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## Graphical Abstract

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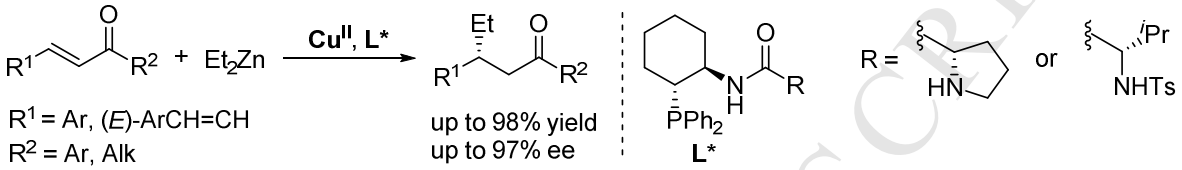

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# Copper-catalyzed enantioselective 1,4-conjugate addition of dialkylzinc reagents to α,β- and α,β,γ,δ-unsaturated ketones

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ABSTRACT

An enantioselective Cu(II)-catalyzed conjugate addition of dialkylzinc reagents to α,β- or α,β,γ,δ-unsaturated ketones with chiral cyclohexane-based amidophosphine ligands was developed. With 2 mol% of $Cu(OAc)_2 \cdot H_2O$/**L5**, the conjugate addition of diethylzinc to α,β-unsaturated ketones was achieved in good-to-excellent yields (up to 98%) and high enantioselectivities (up to 92% ee). This catalytic system was shown to be efficient for the 1,4-conjugate addition of $Et_2Zn$ to (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one with 85% yield and 90% ee. Moreover, with 1 mol% of $Cu(OTf)_2$/**L11**, the conjugate addition of α,β,γ,δ-unsaturated ketones was accomplished with 1,4-regioselectivity, good yields (79—86%) and excellent enantioselectivities (up to 97% ee).



## 1. Introduction

Copper-catalyzed asymmetric conjugate addition of carbon nucleophiles to α,β-unsaturated compounds is one of the most important asymmetric C-C bond-forming reactions in organic synthesis. Over the past two decades, a variety of chiral ligands as well as organometallic reagents (such as RMgX, RLi, and $R_2Zn$) with chiral $Cu^I$ or $Cu^{II}$ complexes have been developed to promote such transformations.[1] However, the developed ligands are mainly based on binaphthol-derived phosphine ligands, amino acid-derived Schiff bases and N-heterocyclic carbenes. The use of organozinc reagents[1c,2] and extended Michael acceptors[3] for the highly enantioselective 1,4-conjugate addition to acyclic enones still remains a challenging task. Although a number of chiral copper catalytic systems have been developed to promote 1,4-conjugate additions of dialkylzinc to structurally diverse enones, only a limited number of reports involving chiral P,N-ligands as the Michael acceptor have demonstrated high enantioselectivity (≥ 90% ee) for acyclic enones.[4] There are few ligands with broad applicability. To the best of our knowledge, the use of chiral P,N-ligands to promote enantioselective 1,4-conjugate addition of organozinc to α,β,γ,δ-unsaturated carbonyl compounds remains vacant.

Comparing to asymmetric 1,4-conjugate addition, conjugate addition to extended Michael acceptors requires an additional control of regioselectivity (1,4- vs 1,6-selectivity). In previous reports, only chiral BINAP[5a,5b] and *tert*-leucine-base N-heterocyclic carbene[5c] have been proven to be capable of producing good 1,4-regioselectivity for the conjugate addition of organozinc to α,β,γ,δ-unsaturated carbonyl compounds. Chiral ligands inarguably play an important role for catalytic asymmetric reactions. Very recently, we have developed chiral hexane-based P,N-ligands for the copper-catalyzed asymmetric C-C bond-forming reactions.[6] We envision that these chiral ligands would also be effective for the copper-catalyzed conjugate addition of organozinc to unsaturated carbonyl compounds. Herein, we report an efficient copper-catalyzed enantioselective 1,4-conjugate addition of a dialkylzinc reagent to both α,β- and α,β,γ,δ-unsaturated ketones.

