (t, J = 6 Hz, 2 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 5.71 (tt, J = 7, 2 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H), 7.47 (ddd, J = 8, 5, 1 Hz, 1 H), 7.83 (ddd, J = 8, 8, 2 Hz, 1 H), 8.13 (ddd, J = 8, 1, 1 Hz, 1 H), 8.78 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (–), 18.8 (+), 22.2 (+), 25.6 (+), 28.2 (+), 31.1 (+), 32.1 (+), 55.3 (–), 66.0 (–), 69.4 (+), 72.6 (+), 87.2 (+), 113.8 (–), 125.4 (–), 126.9 (–), 129.3 (–), 130.6 (+), 137.0 (–), 148.1 (+), 150.1 (–), 159.2 (+), 164.2 (+); HRMS (FAB) calcd for $C_{25}H_{32}NO_4$ [(M + H)$^+$] 410.2331, found 410.2324.

Picolinate (*S*)-1d.

To a solution of **15** (387 mg, 0.945 mmol) in EtOAc (10 mL) was added Lindlar catalyst (Aldrich, 189 mg). The mixture was stirred at rt overnight under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**1d** (308 mg, 79%): $[\alpha]^{24}_{D}$ +40.5 (*c* 0.356, $CHCl_3$); IR (neat) 1739, 1513, 1303, 1246, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7 Hz, 3 H), 1.20–1.45 (m, 6 H), 1.63–1.87 (m, 3 H), 1.88–2.07 (m, 1 H), 2.09–2.32 (m, 2 H), 3.43–3.53 (m, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.49 (ddt, J = 11, 9, 2 Hz, 1 H), 5.61 (dt, J = 11, 7 Hz, 1 H), 5.89 (dt, J = 9, 7 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H), 7.45 (ddd, J = 8, 5, 1 Hz, 1 H), 7.82 (ddd, J = 8, 8, 2 Hz, 1 H), 8.10 (ddd, J = 8, 1, 1 Hz, 1 H), 8.77 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (–), 22.4 (+), 25.5 (+), 27.9 (+), 29.1 (+), 31.4 (+), 31.5 (+), 55.1 (–), 69.5 (+), 71.8 (–), 72.5 (+), 113.7 (–), 125.0 (–), 126.6 (–), 127.4 (–), 129.1 (–), 130.5 (+), 135.1 (–), 136.8 (–), 148.5 (+), 149.8 (–), 159.0 (+), 164.4 (+); HRMS (FAB) calcd for $C_{25}H_{34}NO_4$ [(M + H)$^+$] 412.2488, found 412.2484. The enantiomeric information (93% ee) was determined by chiral HPLC analysis: Chiralcel AD-H; hexane/*i*-PrOH = 95/5, 0.5 mL/min, rt; t_R (min) = 26.0 (*S*), 44.6 (*R*).

Synthesis of Picolinate *rac*-1a. (Scheme 2)

5-(4-Methoxybenzyloxy)-3-pentyn-2-yl Pyridine-2-carboxylate (17).

To an ice-cold solution of *rac*-**16**[9] (244 mg, 1.11 mmol) in CH_2Cl_2 (5 mL) were added picolinic acid (164 mg, 1.33 mmol), DMAP (40.6 mg, 0.332 mmol), and DCC (298 mg, 1.44 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **17** (358 mg, 99%). The ^{1}H and

^{13}C NMR spectra were identical with those reported in Chapter 2.

Picolinate *rac*-1a.

To a solution of **17** (358 mg, 1.09 mmol) in EtOAc (10 mL) was added Lindlar catalyst (Aldrich, 210 mg) at rt. The mixture was stirred at rt for 12 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford *rac*-**1a** (274 mg, 77%). The ^{1}H and ^{13}C NMR spectra were identical with those reported in Chapter 2.

Synthesis of Pyrazinecarboxylate 4. (Scheme 2)

5-(4-Methoxybenzyloxy)pent-3-yn-2-yl Pyrazine-2-carboxylate (18).

To an ice-cold solution of *rac*-**16** (210 mg, 0.953 mmol) in CH_2Cl_2 (4 mL) were added 2-pyrazinecarboxylic acid (142 mg, 1.14 mmol), DMAP (35 mg, 0.286 mmol), and DCC (256 mg, 1.24 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **18** (304 mg, 98%): IR (neat) 1724, 1514, 1288, 1250, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, J = 7 Hz, 3 H), 3.80 (s, 3 H), 4.18 (d, J = 2 Hz, 2 H), 4.52 (s, 2 H), 5.86 (tq, J = 2, 7 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H), 8.76 (dd, J = 2, 1 Hz, 1 H), 8.79 (d, J = 2 Hz, 1 H), 9.34 (d, J = 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (–), 55.2 (–), 56.8 (+), 62.4 (–), 71.2 (+), 82.0 (+), 83.9 (+), 113.8 (–), 129.2 (+), 129.8 (–), 143.2 (+), 144.5 (–), 146.4 (–), 147.8 (–), 159.3 (–), 162.8 (+); HRMS (FAB) calcd for $C_{18}H_{19}N_2O_4$ [(M + H)$^+$] 327.1345, found 327.1347.

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-yl Pyrazine-2-carboxylate (4).

To a solution of **18** (284 mg, 0.870 mmol) in EtOAc (10 mL) was added Lindlar catalyst (Aldrich, 103 mg). The mixture was stirred at rt for 12 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **4** (235 mg, 82%): IR (neat) 1718, 1513, 1303, 1249, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J = 6 Hz, 3 H), 3.80 (s, 3 H), 4.23 (dm, J = 6 Hz, 2 H), 4.47 (s, 2 H), 5.70 (ddt, J = 11, 8, 2 Hz, 1 H), 5.78 (dt, J = 11, 6 Hz, 1 H), 5.95 (dq, J = 8, 6 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H), 8.72 (dd, J = 2, 1 Hz, 1 H), 8.75 (d, J = 2 Hz, 1 H), 9.29 (d, J = 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (–), 55.3 (–), 65.7 (+), 69.3

(–), 72.2 (+), 113.8 (–), 129.4 (–), 130.1 (+), 130.4 (–), 131.0 (–), 143.7 (+), 144.4 (–), 146.3 (–), 147.6 (–), 159.2 (+), 163.2 (+); HRMS (FAB) calcd for $C_{18}H_{21}N_2O_4$ [(M + H)$^+$] 329.1501, found 329.1504.

Synthesis of Racemic Allylic Esters 5–9. (Scheme 2)

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-ol (19).

To a solution of *rac*-**16** (567 mg, 2.57 mmol) in MeOH (20 mL) were added 10% Pd on $BaSO_4$ (39 mg) and quinoline (0.141 mL, 1.19 mmol). The mixture was stirred at rt for 7 min under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **19** (418 mg, 73%): IR (neat) 3397, 1612, 1514, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 7 Hz, 3 H), 2.00 (br s, 1 H), 3.81 (s, 3 H), 3.98–4.17 (m, 2 H), 4.46 (s, 2 H), 4.52–4.64 (m, 1 H), 5.59–5.70 (m, 2 H), 6.89 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (–), 55.3 (–), 63.9 (–), 65.4 (+), 72.2 (+), 113.9 (–), 126.8 (–), 129.5 (–), 130.0 (+), 137.7 (–), 159.3 (+); HRMS (FAB) calcd for $C_{13}H_{18}O_3Na$ [(M + Na)$^+$] 245.1154, found 245.1152.

(*Z*)-Diethyl 5-(4-Methoxybenzyloxy)pent-3-en-2-yl Phosphate (5).

