

Effect of Multinuclear Copper/Aluminum Complexes in Highly Asymmetric Conjugate Addition of Trimethylaluminum to Acyclic Enones**

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Over the past few decades, the asymmetric conjugate addition of organometallic reagents to activated olefins has become one of the most powerful approaches to chiral molecules, especially for installation of a small alkyl group on a chiral carbon atom.^[1] Although there have been various reports on the asymmetric conjugate addition of organometallic reagents to cyclic enones for the creation of an all-carbon substituted chiral quaternary stereogenic center,^[2] the use of acyclic enones still presents a formidable challenge. The steric congestion around a β,β -disubstituted olefin prevents 1,4-addition, but favors 1,2-addition, and the chiral catalyst hardly recognizes the enantioface because of the similarity of substituents on an olefinic carbon atom (Figure 1).^[3]

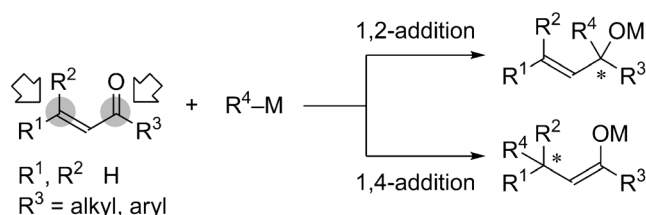


Figure 1. Regioselective addition to β,β -disubstituted α,β -unsaturated ketones.

There have been only a few reports on the construction of a chiral quaternary carbon center by the conjugate addition of

organometallic reagents to acyclic activated olefins. Hayashi and co-workers reported the rhodium-catalyzed asymmetric conjugate addition of organoboron compounds to α,β -unsaturated esters and enones with an excess amount of Ar_2BNa or organoboroxine under thermal conditions, with enones typically providing lower enantioselectivity.^[4] Alexakis, Woodward, and co-workers reported the rhodium-catalyzed asymmetric addition of PhAlMe_2 to β,β -disubstituted enones and the yields were moderate.^[5] Asymmetric addition reactions for the construction of a chiral quaternary carbon center have been developed extensively, but the alkylation remains a challenging transformation. There are various alternate approaches involving the installation of an aryl, vinyl, or alkynyl group to starting materials bearing an alkyl group. Fillion and co-workers reported the copper-catalyzed asymmetric conjugate addition of dialkylzinc reagents to Meldrum's acid derivatives at temperatures ranging from -40°C to room temperature.^[6] They reported that the functional groups present on the aromatic moiety affected the enantioselectivities, and sterically hindered substrates did not give the desired products. Hoveyda and co-workers developed the copper-catalyzed asymmetric conjugate addition of dialkylzinc reagents to nitro alkenes at -78°C , and methylation gave less than 90% *ee*.^[7] These previous results indicate that additional manipulation may be required to establish excellent yields and enantioselectivities for the construction of an all-carbon substituted chiral quaternary center, including a methyl-substituted carbon atom. A facile approach to the installation of a small methyl group on a chiral quaternary carbon atom has generally been difficult to achieve.^[8] Although there are alternate approaches to the creation of a methyl-substituted chiral quaternary carbon center using starting materials containing a methyl group, a new entry for the direct methylation to give an all-carbon-substituted chiral quaternary center would contribute to the synthesis of useful chiral building blocks. We describe herein a novel multinuclear copper/aluminum-catalyzed asymmetric conjugate addition of Me_3Al for the construction of a chiral tertiary carbon center and chiral quaternary carbon center in high to excellent yields with high to excellent *ee* values.

