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Catalytic Enantioselective β-Alkylation of α,β-Unsaturated Aldehydes by Combination of Transition-Metal- and Aminocatalysis: Total Synthesis of Bisabolane Sesquiterpenes

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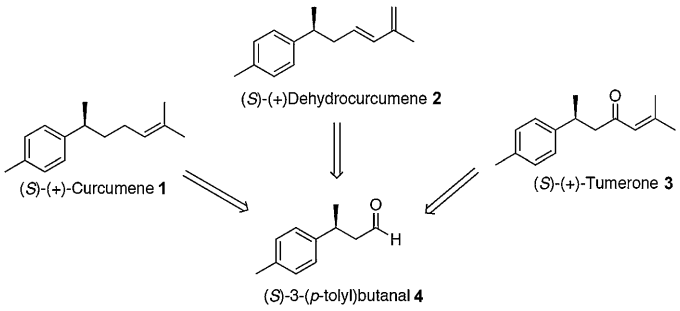
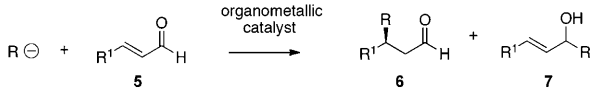
β-Alkyl substituted aldehydes are constituents of biologically active natural products (e.g. (*S*)-citronellal) and valuable chiral building blocks in asymmetric synthesis. For example, they can be used as synthons for the total synthesis of sesquiterpenes and polyketides.[1] In this context, natural products such as bisabolane sesquiterpenes (e.g., (*S*)-(+)-curcumene **1**, (*S*)-(+)-dehydrocurcumene **2**, and (*S*)-(+)-tumerone) **3**, which exhibit anti-cancer as well as antimicrobial activities and are used as additives in perfumes, flavors, and cosmetics,[1a–c,2] could be rapidly assembled according to retrosynthetic analysis from (3*S*)-β-methyl aldehyde (**6k**).



Recently, major breakthroughs in transition-metal-catalyzed enantioselective conjugate addition (ECA) of organometallic reagents to α,β-unsaturated carbonyl compounds have been achieved.[3] In particular, the enantioselective copper-catalyzed conjugate addition of organometallic reagents using different types of chiral ligand systems on the metal provides high stereocontrol.[3] This research has shown that the direct transition-metal-catalyzed enantioselective 1,4-addition of an organometallic reagent to an α,β-unsaturated aldehyde **5** in the presence of a chiral ligand is very challenging due to a competing 1,2-addition reaction, which gives both the β-aldehyde **6** and alcohol **7**, respectively (Scheme 1).[4b–c,5]



Scheme 1.

Based on our research on combination of aminocatalysis and transition-metal catalysis,[6–8] we found that the chiral amine-catalyzed iminium activation[9] of an α,β-unsaturated aldehyde **2** can be combined with a copper-catalyzed conjugate addition of a silyl nucleophile to achieve the stereoselective C–Si-bond formation via transition state **I** (Scheme 2).[10]

According to these findings and a "retrocatalytic" analysis, we envisioned that this type of dual catalysis[10] could be applied to the asymmetric addition of a carbon nucleophile (e.g., organozinc reagent R_2Zn) to α,β-unsaturated aldehydes **5** and afford β-alkyl substituted aldehydes **6** (Scheme 3). Thus, the key to success would be the ability of a chiral amine catalyst to lower the LUMO of an enal **5** by iminium activation in combination with simultaneous copper-catalyzed conjugate addition of an organometallic reagent to this intermediate and favor 1,4-addition over 1,2-addition. If successful, we planned to employ this potential co-catalytic stereoselective reaction as the key transformation for the total synthesis of sesquiterpenes such as **1**–**3**.