To an ice-cold solution of **19** (102 mg, 0.459 mmol) in Et_2O (1 mL) were added *N*-methylimidazole (0.22 mL, 2.79 mmol) and $ClP(O)(OEt)_2$ (0.32 mL, 2.23 mmol). The mixture was stirred at rt overnight, and diluted with EtOAc and saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish phosphate **5** (145 mg, 88%): IR (neat) 1613, 1514, 1250, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (dq, J_{P-H} = 1 Hz, J_{H-H} = 7 Hz, 3 H), 1.26–1.35 (m, 3 H), 1.38 (d, J = 6 Hz, 3 H), 3.81 (s, 3 H), 3.99–4.14 (m, 6 H), 4.45 (s, 2 H), 5.22 (ddq, J_{H-H} = 9 Hz, J_{P-H} = 6 Hz, J_{H-H} = 6 Hz, 1 H), 5.62 (ddt, J = 11, 9, 1 Hz, 1 H), 5.70 (dt, J = 11, 6 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (–, d, J_{C-P} = 7 Hz), 22.6 (–, d, J_{C-P} = 5 Hz), 55.2 (–), 63.46 (+, d, J_{C-P} = 3 Hz), 63.54 (+, d, J_{C-P} = 3 Hz), 65.5 (+), 71.1 (–, d, J_{C-P} = 3 Hz), 72.2 (+), 113.8 (–), 128.8 (–), 129.4 (–), 130.1 (+), 132.5 (–, d, J_{C-P} = 5 Hz), 159.2 (+); HRMS (FAB) calcd for $C_{17}H_{28}O_6P$ [(M + H)$^+$] 359.1624, found 359.1623.

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-yl 2,3,4,5,6-Pentafluorobenzoate (6).

To an ice-cold solution of **19** (113 mg, 0.508 mmol) in CH_2Cl_2 (2 mL) were added pentafluorobenzoic acid (129 mg, 0.608 mmol), DMAP (19 mg, 0.156 mmol) and DCC (137 mg, 0.664 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish ester **6** (192 mg, 91%): IR (neat) 1735, 1507, 1233 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6 Hz, 3 H), 3.81 (s, 3 H), 4.19 (dt, *J* = 6, 2 Hz, 2 H), 4.47 (s, 2 H), 5.61 (ddt, *J* = 11, 9, 2 Hz, 1 H), 5.78 (ddt, *J* = 11, 1, 6 Hz, 1 H), 5.80–5.93 (m, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.28 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 (–), 55.2 (–), 65.6 (+), 70.1 (–), 72.2 (+), 113.8 (–), 129.4 (–), 130.1 (–), 130.6 (–), 130.7 (–), 135.9–146.9 (+, m, 5C), 158.2 (+), 159.3 (+); ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 1.28 (m, 2 F), 12.8 (m, 1 F), 23.2 (m, 2F); HRMS (FAB) calcd for $C_{20}H_{17}F_5O_4$ (M^+) 416.1047, found 416.1052.

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-yl 2-(Diphenylphosphino)benzoate (7).

To an ice-cold solution of **19** (119 mg, 0.535 mmol) in CH_2Cl_2 (2 mL) were added 2-(diphenylphosphino)benzoic acid (197 mg, 0.643 mmol), DMAP (20 mg, 0.18 mmol), and DCC (144 mg, 0.698 mmol). The mixture was stirred at rt for 3 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish DPPB ester **7** (222 mg, 81%): IR (neat) 1738, 1712, 1513, 1249, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7 Hz, 3 H), 3.76 (s, 3 H), 4.05 (dd, *J* = 13, 7 Hz, 1 H), 4.11 (dd, *J* = 13, 7 Hz, 1 H), 4.36 (d, *J* = 11 Hz, 1 H), 4.39 (d, *J* = 11 Hz, 1 H), 5.44 (dd, *J* = 11, 9 Hz, 1 H), 5.60 (dt, *J* = 11, 7 Hz, 1 H), 5.69 (dq, *J* = 9, 7 Hz, 1 H), 6.85 (d, *J* = 9 Hz, 2 H), 6.84–6.93 (m, 1 H), 7.23 (d, *J* = 9 Hz, 2 H), 7.21–7.38 (m, 12 H), 7.99–8.06 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (–), 55.2 (–), 65.7 (+), 68.1 (–), 72.0, (+) 113.7 (–), 128.2 (–), 128.4 (–, d, J_{C-P} = 2 Hz), 128.5 (–, d, J_{C-P} = 2 Hz), 128.5 (–), 128.6 (–), 129.3 (–), 129.4 (–), 130.3 (+), 130.6 (–, d, J_{C-P} = 3 Hz), 131.7 (–), 131.8 (–), 133.8 (–, d, J_{C-P} = 12 Hz), 134.0 (–, d, J_{C-P} = 12 Hz), 134.2 (–), 134.7 (+, d, J_{C-P} = 19 Hz), 137.9 (+, d, J_{C-P} = 8 Hz), 138.1 (+, d, J_{C-P} = 8 Hz), 140.0 (+, d, J_{C-P} = 27 Hz), 159.1 (+), 166.1 (+, d, J_{C-P} = 3 Hz).

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-yl Methyl Carbonate (8).

To an ice-cold solution of **19** (103 mg, 0.463 mmol) in CH_2Cl_2 (1 mL) were added pyridine (0.230 mL, 2.84 mmol) and methyl chloroformate (0.11 mL, 1.42 mmol). The mixture was stirred at rt overnight, and diluted with EtOAc and saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish carbonate **8** (116 mg, 89%): IR (neat) 1744, 1513, 1268, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6 Hz, 3 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.16 (dm, *J* = 6 Hz, 2 H), 4.45 (d, *J* = 11 Hz, 1 H), 4.47 (d, *J* = 11 Hz, 1 H), 5.45 (ddq, *J* = 9, 1, 6 Hz, 1 H), 5.57 (ddt, *J* = 11, 9, 1 Hz, 1 H), 5.73 (ddt, *J* = 11, 1, 6 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.27 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (–), 54.5 (–), 55.2 (–), 65.6 (+), 70.9 (–), 72.1 (+), 113.7 (–), 129.4 (–), 129.6 (–), 130.1 (+), 131.4 (–), 155.0 (+), 159.2 (+); HRMS (FAB) calcd for $C_{15}H_{20}O_5Na$ [$(M + Na)^+$] 303.1208, found 303.1208.

(*Z*)-5-(4-Methoxybenzyloxy)pent-3-en-2-yl Acetate (9).

To an ice-cold solution of **19** (99.9 mg, 0.449 mmol) in CH_2Cl_2 (1 mL) were added pyridine (0.31 mL, 3.83 mmol) and Ac_2O (0.17 mL, 1.80 mmol). The mixture was stirred at rt overnight, and diluted with EtOAc and saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish acetate **9** (102 mg, 86%): IR (neat) 1735, 1514, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6 Hz, 3 H), 2.02 (s, 3 H), 3.81 (s, 3 H), 4.14 (dd, *J* = 6, 2 Hz, 2 H), 4.42 (d, *J* = 11 Hz, 1 H), 4.47 (d, *J* = 11 Hz, 1 H), 4.51 (s, 2 H), 5.46–5.66 (m, 2 H), 5.68 (dt, *J* = 11, 6 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.27 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (–), 21.2 (–), 55.2 (–), 65.6 (+), 66.9 (–), 72.1 (+), 113.7 (–), 129.1 (–), 129.4 (–), 130.2 (+), 132.0 (–), 159.2 (+), 170.2 (+); HRMS (FAB) calcd for $C_{15}H_{20}O_4Na$ [$(M + Na)^+$] 287.1259, found 287.1263.

Synthesis of Racemic Picolinate 32. (Scheme 3)

1-(4-Methoxybenzyloxy)pent-3-yn-2-ol (30).

To an ice-cold solution of (trimethylsilyl)acetylene (0.500 mL, 3.54 mmol) in THF (4 mL) was added *n*-BuLi (2.00 mL, 1.60 M in hexane, 3.20 mmol) slowly. The solution was stirred at 0 °C for 30 min, and cooled to –78 °C. $BF_3{\cdot}OEt_2$ (0.44 mL, 3.47 mmol) was added to it slowly. After 10 min of stirring at –78 °C, a solution of **28** (426 mg, 2.19 mmol) in THF (3 mL) was added slowly. The resulting mixture was allowed to warm to rt, and stirred overnight. Saturated NH_4Cl and EtOAc were added to the mixture. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the corresponding acetylene alcohol, which was used for the next reaction without further purification: ^{1}H NMR δ 0.14 (s, 9 H), 2.40 (d, J = 5 Hz, 1 H), 2.45 (dd, J = 17, 7 Hz, 1 H), 2.51 (dd, J = 17, 6 Hz, 1 H), 3.46 (dd, J = 9, 6 Hz, 1 H), 3.58 (dd, J = 9, 4 Hz, 1 H), 3.80 (s, 3 H), 3.88–3.97 (m, 1 H), 4.50 (s, 2 H), 6.88 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H).

