Synthetic Methods

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 1,4addition, 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 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 Ar₄BNa or organoboroxine under thermal conditions, with enones typically providing lower enantioselectivity.^[4] Alexakis, Woodward, and co-workers reported the rhodium-catalyzed asymmetric addition of PhAlMe₂ 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 Me₃Al for the construction of a chiral tertiary carbon center and chiral quaternary carbon center in high to excellent yields with high to excellent eevalues.

organometallic reagents to acyclic activated olefins. Hayashi

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 Et₂Zn to the β , β -disubstituted enone (*E*)-1, bearing a methyl substituent, in the presence of CuCl₂·2 H₂O (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

$$\begin{array}{c} \text{Me O} \\ \text{Ph} \\ (E)-1 \end{array}^{\text{He O}} + \begin{array}{c} \text{Et}_2\text{Zn} \\ \text{(3 equiv)} \end{array} \xrightarrow{\begin{array}{c} \text{CuCl}_2 \cdot 2\text{H}_2\text{O} \text{ (5 mol \%)} \\ \text{ligands (5 or 10 mol \%)} \\ \text{THF, 0 °C-RT, } t \end{array} \text{ no reaction (1)}$$

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 Me_3Al 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 $CuCl_2 \cdot 2H_2O$ 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.



0	1	SPT (2)	24	25	< 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 (<i>S</i>)
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 (<i>S</i>)
14 ^[c]	2	BP2D (4)	2	85	94 (S)
15 ^[d]	5	BP2-MOM (10)	2 (6)	91 (52)	23 (6) (<i>S</i>)

[[]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-i 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.

	O Me ₃ A	J	Cu salt (ligand (1 or 2 m 1 or 4 mc	ol %) ol %)	M	e O
R ¹	2a–n (2 equi	iv)	TH	F, 0 °C, <i>t</i>		R ¹ *	¹ R ² 3a–n
No.	2 (R ¹ , R ²)	3 ^[c]			3 ^[d]		
		t	Yield	ee	t	Yield	ee
		[h]	[%] ^[a]	[%] ^[b]	[h]	[%] ^[a]	[%] ^[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 (3 b)	92 (+)	1	82 (3 b)	98 (-)
3	2c (4-ClC ₆ H ₄ , Ph)	1	81 (3 c)	93 (-)	1	98 (3 c)	95 (+)
4	2d (4-F ₃ CC ₆ H ₄ , Ph)	5	85 (3 d)	89 (–)	1	46 (3 d)	81 (+)
5	2e (4-MeC ₆ H ₄ , Ph)	3	81 (3 e)	95 (+)	1	91 (3 e)	98 (-)
6	2 f (4-biphenyl, Ph)	4	81 (3 f)	91 (+)	1	81 (3 f)	98 (-)
7	2g (4-MeOC ₆ H ₄ , Ph)	3	86 (3 g)	96 (—)	1	97 (3 g)	98 (+)
8	2h (2-Np, Ph)	2	80 (3 h)	94 (+)	1	82 (3 h)	97 (-)
9	2i (2-furanyl, Ph)	1	48 (3 i)	96 (-)	1	86 (3 i)	98 (+)
10	2j (2-thiophenyl, Ph)	2	91 (3 j)	97 (+)	1	79 (3 j)	98 (-)
11	2 k , cyclohexyl, Ph	1	98 (3 k)	71 (-)	2	94 (3 k)	98 (+)
12	21 (<i>n</i> -pentyl, Ph)	1	4 (3 I)	65 (+)	24	88 (3 I)	83 (-)
13	2m (Ph, Me)	7	32	76 (S)	4	76	98 (R)
			(3 m)			(3 m)	
14	2n (<i>n</i> -butyl, Me)	1	49 (3 n)	33 (R)	4	40 (3 n)	94 (<i>S</i>)

[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] $CuCl_2 \cdot 2H_2O$ (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.^[14e] 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.

Ph Ta Ph + Me ₃ Al (2 equiv)		CuCl₂·2⊦ ligand (5	H ₂ O (5 mol %) or 10 mol %)	Et O		
		THF, 0 °C–RT, <i>t</i>		Ph * Ph 4a		
No.	Ligand (mol%)	<i>t</i> [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 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.