Herein we present the asymmetric β-alkylation of α,β-unsaturated aldehydes by the one-pot combination of a simple chiral amine and transition-metal catalyst without the use of a glove box. Next, this novel co-catalytic β-alkylation was

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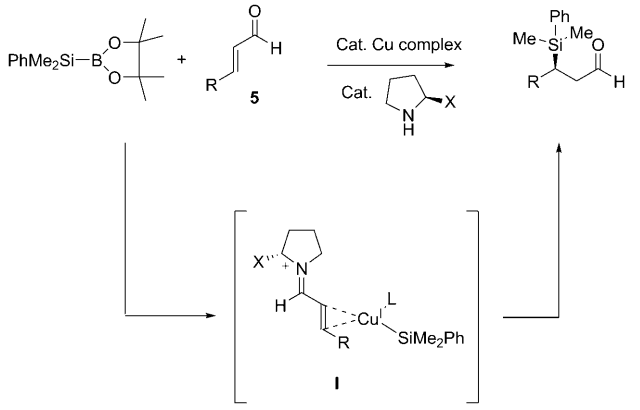
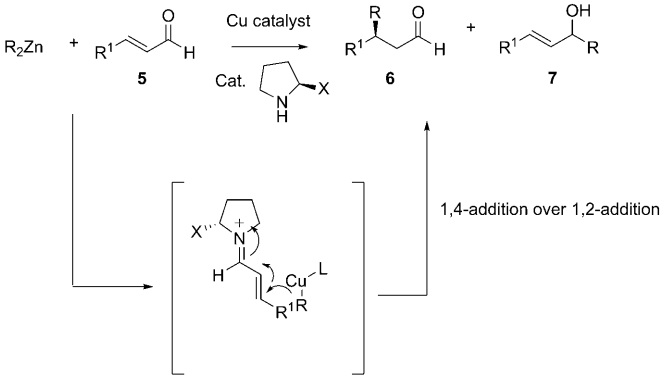


Scheme 2. Chiral amine- and Cu-co-catalyzed enantioselective β-silylation of enals **5**.

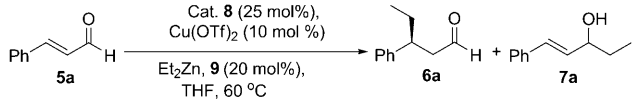


Scheme 3.

employed as the key step for the expeditious total synthesis of bisabolane sesquiterpenes.

We began probing the reaction between Et_2Zn and cinnamic aldehyde **5a** by using different copper salts and chiral amines **8** as catalysts. We found that the highest 1,4-selectivity and enantioselectivity was achieved when copper(II) triflate ($Cu(OTf)_2$, 10 mol%) was employed as the transition-metal co-catalyst and THF as the solvent at 60 °C (Table 1).[11] Key results are shown in Table 1. The reaction that was performed without the chiral amine co-catalyst **8** gave the corresponding racemic aldehyde **6a** and alcohol **7a** in a ratio of 3:97 (Table 1, entry 1). Thus, this reaction was highly 1,2-selective. The reaction performed in the presence of chiral amine catalyst **8a** without a copper-catalyst was also 1,2-selective (**6a**/**7a**; 22:78; Table 1, entry 2), however, (*S*)-**6a**[12] was formed with an enantiomeric ratio (e.r.) of 78:22. To our delight, the combination of chiral amine **8a**[13] and $Cu(OTf)_2$ switched the 1,2-selective reaction towards a 1,4-selective transformation (**6a**/**7a**; 84:16) and gave **6a** with 77:23 e.r. (Table 1, entry 3).