To an ice-cold solution of the above alcohol in MeOH (5 mL) was added K_2CO_3 (910 mg, 6.58 mmol). The mixture was stirred at rt for 4 h, and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to afford acetylene **29** (652 mg), which was used for the next reaction without further purification.

To an ice-cold mixture of the above acetylene **29** (652 mg) in DMSO (4 mL) was added *t*-BuOK (983 mg, 8.76 mmol). The resulting mixture was stirred at rt for 2 h, and diluted with EtOAc and H_2O. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by silica gel chromatography (hexane/EtOAc) to give the methyl acetylene **30** (284 mg, 74% from **i**): IR (neat) 3420, 2242, 1514, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 2 Hz, 3 H), 2.43 (d, J = 4 Hz, 1 H), 3.49 (dd, J = 10, 8 Hz, 1 H), 3.58 (dd, J = 10, 5 Hz, 1 H), 3.81 (s, 3 H), 4.46–4.54 (m, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.56 (d, J = 12 Hz, 1 H), 6.89 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6 (–), 55.3 (–), 61.8 (–), 73.0 (+), 73.6 (+), 77.0 (+), 82.0 (+), 113.9 (–), 129.5 (–), 129.8 (+), 159.4 (+); HRMS (FAB) calcd for $C_{13}H_{16}O_3Na$ [(M + Na)$^+$] 243.0997, found 243.0998.

1-(4-Methoxybenzyloxy)pent-3-yn-2-yl Pyridine-2-carboxylate (31).

To an ice-cold solution of **30** (274 mg, 1.24 mmol) in CH_2Cl_2 (5 mL) were added picolinic acid (184 mg, 1.49 mmol), DMAP (30 mg, 0.246 mmol), and DCC (333 mg, 1.61 mmol). The mixture was stirred at rt for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **31** (397 mg, 98%): IR (neat) 2245, 1722, 1514, 1303, 1246, 1130 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 2 Hz, 3 H), 3.75 (dd, J = 11, 4 Hz, 1 H), 3.79 (s, 3 H), 3.86 (dd, J = 11, 8 Hz, 1 H), 4.54 (d, J = 12 Hz, 1 H), 4.59 (d, J = 12 Hz, 1 H), 5.87 (ddq, J = 8, 4, 2 Hz, 1 H), 6.84 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H), 7.38 (ddd, J = 8, 5, 1 Hz, 1 H), 7.84 (ddd, J = 8, 8, 2 Hz, 1 H), 8.14 (ddd, J = 8, 1, 1 Hz, 1 H), 8.79 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8 (–), 55.3 (–), 64.8 (–), 71.0 (+), 72.8 (+), 73.8 (+), 83.6 (+), 113.8

(–), 125.5 (–), 127.0 (–), 129.4 (–), 129.8 (+), 136.9 (–), 147.9 (+), 150.0 (–), 159.3 (+), 164.2 (+); HRMS (FAB) calcd for $C_{19}H_{20}NO_4$ $[(M + H)^+]$ 326.1392, found 326.1390.

(Z)-1-(4-Methoxybenzyloxy)pent-3-en-2-yl Pyridine-2-carboxylate (32).

To a solution of **31** (397 mg, 1.21 mmol) in EtOAc (15 mL) was added Lindlar catalyst (Aldrich, 100 mg). The mixture was stirred at rt for 12 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **32** (357 mg, 91%): IR (neat) 1717, 1513, 1303, 1247, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (dd, J = 7, 2 Hz, 3 H), 3.62 (dd, J = 11, 4 Hz, 1 H), 3.78 (dd, J = 11, 7 Hz, 1 H), 3.79 (s, 3 H), 4.51 (d, J = 12 Hz, 1 H), 4.57 (d, J = 12 Hz, 1 H), 5.54 (ddq, J = 11, 9, 2 Hz, 1 H), 5.78 (ddq, J = 11, 1, 7 Hz, 1 H), 6.10–6.18 (m, 1 H), 6.84 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H), 7.44 (ddd, J = 8, 5, 1 Hz, 1 H), 7.83 (ddd, J = 8, 8, 2 Hz, 1 H), 8.12 (ddd, J = 8, 1, 1 Hz, 1 H), 8.78 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (–), 55.3 (–), 70.5 (–), 70.9 (+), 72.8 (+), 113.8 (–), 125.3 (–), 126.8 (–), 129.3 (–), 130.1 (+), 130.9 (–), 136.9 (–), 148.4 (+), 149.9 (–), 159.2 (+), 164.5 (+); HRMS (FAB) calcd for $C_{19}H_{22}NO_4$ $[(M + H)^+]$ 328.1549, found 328.1550.

Allylic Substitution.

General Procedure of the Allylic Substitution. (Table 2, entry 2)

To an ice-cold solution of trimethylsilylacetylene (0.032 mL, 0.231 mmol) in THF (0.4 mL) was added BuLi (0.13 mL, 1.60 M in hexane, 0.208 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.60 mL, 0.20 M in THF, 0.320 mmol) and $CuBr{\cdot}Me_2S$ (21.6 mg, 0.105 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (34.1 mg, 0.105 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford a 94:6 mixture of (*S*)-**3a** and **21** (29.5 mg, 93%, 94% regioselectivity): $[\alpha]^{26}_{D}$ +57.8 (*c* 0.816, $CHCl_3$); IR (neat) 2172, 1514, 1250, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.71 (ddd, J = 7, 2, 2 Hz, 3 H), 3.28–3.39 (m, 1 H), 3.42 (dd, J = 9, 7 Hz, 1 H), 3.51 (dd, J = 9, 6 Hz, 1 H), 3.80 (s, 3 H), 4.51 (s, 2 H), 5.43 (ddq, J = 15, 6, 2 Hz, 1 H), 5.78 (ddq, J = 15, 2, 7 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 0.23 (–), 17.9 (–), 36.4 (–), 55.3 (–), 72.7 (+), 72.9 (+), 87.7 (+), 105.6 (+), 113.8 (–), 127.3 (–), 127.7 (–), 129.3 (–), 130.4 (+), 159.2 (+); HRMS (FAB) calcd for $C_{18}H_{26}O_2SiNa$ [$(M + Na)^+$] 325.1600, found 325.1598. The enantiomeric information (97% ee, 99% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 27.6 (*R*), 38.9 (*S*).

*Determination of the absolute configuration of (S)-**3a***: (eq 7)

(*R*)-1-[(2-Ethylpentyloxy)methyl]-4-methoxybenzene (26) from 27.

To a solution of **27** (17.4 mg, 0.0743 mmol) in EtOAc (1 mL) was added 10% Pd/C (8 mg). The mixture was stirred at rt for 1 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **26** (12.2 mg, 69%): $[\alpha]_D^{28}$ –7.2 (*c* 0.166, $CHCl_3$); IR (neat) 1612, 1513, 1248, 1094, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 8 Hz, 3 H), 0.86 (t, J = 8 Hz, 3 H), 1.18–1.64 (m, 7 H), 3.31 (d, J = 6 Hz, 2 H), 3.81 (s, 3 H), 4.42 (s, 2 H), 6.88 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1 (–), 14.6 (–), 20.1 (+), 24.0 (+), 33.3 (+), 39.6 (–), 55.4 (–), 72.7 (+), 73.0 (+), 113.8 (–), 129.2 (–), 131.1 (+), 159.1 (+). Chiralcel OB-H; hexane/*i*-PrOH = 96/4, 0.4 mL/min, 40 °C; t_R (min) = 27.8 (*S*), 34.9 (*R*).

(*S*,*E*)-1-[(2-Ethynylpent-3-enyloxy)methyl]-4-methoxybenzene ((*S*)-25).

To an ice-cold solution of (*S*)-**3a** (101 mg, 0.334 mmol) in THF (0.5 mL) was added a solution of Bu_4NF (0.67 mL, 1.0 M in THF, 0.67 mmol) and AcOH (0.038 mL, 0.664 mmol) in THF (0.5 mL). The resulting solution was stirred at rt overnight, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**25** (73.0 mg, 95%): $[\alpha]^{27}_D$ +54.2 (*c* 0.542, $CHCl_3$); IR (neat) 3292, 1612, 1513, 1249, 1100, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (ddd, J = 6, 2, 2 Hz, 3 H), 2.23 (d, J = 2 Hz, 1 H), 3.26–3.37 (m, 1 H), 3.43 (dd, J = 9, 7 Hz, 1 H), 3.50 (dd, J = 9, 7 Hz, 1 H), 3.81 (s, 3 H), 4.51 (s, 2 H), 5.43 (ddq, J = 15, 6, 2 Hz, 1 H), 5.81 (ddq, J = 15, 2, 6 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 35.2 (–), 55.3 (–), 71.3 (+), 72.7 (+), 72.8 (+), 83.5 (+), 113.8 (–), 126.9 (–), 128.1 (–), 129.4 (–), 130.2 (+), 159.3 (+); HRMS (FAB) calcd for $C_{15}H_{18}O_2$ (M^+) 230.1307, found 230.1308.