Our current interests in the development of multinuclear complexes showed that our original multinuclear complexes based on **BP1**, **BP2**, **SP1**, and **SP2** gave unprecedented catalytic performances in asymmetric alkylation reactions using organozinc reagents (Figure 2).^[9] Thus, we examined the asymmetric conjugate addition of Et_2Zn to the β,β -disubstituted enone (*E*)-**1**, bearing a methyl substituent, in the presence of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (5 mol%) and either **BP1** or **SP2**

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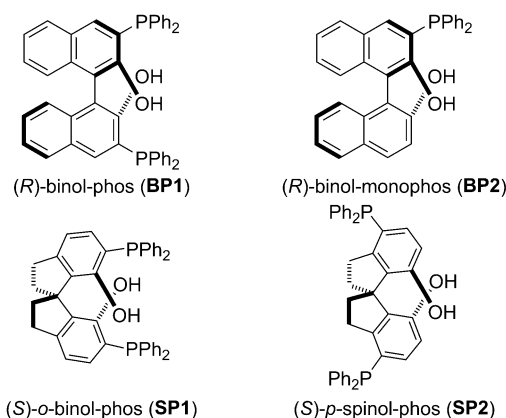
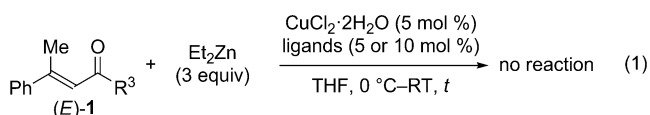


Figure 2. Representative ligands.

(5 mol %) as a ligand [Eq. (1); THF = tetrahydrofuran]. However, the reaction did not proceed at all.^[10] We therefore focused on the use of organoaluminum reagents for the



construction of copper/aluminum multinuclear complexes with the chiral catalysts.^[11,12] Organoaluminum reagents are some of the most useful organometallic reagents, and recently have been shown to broaden the utility of conjugate addition reactions, especially to cyclic enones.^[13,14] Although the conjugate addition of organoaluminum reagents to cyclic enones makes it possible to construct a chiral quaternary carbon atom, there have been no previous reports of the reaction with acyclic β,β -disubstituted α,β -unsaturated ketones. Furthermore, organoaluminum reagents typically promote 1,2-addition without a catalyst because of their hard Lewis-acidic character.^[3]

We initially examined the construction of a chiral tertiary carbon atom through the copper-catalyzed asymmetric conjugate addition of Me₃Al to chalcone (**2a**), since there are only a few successful reports of the highly asymmetric conjugate addition of Me₃Al to acyclic enones (Table 1).^[14] The use of **BP1** with CuCl₂·2H₂O gave moderate *ee* values, and the use of a 2:1 ratio of **BP1** to CuCl₂·2H₂O improved the *ee* value (entries 1 and 2). Thus, the use of **BP2** increased the *ee* value (entries 3 and 4). Although the use of **SP1** gave almost racemic mixtures, the use of **SP2** achieved excellent yield with excellent enantioselectivity (entries 5–8). The reaction in the presence of **SP2** gave the opposite major enantiomer compared to **BP2**. We further examined the use of a modified **BP1**, but the *ee* value was not improved. Thus, the functionalized **BP2** derivatives were examined for the further improvement of the enantioselectivity. The screening of copper salts and ligands revealed that the use of Cu(OTf)₂ and electron-withdrawing groups in a phosphorous moiety achieved the higher catalytic activity and *ee* values (entry 13). The use of a 2 mol % catalyst loading was enough to give the corresponding product **3a** in 85 % yield with 94 % *ee*

Table 1: Screening of catalysts for addition of Me₃Al to chalcone.

BP2A: R = H, Ar = 4-MeC₆H₄
BP2B: R = H, Ar = 2-MeC₆H₄
BP2C: R = H, Ar = 3,5-Me₂C₆H₃
BP2D: R = H, Ar = 3,5-(CF₃)₂C₆H₃
BP2-MOM: R = MOM, Ar = C₆H₅