## 2. Results and Discussion

### *2.1. Enantioselective 1,4-conjugate addition of α,β-unsaturated ketones*

To begin with, the conjugate addition of diethylzinc to chalcone **1a** was carried out using 2 mol% of $Cu(OAc)_2 \cdot H_2O$ and 2 mol% of chiral ligands in dichloromethane at 0 °C. A number of chiral hexane-based P,N-ligands were screened (Figure 1), and the results are summarized in Table 1. The results suggest that the ligand plays an important role for the catalytic activity and stereocontrol. Tridentate amidophosphine ligands **L3**-**L6** produced higher yields than the bidentate aminophosphine **L1** and amidophosphine **L2** and the tridentate iminophosphine **L7** and aminophosphine **L8** (entries 3-6 vs entries 1, 2, 7 and 8). The lower chemical yields of the tridentate ligands might be the result of a low conversion. To improve the yields, more amidophosphine ligands with an additional chiral group were screened (entries 9-12). However, the enantioselectivity did not exceed ligand **L5**. Among all the amidophosphine ligands screened, **L3** and **L5** led to the highest yield and enantioselectivity, respectively (entries 3 and 5). Moreover, there might exist a matched relationship between the chiral

cyclohexane backbone and the amino acid scaffold in the ligands (entry 5 vs entry 6, entry 11 vs entry 12). Product **2a** was assigned as the *R*-configuration by referring to the optical rotation and HPLC spectra in the previous reports.[4h,4j,7] In terms of the enantioselectivity, ligand **L5** was selected for further study.

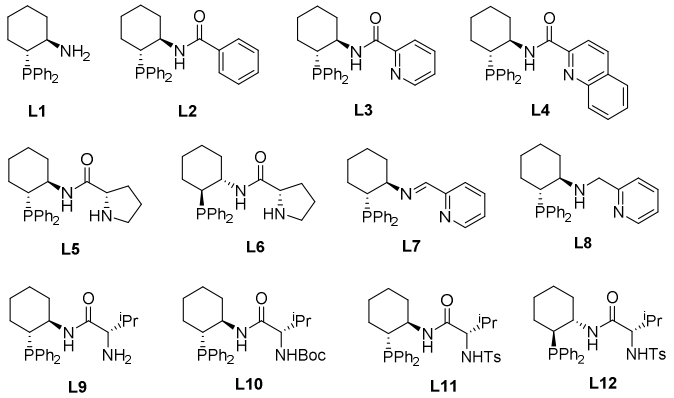
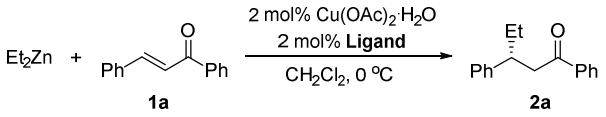



**Figure 1.** The structures of the chiral hexane-based P,N-ligands

**Table 1.** Screening of the chiral ligands for the enantioselective 1,4-conjugate addition of chalcone[a]

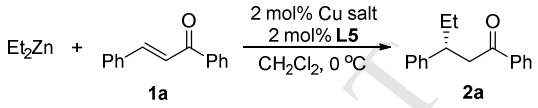



| Entry | Ligand | T (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | **L1** | 36 | 20 | -3 |
| 2 | **L2** | 36 | 31 | -27 |
| 3 | **L3** | 2 | 94 | 64 |
| 4 | **L4** | 2 | 92 | 2 |
| 5 | **L5** | 6 | 78 | 70 |
| 6 | **L6** | 6 | 86 | -64 |
| 7 | **L7** | 8 | 51 | 49 |
| 8 | **L8** | 24 | 28 | 14 |
| 9 | **L9** | 48 | 42 | 32 |
| 10 | **L10** | 48 | 21 | 20 |
| 11 | **L11** | 8 | 80 | 62 |
| 12 | **L12** | 8 | 82 | -58 |

[a] The reactions were carried out with chalcone **1a** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq.), 2 mol% $Cu(OAc)_2·H_2O$ and 2 mol% chiral ligand in 3 mL of dichloromethane at 0 °C.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralpak AD-H column.