(*R*)-1-[(2-Ethylpentyloxy)methyl]-4-methoxybenzene (26) from (*S*)-25.

To a solution of (*S*)-**25** (26.3 mg, 0.114 mmol) in benzene (1 mL) was added $RhCl(PPh_3)_3$ (21 mg, 0.0227 mmol). The solution was stirred at rt for 20 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **26** (19.4 mg, 72%). Retention time for **26** was identical with that derived from **27**.

(*R*,*E*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-7-phenyl-1-(trimethylsilyl)hept-4-en-1-yne ((*R*)-3b).

Table 4, entry 1: To an ice-cold solution of trimethylsilylacetylene (0.029 mL, 0.210 mmol) in THF (1.5 mL) was added BuLi (0.12 mL, 1.60 M in hexane, 0.192 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.50 mL, 0.20 M in THF, 0.300 mmol) and $CuBr{\cdot}Me_2S$ (19.7 mg, 0.0958 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1b** (39.5 mg, 0.0960 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*R*)-**3b** (30.9 mg, 83%, 97% regioselectivity): $[\alpha]^{26}_{D}$ –39.7 (*c* 0.564 $CHCl_3$); IR (neat) 2172, 1251, 1109, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.16 (s, 9 H), 0.90 (s, 9 H), 2.35 (dt, *J* = 7, 8 Hz, 2 H), 2.70 (t, *J* = 8 Hz, 2 H), 3.20 (ddd, *J* = 7, 7, 6 Hz, 1 H), 3.52 (dd, *J* = 9, 7 Hz, 1 H), 3.64 (dd, *J* = 9, 7 Hz, 1 H), 5.44 (dd, *J* = 15, 6 Hz, 1 H), 5.80 (dt, *J* = 15, 7 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.24–7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2 (–), –5.1 (–), 0.25 (–), 18.5 (+), 26.0 (–), 34.4 (+), 35.8 (+), 39.0 (–), 66.7 (+), 87.7 (+), 105.9 (+), 125.9 (–), 126.9 (–), 128.4 (–), 128.5 (–), 132.0 (–), 142.0 (+); HRMS (FAB) calcd for $C_{23}H_{38}OSi_2Na$ [(M + Na)$^+$] 409.2359, found 409.2354. The enantiomeric information (96% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 100/0, 0.05 mL/min, 40 °C; t_R (min) = 88.0 (*R*), 97.5 (*S*).

*Determination of the absolute configuration of (R)-**3b***: (eq 8)

To an ice-cold solution of (*R*)-**3b** (13.9 mg, 0.0359 mmol) in THF (0.5 mL) was added a solution of Bu_4NF (0.11 mL, 1.0 M in THF, 0.11 mmol) and AcOH (0.006 mL, 0.11 mmol) in THF (0.5 mL). The resulting solution was stirred at rt for 20 h, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give alcohol **34** (8.4 mg), which was used for the next reaction without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (br s, 1 H), 2.26 (d, *J* = 3 Hz, 1 H), 2.39 (dt, *J* = 7, 8 Hz, 2 H), 2.72 (t, *J* = 8 Hz, 2 H), 3.16–3.27 (m, 1 H), 3.55 (d, *J* = 6 Hz, 2 H), 5.33 (dd, *J* = 15, 7 Hz, 1 H), 5.83 (ddt, *J* = 15, 1, 7 Hz, 1 H), 7.14–7.23 (m, 3 H), 7.25–7.33 (m, 2 H).

To a solution of the above alcohol in MeOH (1 mL) was added 10% Pd/C (2 mg). The mixture was stirred at rt overnight under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give alcohol **35** (7.6 mg), which was used for the next reaction without further purification.

To an ice-cold solution of the above alcohol in pyridine and CH_2Cl_2 (1 : 1, 1 mL) was added BzCl (0.010 mL, 0.086 mmol). The resulting mixture was stirred at rt overnight and diluted with EtOAc and H_2O. The excess reagent was quenched with *N*,*N*-dimethyl-1,3-propanediamine (0.014 mL, 0.11 mmol). The mixture was stirred at rt for 20 min. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **36** (8.3 mg, 74% from (*R*)-**3b**): The *S* configuration and the structure of **36** were determined by chiral HPLC analysis and ^1H and ^{13}C NMR spectroscopy with the known sample in Chapter 3.

(*R*,*E*)-3-Methyl-7-phenyl-1-(trimethylsilyl)hept-4-en-1-yne ((*R*)-3c).

Table 4, entry 2: To an ice-cold solution of trimethylsilylacetylene (0.035 mL, 0.253 mmol) in THF (0.8 mL) was added BuLi (0.14 mL, 1.60 M in hexane, 0.224 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.70 mL, 0.20 M in THF, 0.34 mmol) and $CuBr·Me_2S$ (23.6 mg, 0.115 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1c** (32.3 mg, 0.115 mmol, 94% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*R*)-**3c** (23.6 mg, 80%, 98% regioselectivity): $[\alpha]^{25}_D$ –26 (*c* 0.532, $CHCl_3$); IR (neat) 2169, 1250, 869, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.21 (d, *J* = 7 Hz, 3 H), 2.33 (dt, *J* = 7, 8 Hz, 2 H), 2.69 (t, *J* = 8 Hz, 2 H), 3.12 (dqq, *J* = 6, 7, 2 Hz, 1 H), 5.40 (ddt, *J* = 15, 6, 1 Hz, 1 H), 5.70 (ddt, *J* = 15, 2, 7 Hz, 1 H), 7.10–7.22 (m, 3 H), 7.24–7.31 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.30 (–), 21.9 (–), 29.6 (–), 34.1 (+), 35.8 (+), 85.8 (+), 109.5 (+), 125.8 (–), 128.3 (–), 128.6 (–), 129.4 (–), 131.5 (–), 142.0 (–); HRMS (EI) calcd for $C_{17}H_{24}Si$ (M^+) 256.1647, found 256.1654. The enantiomeric information (92% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel OD-H; hexane/*i*-PrOH = 100/0, 0.1 mL/min, 40 °C; t_R (min) = 72.9 (*R*), 78.7 (*S*).

(*R*,*E*)-8-(4-Methoxybenzyloxy)-3-pentyl-1-(trimethylsilyl)oct-4-en-1-yne ((*R*)-3d).

Table 4, entry 3: To an ice-cold solution of trimethylsilylacetylene (0.025 mL, 0.181 mmol) in THF (1.8 mL) was added BuLi (0.11 mL, 1.55 M in hexane, 0.171 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.20 mL, 0.20 M in THF, 0.24 mmol) and $CuBr{\cdot}Me_2S$ (17.1 mg, 0.0832 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1d** (34.2 mg, 0.0831 mmol, 93% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*R*)-**3d** (28.5 mg, 89%, 94% regioselectivity): $[\alpha]^{26}_{D}$ –30.2 (*c* 0.570, $CHCl_3$); IR (neat) 2167, 1513, 1249, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 0.89 (t, *J* = 7 Hz, 3 H), 1.19–1.56 (m, 8 H), 1.68 (tt, *J* = 8, 7 Hz, 2 H), 2.11 (dt, *J* = 7, 7 Hz, 2 H), 2.99 (dt, *J* = 7, 6 Hz, 1 H), 3.45 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.34 (dd, *J* = 15, 7 Hz, 1 H), 5.63 (dt, *J* = 15, 7 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.3 (–), 14.1 (–), 22.6 (+), 26.6 (+), 28.9 (+), 29.4 (+), 31.6 (+), 35.5 (–), 35.8 (+), 55.3 (–), 69.5 (+), 72.6 (+), 86.6 (+), 108.8 (+), 113.8 (–), 129.3 (–), 130.2 (–), 130.4 (–), 130.8 (+), 159.2 (+); HRMS (FAB) calcd for $C_{24}H_{38}O_2SiNa$ $[(M + Na)^+]$ 409.2539, found 409.2539. The enantiomeric information (91% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 17.7 (*R*), 25.2 (*S*).