No.	x	Ligand (y)	t [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	5	BP1 (5)	3	98	49 (S)
2	5	BP1 (10)	5	97	55 (S)
3	5	BP2 (5)	3	98	63 (S)
4	5	BP2 (10)	1	98	71 (S)
5	1	SP1 (1)	24	25	< 1
6	1	SP1 (2)	24	23	< 1
7	1	SP2 (1)	1	98	98 (R)
8	1	SP2 (2)	8	52	98 (R)
9 ^[c]	5	BP2 (10)	1	91	88 (S)
10 ^[c]	5	BP2A (10)	4	78	89 (S)
11 ^[c]	5	BP2B (10)	3	93	84 (S)
12 ^[c]	5	BP2C (10)	2	92	82 (S)
13 ^[c]	5	BP2D (10)	1	91	95 (S)
14 ^[c]	2	BP2D (4)	2	85	94 (S)
15 ^[d]	5	BP2-MOM (10)	2 (6)	91 (52)	23 (6) (S)

[a] Yields determined by ¹H NMR spectroscopy. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase.

[c] Cu(OTf)₂ was used. [d] Results using Cu(OTf)₂ are given within parentheses.

(entry 14). The presence of free hydroxy groups was required for high yield and *ee* values (entry 15).

A wide variety of enones was examined (Table 2). The reaction using **BP2D** gave the opposite major enantiomer compared to the one obtained with **SP2**. The reaction of the chalcone derivatives **2a–j** bearing functional groups gave the desired products **3a–j** in high to excellent yields and *ee* values (entries 1–10). In contrast, the reaction of the aliphatic enones **2k–n** typically gave decreased yields. Although the yields were low to moderate in the presence of Cu(OTf)₂ and **BP2D**, the use of CuCl₂·2H₂O and **SP2** achieved moderate to high yields with high *ee* values (entries 11–14).

The achievement of the efficient copper-catalyzed conjugate addition of Me₃Al for the construction of a chiral tertiary carbon center prompted us to examine the formidable challenge of constructing a chiral quaternary carbon center. The reaction of (*E*)-**1a** and Me₃Al (2 equiv) was carried out in the presence of CuCl₂·2H₂O (5 mol %) and our originally developed ligands (5 or 10 mol %) in THF at temperatures ranging from 0 °C to room temperature (Table 3). The copper catalyst derived from **BP1** gave the desired product **4a** in almost quantitative yield with 50 % *ee*. The 1,4-addition reaction proceeded exclusively without any by-products, not even the 1,2-adduct (entry 1). Surprisingly, we discovered that the use of a 2:1 ratio of **BP2** to CuCl₂·2H₂O gave the product in almost quantitative yield with more than 98 % *ee* (entry 2). The free hydroxy groups were required for high yield (entry 3). Further screening of the ligands revealed the specific character of the spinol architecture. The reaction in

Table 2: Enones for methyl-substituted tertiary chiral carbon centers.

$$\text{R}^1\text{CH}=\text{CH}\text{C}(\text{O})\text{R}^2 + \text{Me}_3\text{Al} \xrightarrow[\text{THF, 0 } ^\circ\text{C, } t]{\text{Cu salt (1 or 2 mol \%), ligand (1 or 4 mol \%)}} \text{R}^1\text{CH}(\text{Me})\text{CH}(\text{O})\text{R}^2$$

No.	2 (R ¹ , R ²)	3 ^[c] t [h]	Yield [%] ^[a]	ee [%] ^[b]	3 ^[d] t [h]	Yield [%] ^[a]	ee [%] ^[b]
1	2a (Ph, Ph)	1	85 (3a)	95 (S)	1	91 (3a)	98 (R)
2	2b (4-FC ₆ H ₄ , Ph)	1	75 (3b)	92 (+)	1	82 (3b)	98 (–)
3	2c (4-ClC ₆ H ₄ , Ph)	1	81 (3c)	93 (–)	1	98 (3c)	95 (+)
4	2d (4-F ₃ CC ₆ H ₄ , Ph)	5	85 (3d)	89 (–)	1	46 (3d)	81 (+)
5	2e (4-MeC ₆ H ₄ , Ph)	3	81 (3e)	95 (+)	1	91 (3e)	98 (–)
6	2f (4-biphenyl, Ph)	4	81 (3f)	91 (+)	1	81 (3f)	98 (–)
7	2g (4-MeOC ₆ H ₄ , Ph)	3	86 (3g)	96 (–)	1	97 (3g)	98 (+)
8	2h (2-Np, Ph)	2	80 (3h)	94 (+)	1	82 (3h)	97 (–)
9	2i (2-furanyl, Ph)	1	48 (3i)	96 (–)	1	86 (3i)	98 (+)
10	2j (2-thiophenyl, Ph)	2	91 (3j)	97 (+)	1	79 (3j)	98 (–)
11	2k , cyclohexyl, Ph	1	98 (3k)	71 (–)	2	94 (3k)	98 (+)
12	2l (n-pentyl, Ph)	1	4 (3l)	65 (+)	24	88 (3l)	83 (–)
13	2m (Ph, Me)	7	32 (3m)	76 (S)	4	76 (3m)	98 (R)
14	2n (n-butyl, Me)	1	49 (3n)	33 (R)	4	40 (3n)	94 (S)