Next, our attention was turned to the screening of copper salts (Table 2). The results suggest that the conjugate reaction is sensitive to the copper salts. With $Cu(OAc)_2$ as the precatalyst, similar results as using $Cu(OAc)_2·H_2O$ were obtained (entries 1 and 2). When divalent copper salts such as $Cu(acac)_2$, $Cu(HCO_2)_2·4H_2O$ and $Cu(OTf)_2$ were used as the precatalyst, higher chemical yields were obtained than using $Cu(OAc)_2·H_2O$ (entries 3-5 vs entry 1). Use of $Cu(HCO_2)_2·4H_2O$ gave a slightly higher enantioselectivity than that of $Cu(OAc)_2·H_2O$ (entry 4). When divalent copper salts such as $CuSO_4$, $CuBr_2$ and $CuSO_4·5H_2O$ were used, the reaction rate was sluggish, leading to poor chemical yields and enantioselectivities (entries 6-8). When monovalent copper salts such as CuI, $Cu(CH_3CN)_4ClO_4$ and $Cu(CH_3CN)_4BF_4$ were used as precatalyst, although good chemical yields were achieved, their entioselectivities were lower than using $Cu(OAc)_2·H_2O$ or $Cu(HCO_2)_2·4H_2O$ as prcatalyst (entries 9-11 vs entries 1 and 4). In order to improve enantioselectivity of the model reaction, the catalyst loading of $Cu(OAc)_2·H_2O$/**L5** and $Cu(HCO_2)_2·4H_2O$/**L5** was increased to 5 mol%. The results showed that both the chemical yield and enantioselectivity were improved (entries 12 and 13). Based on the results shown in Table 2, $Cu(OAc)_2·H_2O$ was chosen as the copper source for subsequent reactions.

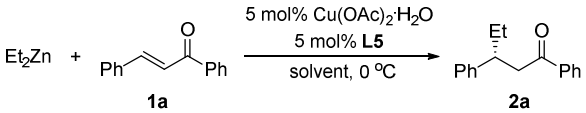
**Table 2.** Screening of copper salts for the enantioselective 1,4-conjugate addition of chalcone[a]




| Entry | Cu salt | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2·H_2O$ | 6 | 78 | 70 |
| 2 | $Cu(OAc)_2$ | 6 | 73 | 69 |
| 3 | $Cu(acac)_2$ | 4 | 87 | 61 |
| 4 | $Cu(HCO_2)_2·4H_2O$ | 6 | 78 | 71 |
| 5 | $Cu(OTf)_2$ | 2 | 86 | -41 |
| 6 | $CuSO_4$ | 36 | 18 | 3 |
| 7 | $CuSO_4·5H_2O$ | 36 | 22 | 3 |
| 8 | $CuBr_2$ | 36 | 28 | 36 |
| 9 | CuI | 6 | 69 | 66 |
| 10 | $Cu(CH_3CN)_4BF_4$ | 6 | 91 | -48 |
| 11 | $Cu(CH_3CN)_4ClO_4$ | 6 | 87 | -27 |
| 12[d] | $Cu(OAc)_2·H_2O$ | 2 | 91 | 75 |
| 13[d] | $Cu(HCO_2)_2·4H_2O$ | 2 | 87 | 76 |

[a] Unless noted otherwise, the reaction was carried out with chalcone **1a** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq), 2 mol% copper salt and 2 mol% chiral ligand **L5** in 3 mL of dichloromethane at 0 °C.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralpak AD-H column.
[d] Using 5 mol% of copper salt and 5 mol% of chiral ligand **L5**.