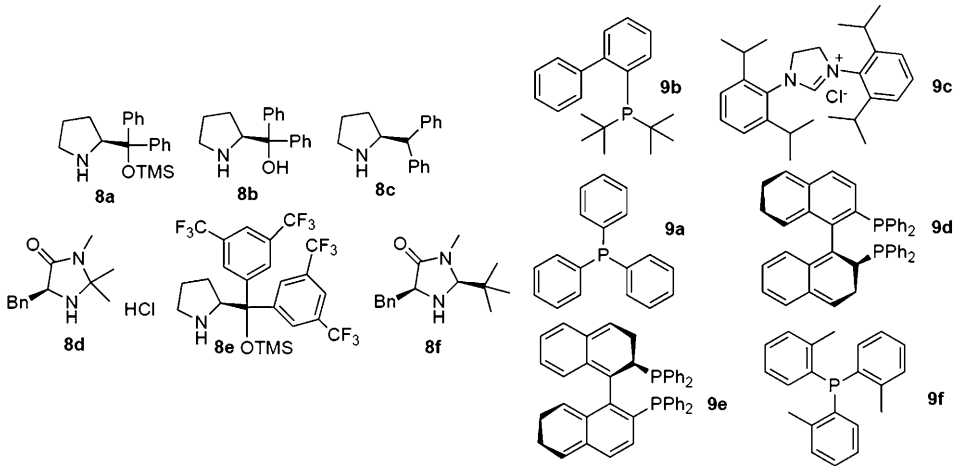
Table 1. Condition screening.[a]



Entry	Cat.	Ligand	*t* [h]	Conv. [%][b]	Ratio **6**/**7**[c]	e.r.[d]
1	–	**9a**	12	91	3:97	50:50
2	**8a**[e]	–	9	29	22:78	78:22
3	**8a**	–	12	18	84:16	7:23
4	**8a**	**9a**	12	58	62:38	96:4
5	**8b**	**9a**	17	53	8:92	61:39
6	**8c**	**9a**	18	60	48:52	90:10
7	**8d**	**9a**	17	38	8:92	47:53
8	**8e**	**9a**	14	>98	19:90	47:53
9	**8f**	**9a**	15	75	12:88	62:38
10	**8a**[f]	**9a**	12	45	58:42	95:5
11	**8a**	**9b**	12	38	76:24	87:13
12	**8a**[g]	**9c**	8	8	77:23	76:24
13	**8a**	**9d**	11	27	49:51	89:11
14	**8a**	**9e**	12	19	86:14	94:6
15	**8a**	**9f**	9	11	36:64	82:18
16	**8a**[h]	**9a**	16	72	34:66	88:12
17	**8a**[i]	**9a**	23	24	76:24	91:9
18	**8a**[j]	–	4	23	16:84	71:29

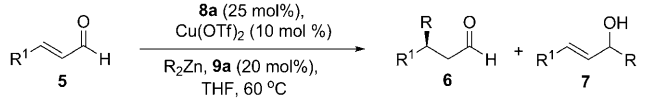
[a] Under N_2 atmosphere. [b] Determined by GC analysis of the crude reaction mixtures. [c] Determined by GC analysis and ^1H NMR analysis of the crude reaction mixtures. [d] Determined by chiral-phase GC analysis. The enantiomeric excess (*ee*) value of **7a** was 0% for all cases. [e] The reaction was performed without $Cu(OTf)_2$ catalyst.[f] **8a** (20 mol%). [g] The ligand was premixed with the base KO*t*Bu and the reaction performed at RT. [h] Reaction run at RT. [i] CuTC (copper thiophene carboxylate, 2 mol%), **9a** (4 mol%) at RT. [j] CuCl (10 mol%) at 50 °C.

To improve the conversion and enantioselectivity of the asymmetric conjugate addition, we decided to employ Lewis bases such as organic phosphines and *N*-heterocyclic carbenes **9** as ligands for the copper catalyst.[14] In most cases, the reaction was 1,4-selective and gave **6a** with good to high



enantiomeric ratios. The highest conversion was achieved when PPh_3 was employed as the additive. Of the screened catalysts of type **8**, the protected diarylprolinol **8a** co-catalyzed the asymmetric conjugate addition with the best enantioselectivity. For example, aldehyde **6a** was formed with up to 96:4 e.r. (Table 1, entry 4). Lowering the catalyst loading of **8a** slightly decreased the e.r. of **6a** to 95:5 (Table 1, entry 10). With these results in hand, we decided to probe the scope of the catalytic ECA of organozinc reagent R_2Zn to α,β-unsaturated aldehydes **5** using $Cu(OTf)_2$ as the metal catalyst, **8a** as the chiral amine, and **9a** as the additive in THF at 60 °C (Table 2).