(*R*,*E*)-3-Cyclohexyl-8-(4-methoxybenzyloxy)-1-(trimethylsilyl)oct-4-en-1-yne ((*R*)-3e).

Table 4, entry 4: To an ice-cold solution of trimethylsilylacetylene (0.025 mL, 0.181 mmol) in THF (0.8 mL) was added BuLi (0.10 mL, 1.60 M in hexane, 0.160 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.20 mL, 0.20 M in THF, 0.24 mmol) and $CuBr{\cdot}Me_2S$ (16.8 mg, 0.0817 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*S*)-**1e** (34.7 mg, 0.0819 mmol, 99% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*R*)-**3e** (21.6 mg, 66%, 86% regioselectivity): ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 0.96–1.84 (m, 13 H), 2.12 (dt, *J* = 7, 7 Hz, 2 H), 2.86 (dd, *J* = 7, 7 Hz, 1 H), 3.45 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.32 (dd, *J* = 15, 7 Hz, 1 H), 5.61 (dt, *J* = 15, 7 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.26 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.4 (–), 26.4 (+), 26.47 (+), 26.52 (+), 29.0 (+), 29.5 (+), 29.6 (+), 31.0 (+), 42.0 (–), 42.3 (–), 55.3 (–), 69.5 (+), 72.7 (+), 87.6 (+), 107.6 (+), 113.8 (–), 128.8 (–), 129.3 (–), 130.8 (+), 131.4 (–), 159.2 (+).

(*S*,*E*)-3-[(4-Methoxybenzyloxy)methyl]-1-phenylhex-4-en-1-yne ((*S*)-3f).

Table 4, entry 5: To an ice-cold solution of phenylacetylene (0.027 mL, 0.246 mmol) in THF (0.5 mL) was added BuLi (0.14 mL, 1.60 M in hexane, 0.224 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.50 mL, 0.20 M in THF, 0.300 mmol) and CuBr·Me_2S (22.6 mg, 0.110 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (24.0 mg, 0.0738 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3f** (15.8 mg, 70%, 95% regioselectivity): $[\alpha]^{25}_{D}$ +38 (*c* 0.412, $CHCl_3$); IR (neat) 1513, 1248, 1099, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, *J* = 7 Hz, 3 H), 3.47–3.64 (m, 3 H), 3.80 (s, 3 H), 4.54 (s, 2 H), 5.52 (dm, *J* = 15 Hz, 1 H), 5.86 (dq, *J* = 15, 7 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.23–7.34 (m, 5 H), 7.38–7.46 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 36.1 (–), 55.3 (–), 72.8 (+), 73.0 (+), 83.7 (+), 88.9 (+), 113.8 (–), 123.7 (+), 127.5 (–), 127.8 (–), 127.9 (–), 128.2 (–), 129.4 (–), 130.4 (+), 131.8 (–), 159.3 (+); HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1628. The enantiomeric information (94% ee, 96% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 69.5 (*R*), 76.4 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyloxy)phenyl]-3-[(4-methoxybenzyloxy)methyl]hex-4-en-1-yne ((*S*)-3g).

Table 4, entry 6: To an ice-cold solution of 4-(*tert*-butyldimethylsilyloxy)phenylacetylene (67.6 mg, 0.291 mmol) in THF (1.2 mL) was added BuLi (0.17 mL, 1.60 M in hexane, 0.272 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.80 mL, 0.20 M in THF, 0.360 mmol) and CuBr·Me_2S (27.2 mg, 0.132 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (28.7 mg, 0.0882 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3g** (23.6 mg, 61%, 93% regioselectivity): $[\alpha]^{27}_{D}$ +43 (*c* 0.354, $CHCl_3$); IR (neat) 1507, 1254, 911, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.97 (s, 9 H), 1.72 (d, *J* = 6 Hz, 3 H), 3.44–3.63 (m, 3 H), 3.81 (s, 3 H), 4.54 (s, 2 H), 5.51 (dm, *J* = 15 Hz, 1 H), 5.85 (ddq, *J* = 15, 1, 6 Hz, 1 H), 6.75 (d, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.29 (d, *J* = 9 Hz, 2 H), 7.31 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.4 (–), 17.9 (–), 18.3 (+), 25.7 (–), 36.1 (–), 55.3 (–), 72.8 (+), 73.1 (+), 83.5 (+), 87.4 (+), 113.8 (–), 116.5 (+), 120.1 (–), 127.7 (–), 127.8 (–), 129.4 (–), 130.4 (+), 133.1 (–), 155.6 (+), 159.2 (+); HRMS (FAB) calcd for $C_{27}H_{37}O_3Si$ [$(M + H)^+$] 437.2512, found 437.2514. The enantiomeric information (93% ee, 95% CT) was determined by chiral HPLC analysis: Chiralcel OJ-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R/min = 51.5 (*S*), 63.1 (*R*).

(*S*,*E*)-3-[(4-Methoxybenzyloxy)methyl]-1-(4-methoxyphenyl)hex-4-en-1-yne ((*S*)-3h).

Table 4, entry 7: To an ice-cold solution of 4-methoxyphenylacetylene (41.3 mg, 0.312 mmol) in THF (1 mL) was added BuLi (0.18 mL, 1.55 M in hexane, 0.279 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.90 mL, 0.20 M in THF, 0.380 mmol) and $CuBr·Me_2S$ (29.2 mg, 0.142 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (30.8 mg, 0.0947 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3h** (21.4 mg, 67%, 92% regioselectivity): $[\alpha]^{27}_{D}$ +67.6 (*c* 0.296, $CHCl_3$); IR (neat) 1607, 1510, 1248, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6 Hz, 3 H), 3.46–3.64 (m, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.54 (s, 2 H), 5.51 (dm, *J* = 15 Hz, 1 H), 5.85 (dq, *J* = 15, 6 Hz, 1 H), 6.81 (d, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.29 (d, *J* = 9 Hz, 2 H), 7.36 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 36.1 (–), 55.32 (–), 55.34 (–), 72.8 (+), 73.1 (+), 83.5 (+), 87.3 (+), 113.8 (–), 115.8 (+), 127.7 (–), 127.8 (–), 129.4 (–), 130.4 (+), 133.1 (–), 159.2 (+), 159.3 (+); HRMS (FAB) calcd for $C_{22}H_{25}O_3$ $[(M + H)^+]$ 337.1804, found 337.1800. The enantiomeric information (95% ee, 97% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 96/4, 0.4 mL/min, rt; t_R (min) = 60.6 (*R*), 78.8 (*S*).

(*S*,*E*)-3-[(4-Methoxybenzyloxy)methyl]-1-(2-methoxyphenyl)hex-4-en-1-yne ((*S*)-3i).

Table 4, entry 8: To an ice-cold solution of 2-methoxyphenylacetylene (48.4 mg, 0.366 mmol) in THF (0.8 mL) was added BuLi (0.20 mL, 1.66 M in hexane, 0.33 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (2.20 mL, 0.20 M in THF, 0.44 mmol) and $CuBr·Me_2S$ (22.9 mg, 0.111 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (36.2 mg, 0.111 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3i** (33.2 mg, 89%, 97% regioselectivity): $[\alpha]^{25}_{D}$ +57.4 (*c* 0.540, $CHCl_3$); IR (neat) 1612, 1513, 1493, 1249, 1098, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, *J* = 6 Hz, 3 H), 3.50–3.68 (m, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.56 (s, 2 H), 5.54 (dm, *J* = 15 Hz, 1 H), 5.93 (dq, *J* = 15, 6 Hz, 1 H), 6.82–6.94 (m, 4 H), 7.20–7.35 (m, 3 H), 7.40 (dd, *J* = 8, 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 36.3 (–), 55.3 (–), 55.8 (–), 72.8 (+), 73.1 (+), 79.9 (+), 93.0 (+), 110.6 (–), 112.8 (+), 113.8 (–), 120.4 (–), 127.6 (–), 127.7 (–), 129.25 (–), 129.35 (–), 130.5 (+), 133.7 (–), 159.2 (+), 160.1 (+); HRMS (FAB) calcd for $C_{22}H_{24}O_3Na$ $[(M + Na)^+]$ 359.1623, found 359.1623. The enantiomeric information (95% ee, 97% CT) was determined by chiral

HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 96/4, 0.4 mL/min, rt; t_R (min) = 15.5 (*R*), 17.1 (*S*).