[a] Yield of isolated product. [b] The *ee* value was determined by either HPLC or GC analysis using a chiral stationary phase. [c] Cu(OTf)₂ (2 mol %) and **BP2D** (4 mol %). [d] CuCl₂·2H₂O (1 mol %) and **SP2** (1 mol %) were used.

the presence of **SP1** gave a poor result (entry 4). In sharp contrast, the reaction in the presence of **SP2** gave **4a** in excellent yield, and showed a dramatic inversion of the major enantiomer (entry 5). The present result is the first example of the asymmetric conjugate addition of Me₃Al to acyclic enones to give a chiral quaternary carbon center in excellent yield with excellent enantioselectivity under mild reaction conditions. In sharp contrast, the reaction in the presence of binap (binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl) did not proceed at all.^[14c] The use of 2-(diphenylphosphino)-[1,1'-binaphthalen]-2-ol bearing phosphorous and hydroxy moieties as a ligand gave a trace amount of product.^[15]

A variety of enones were examined for the construction of a chiral quaternary carbon center (Table 4). The reaction of (*E*)-**1a** in the presence of **BP2** gave **4a** in excellent yield upon isolation with an excellent *ee* value (entry 1; using **BP2**). The reaction in the presence of **SP2** gave the opposite major enantiomer compared to **BP2** (entry 1). The olefinic geometry affected the *ee* value of the products,^[16] that is, the reaction of (*Z*)-**1a** gave **2a** in more than 98% yield with 35% *ee* (–) using **BP2** and more than 98% yield with 75% *ee* (–) in the presence of **SP2**. The major enantiomer was the same using (*E*)-**1a** (entry 2). The reaction of (*E*)-**1b** and (*E*)-**1c** bearing either an *n*-pentyl or benzyl substituent at the β position gave the products **4b** and **4c**, respec-

Table 3: Screening of catalysts for chiral quaternary carbon center.

$$\text{PhCH}=\text{CH}\text{C}(\text{O})\text{Ph} + \text{Me}_3\text{Al} \xrightarrow[\text{THF, 0 } ^\circ\text{C-RT, } t]{\text{CuCl}_2\cdot 2\text{H}_2\text{O (5 mol \%), ligand (5 or 10 mol \%)}} \text{PhCH}(\text{Me})\text{CH}(\text{O})\text{Ph}$$

No.	Ligand (mol %)	t [h]	Yield [%] ^[a]	ee [%] ^[b]
1	BP1 (5)	3	> 98	50 (+)
2	BP2 (10)	1	> 98	> 98 (+)
3	BP2-MOM (10)	24	trace	n.d.
4	SP1 (5)	24	53	2 (–)
5	SP2 (5)	3	> 98	95 (–)