Table 2. The scope of the co-catalyzed ECA of R_2Zn to enals **5**.[a]



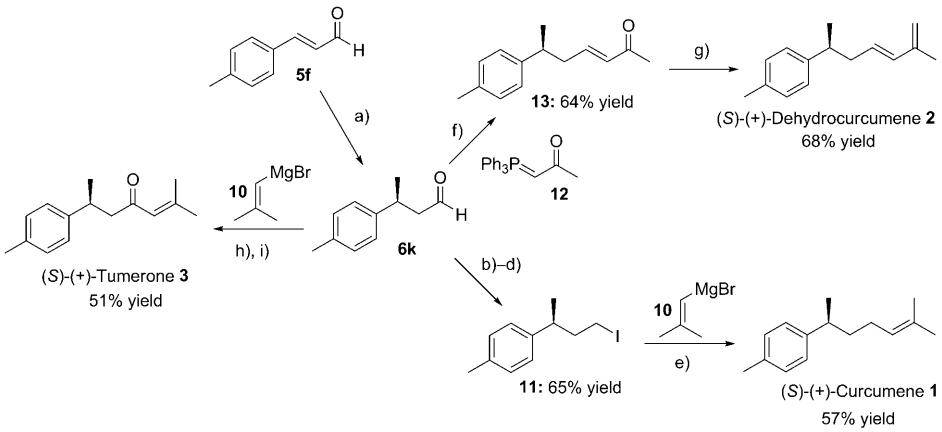
Entry	R^1	R	Product	*t* [h]	Yield **6** [%][b]	Ratio **6**:**7**[c]	e.r.[d]
1	4-$MeOC_6H_4$	Et	**6b**	13	83	85:15	98:2
2	2-naphth	Et	**6c**	16	62	64:36	98:2
3	4-ClC_6H_4	Et	**6d**	18	60	63:37	95:5
4	4-BrC_6H_4	Et	**6e**	13	47	78:22	96:4
5	4-MeC_6H_4	Et	**6f**	13	44	75:25	98:2
6	4-*i*PrC_6H_4	Et	**6g**	9	71	83:17	97:3
7	3-ClC_6H_4	Et	**6h**	9	44	79:21	97:3
8	3-$MeOC_6H_4$	Et	**6i**	11	79	80:20	98:2
9	4-$MeOC_6H_4$	Me[f]	**6j**	16	76	91:9	98:2
10	3-MeC_6H_4	Me[f]	**6k**	14	65	93:7	97:3
11	*n*Bu	Me[g,h]	**6l**	14	23[j]	51:49	92:8
12	*n*Bu	Me[g,i]	**6l**	16	60[j]	80:20	83:17

[a] Under N_2 atmosphere. [b] Yield of pure isolated **6** after silica gel column chromatography. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by chiral-phase HPLC or chiral GC analyses. The *ee* value of products **7** is 0%. [f] Reaction run at 22 °C. [g] Reaction run at 45 °C. [h] Me_2Zn added at 22 °C. [i] Me_2Zn added at −78 °C. [j] Yield determined by GC.