**Table 3.** The solvent survey for the enantioselective 1,4-conjugate addition of chalcone[a]



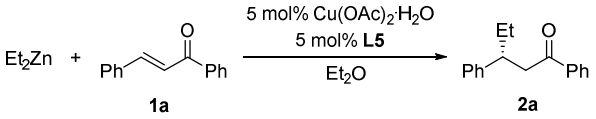

| Entry | Solvent | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | hexane | 36 | 37 | 39 |
| 2 | toluene | 2 | 96 | 85 |
| 3 | $CH_2Cl_2$ | 2 | 91 | 75 |
| 4 | $CHCl_3$ | 24 | 33 | 35 |
| 5 | $ClCH_2CH_2Cl$ | 24 | 32 | -1 |
| 6 | $Et_2O$ | 0.5 | 97 | 88 |
| 7 | MTBE | 0.5 | 94 | 88 |
| 8 | THF | 24 | 57 | -36 |
| 9 | 1,4-dioxane | 1 | 92 | 60 |
| 10 | EtOAc | 6 | 89 | 52 |
| 11 | $CH_3CN$ | 48 | 22 | 54 |
| 12 | DMF | 24 | 14 | 20 |
| 13 | 1:1 $CH_2Cl_2$/MTBE | 1.5 | 94 | 88 |
| 14[d] | $Et_2O$ | 48 | trace | - |
| 15[e] | $Et_2O$ | 1 | 96 | -82 |
| 16[f] | $Et_2O$ | 4 | 90 | 80 |

[a] Unless noted otherwise, the reactions were carried out with chalcone **1a** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq), 5 mol% $Cu(OAc)_2·H_2O$ and 5 mol% chiral ligand **L5** in 3 mL of solvent at 0 °C.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralpak AD-H column.
[d] Ligand **L3** was used instead of ligand **L5**.
[e] Ligand **L6** was used instead of ligand **L5**.
[f] Ligand **L11** was used instead of ligand **L5**.

Encouraged by the preliminary results, the solvent effect was investigated and the results are summarized in Table 3. The results show that, with hexane as solvent, the model reaction was very slow and led to poor yield and low enantioselectivity (entry

1). The conjuate reaction in toluene was achieved in 96% yield with 85% ee in 2 hours (entry 2). Halohydrocarbon solvents such as $CHCl_3$ and $ClCH_2CH_2Cl$ led to a slow reaction rate and poor enantioselectivity, which is different from that in $CH_2Cl_2$ (entries 3-5). Acyclic ethers such as $Et_2O$ and MTBE (methyl *tert*-butyl ether) gave better results than cyclic ethers such as THF and 1,4-dioxane, and the former solvents produced excellent yields and high enantioselectivities (entries 6 and 7 vs entries 8 and 9). In EtOAc, the model reaction was achieved in 89% yield in 6 hours, but the enantioselectivity was unsatisfactory (entry 10). In stronger coordinating solvents including DMF and $CH_3CN$, the conjugate reaction was sluggish, leading to poor chemical yields and enantioselectivities (entries 11 and 12). The solvent effect observed agreed with the conclusion drawn in Alexakis's review.[1b] A mixing solvent such as $CH_2Cl_2$ and MTBE in 1:1 volume ratio was also examined, and the results were similar to that with MTBE as solvent (entry 13 vs entry 7). The solvent survey suggests that diethyl ether is the most suitable solvent for this asymmetric transform. Moreover, the results in Table 1 indicated that ligand **L3**, **L6** and **L11** provided higher chemical yields and a litter lower enantioselectivities than ligand **L5**, so these ligands were also examined using ether as solvent (Table 3, entries 14-16). Ligand **L3** was ineffective for the sake of its insolubility in ether. Although using ligand **L6** and **L11** in ether could improve the enantioselectivity, ligand **L5** was still the optimal one.

**Table 4.** Effects of substrate concentration and reaction temperature on the enantioselective 1,4-conjugate addition of chalcone[a]

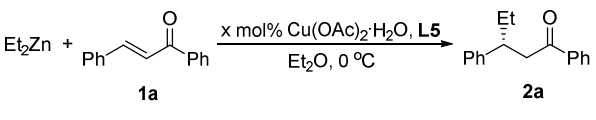



1a 2a

| Entry | Conc. (M)[b] | Temp ($^oC$) | Time (min) | Yield (%)[c] | Ee (%)[d] |
|---|---|---|---|---|---|
| 1 | 0.25 | 0 | 30 | 95 | 88 |
| 2 | 0.167 | 0 | 30 | 97 | 88 |
| 3 | 0.125 | 0 | 30 | 99 | 88 |
| 4 | 0.1 | 0 | 30 | 95 | 88 |
| 5 | 0.125 | -10 | 50 | 98 | 88 |
| 6 | 0.125 | -20 | 60 | 97 | 86 |
| 7 | 0.125 | -30 | 180 | 94 | 84 |
| 8 | 0.125 | 10 | 20 | 96 | 84 |
| 9 | 0.125 | 25 | 10 | 96 | 63 |

[a] The reactions were carried out with chalcone **1a** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution), 5 mol% $Cu(OAc)_2\cdot H_2O$ and 5 mol% chiral ligand **L5** in ether.
[b] The concentration of substrate **1a** with respect to the volume of ether.
[c] Isolated yields.
[d] The ee values were determined by HPLC using a Chiralpak AD-H column.