[a] Yields determined by ¹H NMR analysis. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase. n.d. = not determined

tively, in high to excellent yields with excellent *ee* values (entries 3 and 4). Unexpectedly, the reaction of (*E*)-**1d** bearing an isopropyl group at the β position did not give reproducible results, and the isomerization of (*E*)-**1d** to (*Z*)-**1d** was observed by TLC analysis during the reaction (entry 5). In contrast, the reaction of (*Z*)-**1d** gave the product **4d** in 28% yield with 97% *ee* (–) using **BP2** and 73% yield with more than 98% *ee* (+) using **SP2**, and unreacted (*Z*)-**1d** was recovered in each case (entry 6). The same reaction conditions in the absence of CuCl₂·2H₂O and a ligand significantly promoted the isomerization of (*E*)-**1d**. The

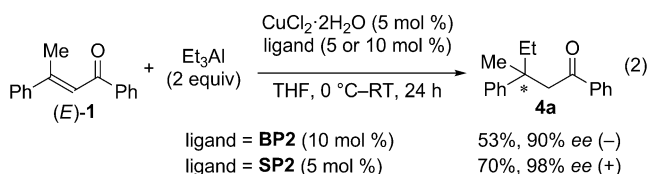
Table 4: Scope of enones for chiral quaternary carbon centers.

$$\text{R}^1\text{CH}=\text{CH}\text{C}(\text{O})\text{R}^3 + \text{Me}_3\text{Al} \xrightarrow[\text{THF, 0 } ^\circ\text{C-RT, } t]{\text{CuCl}_2\cdot 2\text{H}_2\text{O (5 mol \%), ligand (10 mol \%)}} \text{R}^1\text{CH}(\text{Me})\text{CH}(\text{O})\text{R}^3$$

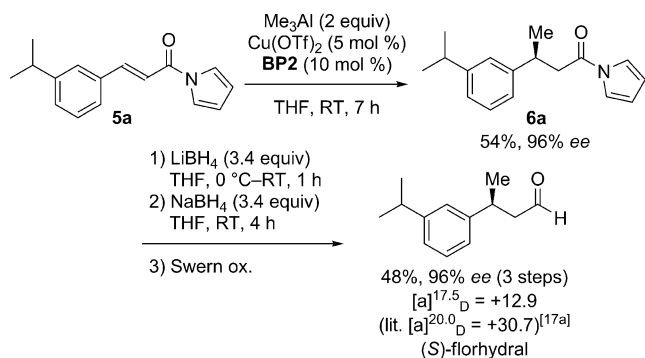
No.	1 (R ¹ , R ² , R ³)	4 Yield [%] ^[a]	ee [%] ^[c]	4 Yield [%] ^[b]	ee [%] ^[c]
1	(<i>E</i>)- 1a (Ph, Et, Ph)	> 98 (4a) ^[f]	> 98 (+)	> 98 (4a) ^[g]	95 (–)
2	(<i>Z</i>)- 1a (Et, Ph, Ph)	> 98 (4a) ^[f]	35 (–)	> 98 (4a) ^[h]	75 (–)
3	(<i>E</i>)- 1b (Ph, <i>n</i> -pent, Ph)	> 98 (4b) ^[f]	> 98 (+)	> 98 (4b) ^[g]	97 (–)
4	(<i>E</i>)- 1c (Ph, Bn, Ph)	80 (4c) ^[i]	97 (+)	72 (4c) ^[i]	94 (–)
5	(<i>E</i>)- 1d (Ph, <i>i</i> Pr, Ph)	– ^[d]	–	– ^[d]	–
6	(<i>Z</i>)- 1d (<i>i</i> Pr, Ph, Ph)	28 (4d) ^[f]	97 (–)	73 (4d) ^[i]	> 98 (+)
7	(<i>E</i>)- 1e (4-MeC ₆ H ₄ , Et, Ph)	95 (4e) ^[f]	> 98 (+)	97 (4e) ^[g]	98 (–)
8	(<i>E</i>)- 1f (4-MeOC ₆ H ₄ , Et, Ph)	> 98 (4f) ^[f]	> 98 (+)	86 (4f) ^[g]	> 98 (–)
9	(<i>E</i>)- 1g (3-MeOPh, Et, Ph)	93 (4g) ^[f]	> 98 (+)	60 (4g) ^[i]	95 (–)
10	(<i>E</i>)- 1h (2-MeOC ₆ H ₄ , Et, Ph)	97 (4h) ^[f]	94 (+)	89 (4h) ^[g]	98 (–)
11	(<i>E</i>)- 1i (4-FC ₆ H ₄ , Et, Ph)	93 (4i) ^[f]	98 (+)	90 (4i) ^[g]	> 98 (–)
12	(<i>E</i>)- 1j (2-FC ₆ H ₄ , Et, Ph)	98 (4j) ^[f]	98 (+)	92 (4j) ^[g]	> 98 (–)
13	(<i>E</i>)- 1k (4-ClC ₆ H ₄ , Et, Ph)	93 (4k) ^[f]	96 (+)	98 (4k) ^[g]	95 (–)
14	(<i>E</i>)- 1l (4-FC ₃ C ₆ H ₄ , Et, Ph)	97 (4l) ^[f]	95 (+)	> 98 (4l) ^[g]	95 (–)
15	(<i>E</i>)- 1m (2-naphthyl, Et, Ph)	93 (4m) ^[f]	95 (+)	97 (4m) ^[g]	97 (–)
16	(<i>E</i>)- 1n (4-biphenyl, Et, Ph)	> 98 (4n) ^[f]	98 (+)	> 98 (4n) ^[g]	97 (–)
17	(<i>E</i>)- 1o (Ph, Et, 4-MeOC ₆ H ₄)	97 (4o) ^[f]	> 98 (R) ^[e]	> 98 (4o) ^[g]	> 98 (S) ^[e]
18	(<i>E</i>)- 1p (Ph, Et, 4-ClC ₆ H ₄)	> 98 (4p) ^[f]	98 (+)	96 (4p) ^[g]	98 (–)
19	(<i>E</i>)- 1q (Ph, Et, Me)	97 (4q) ^[f]	93 (–)	76 (4q)	> 98 (+)