(*S*,*E*)-3-[(4-Methoxybenzyloxy)methyl]-1-(4-methylphenyl)hex-4-en-1-yne ((*S*)-3j).
Table 4, entry 9: To an ice-cold solution of 4-methylphenylacetylene (0.043 mL, 0.339 mmol) in THF (1 mL) was added BuLi (0.19 mL, 1.66 M in hexane, 0.32 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (2.10 mL, 0.20 M in THF, 0.42 mmol) and $CuBr{\cdot}Me_2S$ (31.8 mg, 0.155 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (33.4 mg, 0.103 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3j** (27.8 mg, 84%, 94% regioselectivity): $[\alpha]^{27}_D$ +66.7 (*c* 0.426, $CHCl_3$); IR (neat) 1612, 1511, 1248, 1099, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6 Hz, 3 H), 2.33 (s, 3 H), 3.47–3.63 (m, 3 H), 3.80 (s, 3 H), 4.54 (s, 2 H), 5.52 (dm, *J* = 15 Hz, 1 H), 5.86 (dq, *J* = 15, 6 Hz, 1 H), 6.84 (d, *J* = 9 Hz, 2 H), 7.09 (d, *J* = 8 Hz, 2 H), 7.28 (d, *J* = 8 Hz, 2 H), 7.31 (d, *J*= 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 21.5 (–), 36.1 (–), 55.3 (–), 72.8 (+), 73.0 (+), 83.8 (+), 88.0 (+), 113.8 (–), 120.6 (+), 127.67 (–), 127.71 (–), 129.0 (–), 129.4 (–), 130.4 (+), 131.6 (–), 137.8 (+), 159.2 (+); HRMS (FAB) calcd for $C_{22}H_{24}O_2Na$ [(M + Na)$^+$] 343.1674, found 343.1670. The enantiomeric information (95% ee, 97% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 22.3 (*R*), 26.5 (*S*).

(*S*,*E*)-1-(4-Fluorophenyl)-3-[(4-Methoxybenzyloxy)methyl]hex-4-en-1-yne ((*S*)-3k).
Table 4, entry 10: To an ice-cold solution of 4-fluorophenylacetylene (0.037 mL, 0.323 mmol) in THF (1 mL) was added BuLi (0.18 mL, 1.66 M in hexane, 0.30 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.90 mL, 0.20 M in THF, 0.38 mmol) and $CuBr{\cdot}Me_2S$ (30.0 mg, 0.146 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (31.7 mg, 0.0974 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford (*S*)-**3k** (27.8 mg, 88%, 95% regioselectivity): $[\alpha]^{25}_D$ +58.5 (*c* 0.496, $CHCl_3$); IR (neat) 1612, 1507, 1248, 1093, 1037, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, *J* = 6 Hz, 3 H), 3.46–3.62 (m, 3 H), 3.80 (s, 3 H), 4.54 (s, 2 H), 5.50 (dm, *J* = 15 Hz, 1 H), 5.84 (dq, *J* = 15, 6 Hz, 1 H), 6.88 (d, *J* = 8 Hz, 2 H), 6.98 (dd, $J_{H\text{-}H}$ = 9 Hz, $J_{F\text{-}H}$ = 9 Hz, 2 H), 7.29 (d, *J* = 8 Hz, 2 H), 7.39 (dd, $J_{H\text{–}H}$ = 9 Hz, $J_{F\text{–}H}$ = 5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (–), 36.0 (–), 55.3 (–), 72.8 (+), 72.9 (+), 82.6 (+), 88.6 (+), 113.8 (–), 115.4 (–, d, $J_{C\text{–}F}$ = 22 Hz), 119.7 (+, d, $J_{C\text{–}F}$ = 4 Hz), 127.4 (–), 127.9 (–), 129.4 (–), 130.3 (+), 133.6 (–, d, $J_{C\text{–}F}$ = 8 Hz), 159.3 (+), 162.3 (+, d, $J_{C\text{–}F}$ = 247 Hz); ^{19}F NMR

(470 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 49.8 (tt, $J_{F\text{–}H}$ = 9, 6 Hz, 1 F); HRMS (FAB) calcd for $C_{21}H_{21}FO_2Na$ [(M + Na)$^+$] 347.1423, found 347.1418. The enantiomeric information (96% ee, 98% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, rt; t_R (min) = 31.3 (*R*), 38.1 (*S*).

(*E*)-6-(4-Methoxybenzyloxy)-3-methyl-1-(trimethylsilyl)hex-4-en-1-yne (33).

Scheme 3: To an ice-cold solution of trimethylsilylacetylene (0.034 mL, 0.246 mmol) in THF (0.4 mL) was added BuLi (0.14 mL, 1.60 M in hexane, 0.22 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.60 mL, 0.20 M in THF, 0.32 mmol) and $CuBr{\cdot}Me_2S$ (22.1 mg, 0.108 mmol) were added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of picolinate **32** (35.0 mg, 0.108 mmol) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h to afford **33** (26.7 mg, 82%, 91% regioselectivity): IR (neat) 2170, 1513, 1250, 843 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.26 (d, *J* = 7 Hz, 3 H), 3.20 (dq, *J* = 6, 7 Hz, 1 H), 3.81 (s, 3 H), 3.99 (d, *J* = 6 Hz, 1 H), 4.45 (s, 2 H), 5.67 (dd, *J* = 16, 6 Hz, 1 H), 5.82 (dt, *J* = 16, 6 Hz, 1 H), 6.88 (d, *J* = 8 Hz, 2 H), 7.27 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.3 (–), 21.5 (–), 29.4 (–), 55.4 (–), 70.1 (+), 71.8 (+), 86.2 (+), 108.7 (+), 113.9 (–), 126.4 (–), 129.5 (–), 130.5 (+), 134.3 (–), 159.3 (+); HRMS (FAB) calcd for $C_{18}H_{26}O_2Si$ (M$^+$) 302.1702, found 302.1700.

Transformations of (*S*)-25. (Scheme 4)

(*S*,*E*)-1-Methoxy-4-(2-propenylundec-5-en-3-ynyloxy)methylbenzene ((*S*)-45).

To an ice-cold solution of (*S*)-**25** (15.7 mg, 0.0682 mmol; see the text for the preparation) and (*E*)-1-iodoheptene (**44**) (23 mg, 0.103 mmol) in THF (1 mL) were added Et_3N (0.012 mL, 0.086 mmol), CuI (1.3 mg, 0.0068 mmol) and $Pd(PPh_3)_4$ (2.4 mg, 0.0021 mmol). The resulting mixture was stirred at rt for 18 h, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**45** (15.2 mg, 68%): $[\alpha]^{28}_{D}$ +61.9 (*c* 0.430, $CHCl_3$); IR (neat) 1612, 1513, 1249, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3 H), 1.20–1.43 (m, 6 H), 1.70 (d, *J* = 6 Hz, 3 H), 2.07 (ddt, *J* = 7, 2, 7 Hz, 2 H), 3.36–3.57 (m, 3 H), 3.81 (s, 3 H), 4.50 (s, 2 H), 5.44 (dm, *J* = 15 Hz, 1 H), 5.48 (dm, *J* = 15 Hz, 1 H), 5.77 (dq, *J* = 15, 6 Hz, 1 H), 6.10 (dt, *J* = 15, 7 Hz, 1 H), 6.87 (d, *J* = 8

Hz, 2 H), 7.27 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (–), 17.9 (–), 22.6 (+), 28.5 (+), 31.4 (+), 33.0 (+), 36.0 (–), 55.4 (–), 72.7 (+), 73.0 (+), 82.4 (+), 87.0 (+), 109.6 (–), 113.8 (–), 127.6 (–), 127.8 (–), 129.4 (–), 130.4 (+), 144.3 (–), 159.3 (+); HRMS (FAB) calcd for $C_{22}H_{31}O_2$ [(M + H)$^+$] 327.2324, found 327.2318.

(*S*,*E*)- 3-[(4-Methoxybenzyloxy)methyl]-1-phenylhex-4-en-1-yne ((*S*)-3f).