**Table 5.** Effects of the loading amount of $Cu(OAc)_2\cdot H_2O$ and chiral ligand **L5**[a]




1a 2a

| Entry | x | **L5**/Cu | Time (min) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 5 | 1 | 30 | 99 | 88 |
| 2 | 5 | 1.5 | 40 | 94 | 85 |
| 3 | 5 | 2 | 60 | 92 | 83 |
| 4 | 10 | 0.5 | 180 | 87 | 85 |
| 5 | 2 | 1 | 30 | 96 | 88 |
| 6 | 1 | 1 | 60 | 92 | 85 |
| 7 | 0.5 | 1 | 240 | 86 | 81 |

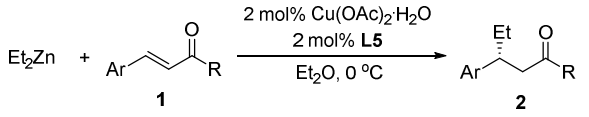
[a] The reactions were carried out with chalcone **1a** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq) in 4 mL ether at 0 $^oC$.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralpak AD-H column.

After surveying the solvent, we turned our attention to other conditions such as the substrate concentration, ratio of ligand to copper salt, catalyst loading and reaction temperature. The results are summarized in Table 4 and Table 5. The results shown in Table 4 shows that within a certain range of chalcone concentration (0.1 M~0.25 M with respect to the volume of ether) at 0 $^oC$, no influence on the reaction rate, the chemical yield and the enantioselectivity was observed (entries 1-4). The reaction temperature varying from -30 $^oC$ to 10 $^oC$ affected the reaction rate rather than yield and enantioselectivity, and a higher temperature led to a faster reaction rate (entries 3 and 5-8). However, when the reaction temperature was raised to 25 $^oC$, the enantioselectivity was decreased evidently (entry 9).

The effect of the molar ratio of ligand **L5** to $Cu(OAc)_2\cdot H_2O$ was listed in Table 5. With an increment of chiral ligand loading, a decrement of reaction rate, chemical yield and enantioselectivity was observed (entries 1-3). The presence of excess copper salt led to a similar effect (entry 4). The loading amount of $Cu(OAc)_2\cdot H_2O$/**L5** could be reduced to 2 mol% with a retained reaction efficiency (entry 5 vs entry 1). A subsequent reduction of catalyst loading resulted in a longer reaction time, and the chemical yield and enantioselectivity decreased obviously (entries 6 and 7). However, 86% yield and 81% ee could be accomplished with 0.5 mol% of chiral catalyst (entry 7).

Based on the results shown in Table 4 and Table 5, the optimal reaction condition was established to be 2 mol% $Cu(OAc)_2\cdot H_2O$ and 2 mol% **L5** in ether (0.125 M) at 0 $^oC$.