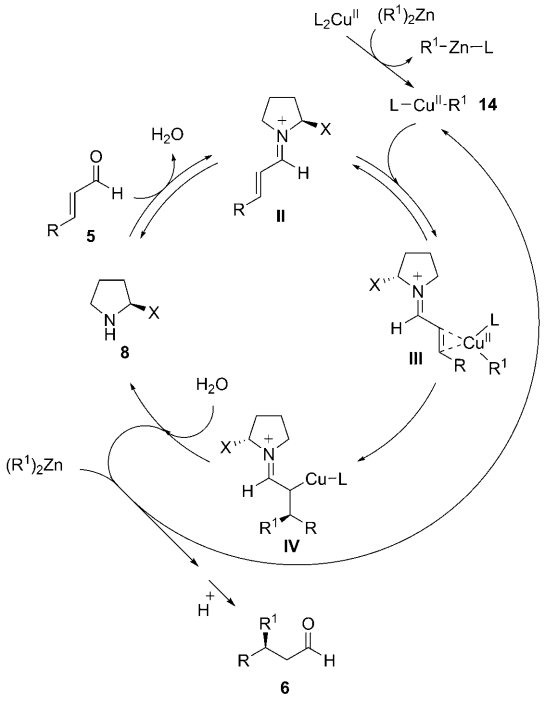
The co-catalytic ECA of Et_2Zn to enals **5** with an aryl substituent at the β position proceeded with good 1,4-selectivities and high enantioselectivity to give the corresponding β-alkylaldehyde products **6a–6i** (Table 2, entries 1–8). The highest selectivities for the co-catalytic asymmetric reactions were achieved when 3-substituted enals **5** with a 3- or 4-MeOPh group was used as the substrates (Table 2, entries 1 and 8). The co-catalytic transformations using Me_2Zn as the reagent was 1,4-selective and gave the corresponding product **6** with a high e.r. value. For example, the ECA of Me_2Zn to enals **5b** and **5f** gave the corresponding aldehydes **6j** and **6k** with 98:2 and 97:3 e.r., respectively (Table 2, entries 9 and 10). The co-catalytic asymmetric conjugate addition of dialklzinc reagent Me_2Zn did also work for aliphatic enals **5** as acceptors but gave lower e.r. values (Table 2, entries 11 and 12).

Finally the methodology was applied to the short total synthesis of (*S*)-(+)-curcumene **1**, (*E*)-(*S*)-(+)-3-dehydrocurcumene **2**, and (*S*)-(+)-tumerone **3** (Scheme 4), which have been popular targets for the synthetic community. However, there have been fewer enantioselective syntheses to date of tumerone **3**.[15] Our syntheses began with the synthesis of aldehyde (*S*)-**6k**[12] (97:3 e.r.), derived by co-catalytic ECA of Me_2Zn to enal **5f**. The subsequent reduction of **6k**, tosylation and nucleophilic displacement gave iodine **11** in 65% overall yield (three steps). Grignard addition of **10** to **11** gave curcumene **1** in 57% yield. The synthesis of dehydrocurcumene **2** began with a Wittig reaction between aldehyde **6k** and **12** to give enone **13** in 64% yield. A subsequent Wittig reaction gave dehydrocurcumene **2** in 68% yield. Turmerone **3** was rapidly assembled in 51% overall yield in a one-pot procedure involving a Grignard addition of **10** with aldehyde **6k** followed by oxidation with tetrapropylammonium perruthenate (TPAP).[16] Thus, this synthesis was completed in two purification steps from α,β-unsaturated aldehyde **5f** and delivered the target compound with 97:3 e.r.

The absolute configuration at C3 of β-alkyl aldehyde **6k** was *S* (R = Ar) as established by the above enantioselective total synthesis. Thus, employing (*S*)-**8a** as the chiral co-catalyst gave the corresponding β-branched aldehydes (*S*)-**6**. We also investigated the crude reaction with HRMS[17] and found that iminium intermediates **II** (Scheme 5) were formed by condensation between chiral amine **8a** and enals **5** (Figure 1). In addition, the iminium intermediate formed between product **6a** and the chiral amine catalyst **8a** was observed. Moreover, the ability of chiral amine **8a** to switch the 1,2-selectivity of the copper-catalyzed organozinc addi-