To an ice-cold solution of (*S*)-**25** (11.8 mg, 0.0512 mmol) and iodobenzene (**46**) (16 mg, 0.078 mmol) in THF (1 mL) were added Et_3N (0.010 mL, 0.072 mmol), CuI (1.0 mg, 0.0053 mmol) and $Pd(PPh_3)_4$ (1.8 mg, 0.0016 mmol). The resulting mixture was stirred at rt overnight, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**3f** (14.8 mg, 94%). The ^{1}H and ^{13}C spectra of the product was identical with those prepared by the allylic substitution of (*R*)-**1a** with $(PhC{\equiv}C)_2Cu(MgBr)$ (Table 4, entry 5; see above for the procedure).

(*S*,*E*)-Ethyl 4-[3-((4-Methoxybenzyloxy)methyl)hex-4-en-1-ynyl]benzoate ((*S*)-48).

To an ice-cold solution of (*S*)-**25** (20.9 mg, 0.0908 mmol) and ethyl 4-iodobenzoate (**47**) (0.023 mL, 0.137 mmol) in THF (1 mL) were added Et_3N (0.015 mL, 0.108 mmol), CuI (1.7 mg, 0.009 mmol), and $Pd(PPh_3)_4$ (3.2 mg, 0.0027 mmol). The resulting mixture was stirred at rt for 18 h, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and brine successively, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**48** (33.7 mg, 98%): $[\alpha]^{24}_D$ +45.0 (*c* 0.462, $CHCl_3$); IR (neat) 2231, 1717, 1273, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7 Hz, 3 H), 1.73 (d, *J* = 6 Hz, 3 H), 3.47–3.64 (m, 3 H), 3.80 (s, 3 H), 4.37 (q, *J* = 7 Hz, 2 H), 4.54 (s, 2 H), 5.50 (dm, *J* = 15 Hz, 1 H), 5.85 (dq, *J* = 15, 6 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.29 (d, *J* = 9 Hz, 2 H) 7.47 (d, *J* = 8 Hz, 2 H), 7.97 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (–), 17.9 (–), 36.2 (–), 55.3 (–), 61.1 (+), 72.7 (+), 72.8 (+), 83.1 (+), 92.3 (+), 113.8 (–), 127.1 (–), 128.1 (–), 128.3 (+), 129.36 (–), 129.38 (–), 129.5 (+), 130.2 (+), 131.6 (–), 159.3 (+), 166.2 (+); HRMS (FAB) calcd for $C_{24}H_{27}O_4$ [(M + H)$^+$] 379.1909, found 379.1900.

(*S*,*E*)-4-[1-(4-Methoxybenzyloxy)methylbut-2-enyl]-1-(3-phenylpropyl)-1*H*-[1,2,3]triazole ((*S*)-50).

To a mixture of (*S*)-**25** (15.2 mg, 0.066 mmol) and (3-azidopropyl)benzene (**49**) (12.8 mg, 0.0794 mmol) in *t*-BuOH (1 mL) and H_2O (0.3 mL) were added $CuSO_4{\cdot}5H_2O$ (6.4 mg, 0.026 mmol) and sodium ascorbate (10.4 mg, 0.0523 mmol) at rt. The resulting mixture was stirred at rt for 2 h, and diluted with EtOAc and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**50** (23.4 mg, 91%): $[\alpha]^{25}_{D}$ +26 (*c* 0.370, $CHCl_3$); IR (neat) 1612, 1513, 1248, 1097, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* = 6 Hz, 3 H), 2.22 (tt, *J* = 8, 7 Hz, 2 H), 2.64 (t, *J* = 8 Hz, 2 H), 3.66 (dd, *J* = 9, 6 Hz, 1 H), 3.69–3.86 (m, 2 H), 3.78 (s, 3 H), 4.30 (t, *J* = 7 Hz, 2 H), 4.46 (s, 2 H), 5.52–5.71 (m, 2 H), 6.84 (d, *J* = 9 Hz, 2 H), 7.13–7.34 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (–), 31.8 (+), 32.6 (+), 40.8 (–), 49.5 (+), 55.3 (–), 72.8 (+), 72.9 (+), 113.8 (–), 121.3 (–), 126.4 (–), 127.7 (–), 128.5 (–), 128.7 (–), 129.3 (–), 129.9 (–), 130.4 (+), 140.3 (+), 148.6 (+), 159.2 (+); HRMS (FAB) calcd for $C_{24}H_{30}N_3O_2$ $[(M + H)^+]$ 392.2338, found 392.2341.

(*R*,4*E*)-Ethyl *N*-4-Acetamidophenylsulfonyl-3-[(4-methoxybenzyloxy)methyl]hex-4-enimidate ((*R*)-52).

To an ice-cold solution of (*S*)-**25** (14.4 mg, 0.0625 mmol) and azide **51** (16.5 mg, 0.0687 mmol) in $CHCl_3$ (0.5 mL) were added 2,6-lutidine (0.01 mL, 0.086 mmol) and CuI (2.4 mg, 0.013 mmol). The resulting mixture was stirred at 0 °C for 20 h, and EtOH (0.2 mL) was added to it. After stirring at rt for 30 min, the mixture was diluted with CH_2Cl_2 and saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**52** (24.8 mg, 81%): $[\alpha]^{28}_{D}$ –11 (*c* 0.45, $CHCl_3$); IR (neat) 3330, 2127, 1593, 1533, 1316, 1249, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7 Hz, 3 H), 1.61 (dd, *J* = 7, 1 Hz, 3 H), 2.19 (s, 3 H), 2.88 (dd, *J* = 13, 8 Hz, 1 H), 2.90–3.02 (m, 1 H), 3.08 (dd, *J* = 13, 5 Hz, 1 H), 3.32 (dd, *J* = 9, 8 Hz, 1 H), 3.43 (dd, *J* = 9, 5 Hz, 1 H), 3.80 (s, 3 H), 3.97–4.14 (m, 2 H), 4.42 (s, 2 H), 5.26 (ddd, *J* = 15, 8, 1 Hz, 1 H), 5.54 (dq, *J* = 15, 7 Hz, 1 H), 6.86 (d, *J* = 9 Hz, 2 H), 7.24 (d, *J* = 9 Hz, 2 H), 7.61 (d, *J* = 9 Hz, 2 H), 7.77–7.88 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (–), 18.1 (–), 24.7 (–), 36.7 (+), 40.7 (–), 55.4 (–), 64.5 (+), 72.7 (+), 73.2 (+), 113.8 (–), 119.1 (–), 127.7 (–), 127.8 (–), 129.0 (–), 129.4 (–), 129.9 (–), 130.4 (+), 137.0 (+), 141.8 (+), 159.2 (+), 168.9 (+), 175.4 (+); HRMS (FAB) for $C_{25}H_{32}N_2O_6SNa$ [$(M + Na)^+$] 511.1879, found 511.1874.

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第８章「総括」

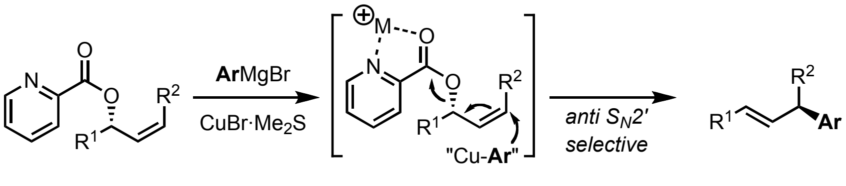
著者は博士論文研究として、ピコリン酸アリル化合物へのアリル化反応の開発研究を行った。本章では、各章の結果をまとめ、今後の展望について概観した。

標的化合物の合成において、光学活性な炭素－炭素結合を立体・位置選択的に構築する事は非常に重要な課題である。その不斉炭素構築方法の一つとして、著者は、有機銅試薬による２級アリルアルコール誘導体のアリル化反応に注目した。反応は、一般的にアンチ S_N2' 選択的にアルキル基 (sp^3 炭素基) を導入できる事が知られているが、求核性が低い炭素団 (sp^2 炭素や sp 炭素基) を位置・立体選択的に導入でき、経済性（試薬の当量や価格）に優れた反応系は見出されていなかった。そこで、これらの課題を解決したアリル化の反応系が創出できれば、ターゲット合成の際の新たな方法論を提供する事ができると考え、著者は新規反応系の開発を研究課題に決めた。