**Table 6.** Substrate scope of the enantioselective 1,4-conjugate addition of α,β-unsaturated ketones[a]




1 2

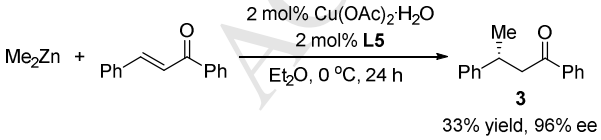
| Entry | Ar | R | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 0.5 | 96 (**2a**) | 88 |
| 2 | 4-$CF_3C_6H_4$ | $C_6H_5$ | 1 | 76 (**2b**) | 79 |
| 3 | 4-$BrC_6H_4$ | $C_6H_5$ | 0.5 | 82 (**2c**) | 85 |
| 4 | 4-$ClC_6H_4$ | $C_6H_5$ | 0.5 | 86 (**2d**) | 86 |
| 5 | 3-$ClC_6H_4$ | $C_6H_5$ | 0.5 | 81 (**2e**) | 78 |
| 6 | 2-$ClC_6H_4$ | $C_6H_5$ | 1 | 98 (**2f**) | 38 |
| 7 | 4-$FC_6H_4$ | $C_6H_5$ | 1 | 84 (**2g**) | 83 |
| 8 | 4-$MeC_6H_4$ | $C_6H_5$ | 0.5 | 93 (**2h**) | 88 |
| 9 | 3-$MeC_6H_4$ | $C_6H_5$ | 0.5 | 92 (**2i**) | 85 |
| 10 | 2-$MeC_6H_4$ | $C_6H_5$ | 12 | 81 (**2j**) | 62 |
| 11 | 4-$MeOC_6H_4$ | $C_6H_5$ | 4 | 72 (**2k**) | 72 |
| 12 | 1-Naphthyl | $C_6H_5$ | 3 | 93 (**2l**) | 65 |
| 13[d] | 2- Naphthyl | $C_6H_5$ | 2 | 82(**2m**) | 87 |
| 14 | $C_6H_5$ | 4-$ClC_6H_4$ | 1 | 88 (**2n**) | 73 |

| | | | | | |
|---|---|---|---|---|---|
| 15 | $C_6H_5$ | 4-Me$C_6H_4$ | 1 | 92 (**2o**) | 89 |
| 16 | $C_6H_5$ | 4-MeO$C_6H_4$ | 6 | 70 (**2p**) | 91 |
| 17 | 4-Me$C_6H_4$ | 4-Me$C_6H_4$ | 1 | 92 (**2q**) | 90 |
| 18 | $C_6H_5$ | 2-Thienyl | 0.5 | 66 (**2r**) | 91 |
| 19 | $C_6H_5$ | Me | 0.5 | 72 (**2s**) | 92 |
| 20 | $C_6H_5$ | Et | 8 | 62 (**2t**) | 90 |
| 21 | $C_6H_5$ | *i*-Pr | 24 | 56 (**2u**) | 78 |

[a] Unless noted otherwise, the reaction was carried out with substrate **1** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq), 2 mol% $Cu(OAc)_2 \cdot H_2O$ and 2 mol% chiral ligand **L5** in 4 mL ether at 0 °C.
[b] Isolated yields.
[c] The *ee* values were determined by HPLC using chiral column.
[d] The solvent was toluene.

Under the optimized reaction conditions, the substrate scope of α,β-unsaturated ketones was investigated (Table 5). For chalcones, except for 4-$CF_3$ and 4-MeO substituted substrates (entries 2, 11 and 16), other chalcones examined provided good yields (81-96%, entries 3-10, 12-15 and 17). The enantioselectivities of the diverse chalcones varied largely (38-91% ee). The presence of both electron-withdrawing and donating groups at the *ortho*-position in the β-aryl of α,β-unsaturated ketones appeared to be disadvantageous to the conjugate addition. Both the reaction rate and enantioselectivity were lower than those of the *para*- or *meta*-substituted analogues (entry 6 vs entries 4 and 5, entry 10 vs entries 8 and 9, entry 12 vs entry 13). Note that the solubility of 2-naphthyl chalcone is poor in ether. As a result, toluene was used as the solvent, leading to a good yield and enantioselectivity (entry 13). When (*E*)-1,3-di-*p*-tolylprop-2-en-1-one was used as Michael acceptor, 92% yield with 90% ee was accomplished in one hour (entry 17). Heteroaromatic-containing enone was also examined. However, the use of (*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one gave high enantioselectivity but moderate chemical yield (entry 18), and the low chemical yield was resulted from the Michael/Michael tandem side reaction. Moreover, the catalytic system is suitable for alkyl enones (entries 19-21). However, β-alkyl α,β-unsaturated ketones such as (*E*)-1-phenylbut-2-en-1-one were unreactive under the typical reaction conditions.