[a] Yield of isolated product obtained using **BP2**. [b] Yield of isolated product obtained using **SP2**. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] The results were not reproducible. [e] The absolute configuration of **4o** was determined after the conversion into the known carboxylic acid. [f] Reaction time of 1–3 h. [g] Reaction time of 3–5 h. [h] Reaction time of 7 h. [i] Reaction time of 24 h.

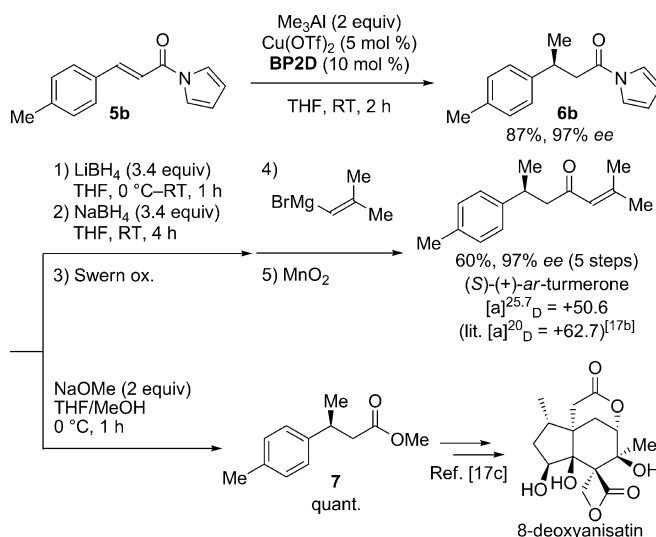
absence of Me_3Al also promoted the isomerization at relatively lower reaction rate, thus, the Lewis acidic character might induce the isomerization. The enones (*E*)-**1e–l** bearing electron-donating or electron-withdrawing substituents gave the products **4e–l** in high to excellent yields with excellent *ee* values (entries 7–14). The enones (*E*)-**1m** and (*E*)-**1n** bearing electron-rich aryl substituents, such as naphthyl and biphenyl, gave the corresponding products **4m** and **4n** in excellent yields with excellent *ee* values (entries 15 and 16). The enones (*E*)-**1o** and (*E*)-**1p** bearing an electron-donating or electron-withdrawing substituent, respectively, attached to a benzoyl moiety improved the yields and *ee* values (entries 17 and 18). An aliphatic enone, such as that of (*E*)-**1q** participated in the reaction (entry 19). The tentative examination for the use of various organoaluminum reagents showed that the reaction of Et_3Al instead of Me_3Al in the presence of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and **BP2** or **SP2** gave moderate to good yields with high to excellent *ee* values and the unreacted (*E*)-**1** was recovered [Eq. (2)].