	R ² O Me ₃ Al	CuCl ₂ ·2H ₂ O (5 mol %) ligand (10 mol %)		R ² O		
	$R^1 \xrightarrow{\qquad } R^3 (2 \text{ equiv})$ 1a-q	THF, 0	°C–RT, <i>t</i>	R ¹ * 4a–q	R ³	
No.	1 (R ¹ , R ² , R ³)	4		4		
		Yield [%] ^[a]	ee [%] ^[c]	Yield [%] ^[b]	ee [%] ^[c]	
1	(<i>E</i>)- 1 a (Ph, Et, Ph)	> 98 (4 a) ^[f]	>98 (+)	> 98 (4 a) ^[g]	95 (-)	
2	(Z)- 1 a (Et, Ph, Ph)	> 98 (4 a) ^[f]	35 (—)	> 98 (4 a) ^[h]	75 (—)	
3	(<i>E</i>)- 1 b (Ph, <i>n</i> -pent, Ph)	>98 (4b) ^[f]	>98 (+)	>98 (4b) ^[g]	97 (—)	
4	(<i>E</i>)- 1 c (Ph, Bn, Ph)	80 (4 c) ^[]	97 (+)	72 (4c) ^[]	94 (-)	
5	(<i>E</i>)- 1 d (Ph, <i>i</i> Pr, Ph)	_[d]		_[d]		
6	(Z)- 1 d (<i>i</i> Pr, Ph, Ph)	28 (4d) ^[f]	97 (—)	73 (4d) ^[]	>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>)- 1 f (4-MeOC ₆ H ₄ , Et, Ph)	>98 (4 f) ^[f]	>98 (+)	86 (4 f) ^[g]	>98 (-)	
9	(<i>E</i>)- 1 g (3-MeOPh, Et, Ph)	93 (4g) ^[f]	>98 (+)	60 (4g) ^[]	95 (-)	
10	(<i>E</i>)- 1 h (2-MeOC ₆ H ₄ , Et, Ph)	97 (4 h) ^[f]	94 (+)	89 (4 h) ^[g]	98 (-)	
11	(<i>E</i>)- 11 (4-FC ₆ H ₄ , Et, Ph)	93 (4 i) ^[f]	98 (+)	90 (4i) ^[g]	>98 (-)	
12	(<i>E</i>)- 1 j (2-FC ₆ H ₄ , Et, Ph)	98 (4j) ^[f]	98 (+)	92 (4j) ^[g]	>98 (-)	
13	(<i>E</i>)- 1 k (4-ClC ₆ H ₄ , Et, Ph)	93 (4k) ^[f]	96 (+)	98 (4k) ^[g]	95 (-)	
14	(<i>E</i>)- 11 (4-CF ₃ C ₆ H ₄ , Et, Ph)	97 (41) ^[f]	95 (+)	>98 (4 l) ^[g]	95 (-)	
15	(E)- 1 m (2-naphthyl, Et, Ph)	93 (4 m) ^[f]	95 (+)	97 (4 m) ^[g]	97 (-)	
16	(<i>E</i>)- 1 n (4-biphenyl, Et, Ph)	>98 (4n) ^[f]	98 (+)	≥98 (4 n) ^[g]	97 (-)	
17	(E)-1o (Ph, Et, 4-MeOC ₆ H ₄)	97 (4 o) ^[f]	>98 (R) ^[e]	>98 (4 o) ^[g]	>98 (S) ^[e]	
18	(<i>E</i>)- 1 p (Ph, Et, 4-ClC ₆ H ₄)	>98 (4p) ^[f]	98 (+)	96 (4p) ^[g]	98 (-)	
19	(<i>E</i>)- 1q (Ph, Et, Me)	97 (4 q) ^[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 **40** 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 Me₃Al 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)-10 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 Et₃Al instead of Me₃Al in the presence of CuCl₂·2H₂O and BP2 or SP2 gave moderate to good yields with high to excellent ee values and the unreacted (E)-1 was recovered [Eq. (2)].

$$\begin{array}{c} \begin{array}{c} \text{Me} & \text{O} \\ \text{Ph} & \text{Et}_{3}\text{Al} \\ \text{(E)-1} \end{array} + \begin{array}{c} \text{Et}_{3}\text{Al} \\ \text{Igand} & \text{Image for a structure} \end{array} \xrightarrow{\begin{array}{c} \text{CuCl}_{2} \cdot 2H_{2}\text{O} (5 \text{ mol } \%) \\ \text{Iigand} (5 \text{ or } 10 \text{ mol } \%) \\ \text{THF, 0 °C-RT, 24 h} \end{array} \xrightarrow{\begin{array}{c} \text{Me} \\ \text{Ph} & \text{He} \\ \text{Ph} & \text{He} \\ \text{H$$

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 Me₃Al to N-acylpyrrole derivatives.^[18] The reaction of **5a** and Me₃Al 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 LiBH₄ and NaBH₄, 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 Me₃Al to **5b** under the optimum reaction conditions gave the product **6b** in high yield with an excellent ee value. The reduction of 6b using LiBH₄ and NaBH₄ gave the corresponding alcohol, and subsequent oxidation to the aldehyde, nucleophilic addition of a Grignard



Scheme 1. Synthesis of (S)-florhydral.

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Scheme 2. Synthesis of turmerone.

reagent, and MnO₂-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 8deoxyanisatin, 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 Me₃Al 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 coppercatalyzed asymmetric conjugate addition of Me₃Al 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 spinol 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, multinuclear catalysts, and their characteristic features are being studied in our laboratory.

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