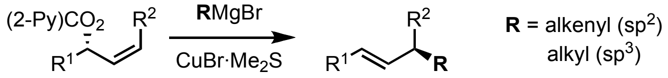
以下に、各章の結果をまとめる。

第２章「アリールグリニャール試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」では、sp^2 炭素基であるアリールグリニャール試薬と銅塩から生じるアリール銅試薬を用いてアリル化反応について検討した。その結果、ピコリン酸基が良好な脱離基となり､反応は高いアンチ S_N2' 選択性で進行する事を見出した。基質の適応範囲も広く、導入するベンゼン環のオルト位に置換基があっても立体障害にはならなかった。なお、グリニャール試薬は 2 当量用いて反応検討したが、小過剰 (1.2 当量) でも反応は完結した。また、応用研究として(–)-セスキカマエノールの全合成に成功した。

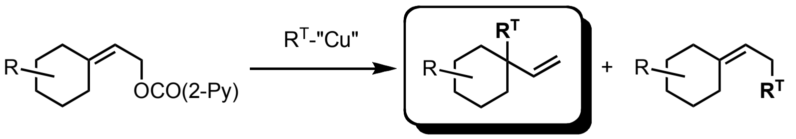
このアリル化反応のさらなる利点として、ピコリン酸, DCC, RMgBr と $CuBr{\cdot}Me_2S$ は安価である。そして、基質ピコリン酸アリルの原料となる、アリルアルコール類の両方の鏡像異性体は、不斉化反応又はキラルプールから簡単に合成できる事も示せた。



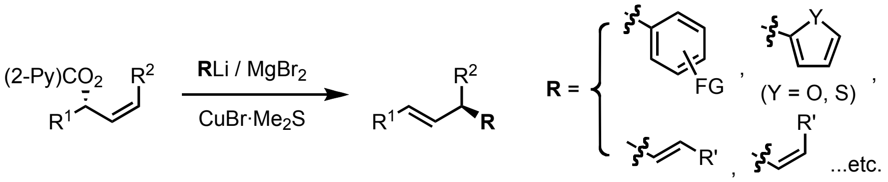
第３章「アルケニル及びアルキルグリニャール試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」では、グリニャール試薬と銅塩から生じる有機銅試薬をピコリン酸アリルと反応させ、アルケニル基 (sp^2-C) やアルキル基 (sp^3-C) を高アンチ S_N2’ 選択的に導入できる事を見出した。特に、これまで一般性の高い例が知られていないアルケニル基の導入を円滑に行なう事が出来た事は特筆に値する。



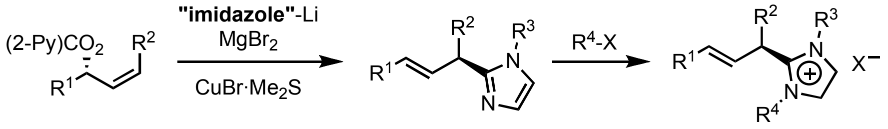
第４章「２−シクロヘキシリデンエチルピコリン酸エステルと有機銅試薬を用いた環上４級炭素の構築」では、従来困難とされてきた環上４級炭素の構築において、ピコリン酸基を脱離基としたアリル化反応を利用する事とした。その結果、シクロヘキサン環の置換基に依らず、高い位置・立体選択性で環上４級炭素を構築できる条件を見出した。得られた４級炭素は、容易に種々の変換が可能なビニル基を有しているため、更なる誘導化が可能であるという利点があり、今後の展開が期待できる。



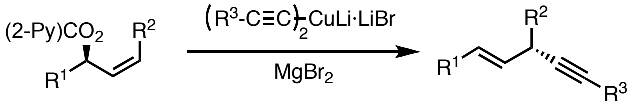
第５章「有機リチウム試薬と銅塩を用いたピコリン酸アリルのアリル化反応の開発」では、グリニャール試薬の調製が難しい sp^2 炭素基（芳香族複素環，アルケニル基など）をアリル化反応に適用することを考え、有機リチウム試薬を用いて検討を行った。その結果、有機リチウムと $CuBr{\cdot}Me_2S$ から調製した有機銅試薬によるピコリン酸アリルのアリル化反応は、$MgBr_2$ の添加によって効果的に加速され、高選択的にアンチ S_N2’ 生成物が得られる事を明らかにした。ピコリン酸アリルの一般性も良く、また、立体的・電子的な要因に依らずに様々なアリール基や、シス及びトランスアルケニル基、フリル、チエニル、アルキル基等をアンチ S_N2’ 選択的に導入できた。この時、ハロゲン−リチウム交換やオルトリチエーションのような、有機リチウムの様々な調製法がこのアリル化反応に適応可能な事も示せた。また、応用研究として、ACAT 阻害活性化合物のより簡便な合成ルートを提示する事ができた。



第６章「ピコリン酸アリルのアリル化反応を活用した，光学活性なイミダゾリウム塩とピリジニウム塩の合成」では、ピコリン酸アリルのアリル化反応を活用して隣接炭素に不斉中心を有するイミダゾール、ピリジン誘導体を合成した。さらに生成物を四級塩化することで新規な構造を有するイミダゾリウム塩とピリジニウム塩の合成に成功した。得られる C2 位の側鎖は二重結合の他にも官能基を有する事ができ、今回得られた構造から更なる誘導体を合成することも可能であり、新規４級塩の応用展開が期待できる。

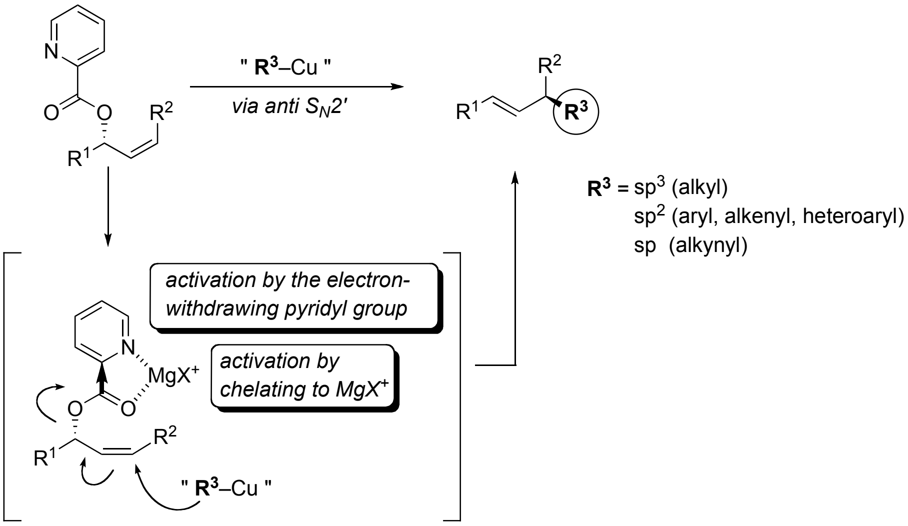


第７章「アルキニル銅試薬を用いたピコリン酸アリルのアリル化反応の開発」では、マグネシウム塩存在下でのピコリン酸基の卓越した脱離能に着目し、これまで全く報告がなかった、アルキニル銅試薬を用いた第２級アリルアルコール誘導体へのアリル化反応について検討した。その結果、ピコリン酸基を脱離基とする事が非常に重要であり、高い位置・立体選択性でアンチ S_N2' 生成物を得ることが出来る反応系を初めて見出した。



以上の研究成果をまとめると、本研究では、Scheme 1 に示したように、ピコリン酸基が、(a) 電子吸引性のピリジル基による活性化、(b) 金属 MgX^+ のピコリン酸基へのキレーションによる脱離能の活性化、によって良好な脱離基となり、様々な有機銅試薬とアンチ S_N2' 選択的に反応が進行する事を見出すことができた。

Scheme 1. Expected activations of the picolinoxy group in the allylic substitution.



このアリル化反応は、これまでの有機銅試薬のアリル化反応で実現されていなかった、求核性が低い炭素団 (sp^2 炭素や sp 炭素基) を位置・立体選択的に導入でき、かつ経済性（試薬の当量や価格）に優れた反応系である。また、ピコリン酸アリルの置換基 R^1, R^2 の適応範囲も広いので、生成物は、非常に自由度が高い置換基 R^1~R^3 を利用して様々な変換をする事が可能と言える。このアリル化反応が、天然物や医薬等の生理活性物質や、触媒などの新規材料の研究の際の一助となれば幸いである。

業績リスト

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