Scheme 4. a) Me_2Zn, cat. **8a**, cat. $Cu(OTf)_2$, cat. **9a**, THF, 60 °C. b) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C; c) TsCl, pyridine, CH_2Cl_2, RT, 5 h; d) NaI, acetone, reflux, 2 h; e) **10**, CuI, THF, 0 °C, 5 h; f) **12**, $CHCl_3$, reflux, 16 h; g) Ph_3PMeBr, BuLi, Et_2O; h) **10**, THF, 0 °C, 1 h; i) tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine-*N*-oxide (NMO), CH_2Cl_2, MS (4 Å), 3 h.



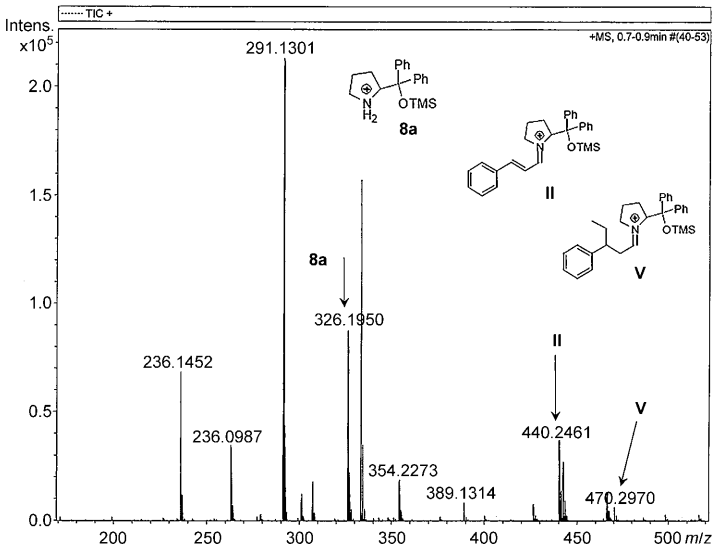


Figure 1. HRMS (ESI) of the crude reaction mixture.

Scheme 5. Proposed reaction mechanism.

tion to a 1,4-selective reaction in the presence of **9a** also supports that the reaction proceeds via a chiral iminium intermediate (Table 1, entries 1 and 4). DFT calculations have also shown that the direct addition of a copper-activated nucleophile to an enal is much higher in energy than the same addition to the corresponding iminium species even when the amine serves as a ligand on the copper.[10]

Based on the absolute configuration of β-alkyl aldehydes **6**, these results and our previous DFT calculations,[10] we propose that the in situ generated L-Cu^{II}-alkyl complex **14** approaches the less sterically hindered *Si* face (R = Ar) of the chiral iminium intermediate **III** and performs the selective 1,4-addition of the carbon nucleophile at its β carbon to give intermediate **IV** (Scheme 5). Subsequent hydrolysis of iminium intermediate **IV** regenerates the chiral catalyst **8** as well as the active copper catalyst complex **14**. Aqueous work up gives the desired β-alkyl aldehyde product **6**.

In summary, we disclose the first example of enantioselective β-alkylation of α,β-unsaturated aldehydes by combination of aminocatalysis and transition-metal catalysis. The co-catalyzed asymmetric 1,4-addition gave the corresponding β-alkyl aldehydes with up to 98:2 e.r. Thus, simple bench-stable chiral amines can be used as catalyst in combination with a copper salt without the use of a glove box to achieve catalytic asymmetric addition of dialkylzinc reagents to enals with high enantioselectivity. The novel co-catalytic reaction was utilized as the key step for the expeditious total synthesis of bisabolane sesquiterpenes. Further development of this class of co-catalytic asymmetric conjugate additions and its application in total synthesis is ongoing in our laboratories.

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Keywords: aldehydes · alkylation · asymmetric conjugate additions · enantioselectivity · co-catalysis · zinc

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