The preliminary examination using our original catalysts for asymmetric methylation are demonstrated for the synthesis of natural products.^[17] We achieved the first example of the asymmetric conjugate addition of Me_3Al to *N*-acylpyrrole derivatives.^[18] The reaction of **5a** and Me_3Al under the optimized reaction conditions gave the product **6a** in 54% yield with 96% *ee*, and **BP2** was found to be a superior ligand (Scheme 1). The subsequent reduction using LiBH_4 and NaBH_4 , with subsequent Swern oxidation could give (*S*)-florhydral in 48% yield (3 steps).^[17a] We also succeeded in the synthesis of (*S*)-(+)-*ar*-turmerone (Scheme 2).^[17b] The asymmetric conjugate addition of Me_3Al to **5b** under the optimum reaction conditions gave the product **6b** in high yield with an excellent *ee* value. The reduction of **6b** using LiBH_4 and NaBH_4 gave the corresponding alcohol, and subsequent oxidation to the aldehyde, nucleophilic addition of a Grignard

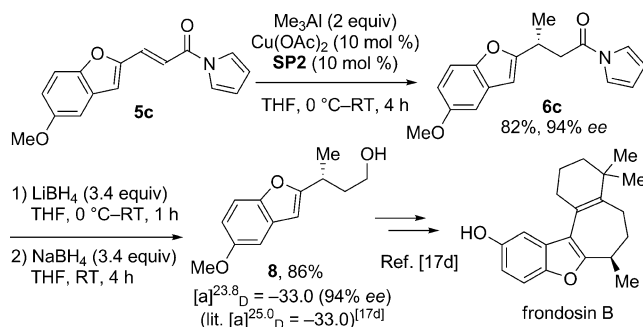


Scheme 1. Synthesis of (*S*)-florhydral.



Scheme 2. Synthesis of turmerone.

reagent, and MnO_2 -mediated oxidation without purification gave the desired (*S*)-(+)-*ar*-turmerone in 60% yield (5 steps). Furthermore, the mild esterification of **6b** provided the product **7**, which is the key intermediate for the synthesis of 8-deoxyanisatin, in quantitative yield.^[17c] The use of **SP2** as a ligand for opposite stereoselectivity gave the intermediate for the synthesis of frondosin B (Scheme 3).^[17d] The asymmetric conjugate addition of Me_3Al to **5c**, and the following reduction gave the desired product **8** in high to excellent yield, which can readily be converted into frondosin B by a known literature procedure. Additional investigations into the preparation of natural products bearing chiral quaternary carbon centers are currently underway.



Scheme 3. Synthesis of intermediate for frondosin B.

In conclusion, we have described the specific character of our original ligands for the first example of the copper-catalyzed asymmetric conjugate addition of Me_3Al to acyclic enones at ambient conditions for the creation of a chiral quaternary carbon center. Most reactions proceeded in greater than 95% *ee*. The ligands based on either a binol or spiro architecture gave products, albeit with the major products having opposite enantioselectivity. The practical advantage of the present reaction is the low cost and stability

of copper salts compared to the precedented rhodium- and palladium-catalyzed construction of a chiral quaternary carbon center. Since a methyl-substituted chiral quaternary carbon center is found in various natural products, the present discovery could be a new entry into the preparation of potentially useful chiral molecules. The application of the present reaction in the synthesis of natural products, multi-nuclear catalysts, and their characteristic features are being studied in our laboratory.

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