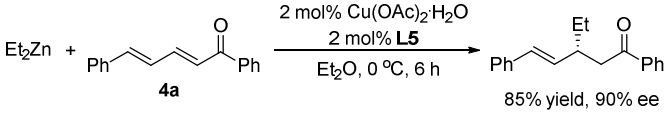
Under the typical reaction conditions, dimethylzinc was used as a nucleophile instead of diethylzinc for the conjugate reaction (Scheme 1). The results indicated that the reaction was slow, and side reactions occurred. Although the chemical yield was only 33% in 24 hours, the desired product was achieved in higher enantioselectivity (96% ee) than the 1,4-adducts of diethylzinc. Dibutylzinc and diphenylzinc were also examined as nucleophile. The addition reaction with dibutylzinc was complicated, and diphenylzinc was not reactive.




**Scheme 1.** The conjugate addition of dimethylzinc to chalcone **1a**

*2.2 Enantioselective 1,4-conjugate addition of α,β,γ,δ-unsaturated ketones*

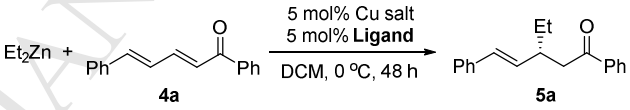
Under the above-mentioned reaction conditions, the conjugate addition of diethylzinc to acyclic α,β,γ,δ-unsaturated ketone **4a** was examined. To our delight, 85% yield and 90% ee were obtained, and the conjugate addition reaction showed 1,4-regioselectivity (Scheme 2). To further improve the results, the reaction conditions for the conjugate addition of dienone **4a** were re-optimized, including the choice of chiral ligand, copper salt, solvent and substrate.




**Scheme 2.** The conjugate addition of diethylzinc to dienone **4a**

Initially, chiral hexane-based P,N-ligands **L1**-**L7** and **L9**-**L12** were screened (Table 7, entries 1-11). $CH_2Cl_2$ was used as solvent, as a result of the solubility of these chiral ligands. The results suggest that ligand **L11** gave better results than other ligands. However, both chemical yield and enantioselectivity were unsatisfied (48% yield and 50% ee, entry 10). GC-MS analysis of the crude products suggests that no 1,6-regioisomer was formed in this process. To improve the catalytic system, chiral ligand **L11** was selected for further studies. Product **5a** was assigned as *R*-configuration by referring to the optical rotation direction in the previous report.[8]

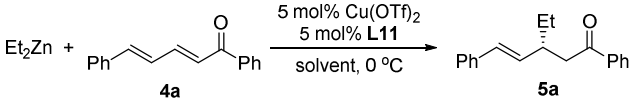
**Table 7.** Screening of copper salts and chiral ligands for the enantioselective 1,4-conjugate addition of dienone **4a**[a]




| Entry | Cu salt | Ligand | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2 \cdot H_2O$ | **L1** | 6 | -15 |
| 2 | $Cu(OAc)_2 \cdot H_2O$ | **L2** | 45 | -14 |
| 3 | $Cu(OAc)_2 \cdot H_2O$ | **L3** | 49 | 26 |
| 4 | $Cu(OAc)_2 \cdot H_2O$ | **L4** | 41 | 6 |
| 5 | $Cu(OAc)_2 \cdot H_2O$ | **L5** | 45 | 45 |
| 6 | $Cu(OAc)_2 \cdot H_2O$ | **L6** | 45 | 24 |
| 7 | $Cu(OAc)_2 \cdot H_2O$ | **L7** | 13 | 34 |
| 8 | $Cu(OAc)_2 \cdot H_2O$ | **L9** | 45 | 42 |
| 9 | $Cu(OAc)_2 \cdot H_2O$ | **L10** | 42 | 45 |
| 10 | $Cu(OAc)_2 \cdot H_2O$ | **L11** | 48 | 50 |
| 11 | $Cu(OAc)_2 \cdot H_2O$ | **L12** | 46 | 34 |
| 12 | $Cu(OAc)_2$ | **L11** | 44 | 60 |
| 13 | $Cu(acac)_2$ | **L11** | 34 | 57 |
| 14 | $Cu(HCOO)_2 \cdot 4H_2O$ | **L11** | 47 | 82 |
| 15 | $Cu(HCOO)_2$ | **L11** | 45 | 87 |
| 16 | $Cu(OTf)_2$ | **L11** | 64 | 94 |
| 17 | $CuCl_2$ | **L11** | 40 | 48 |
| 18 | CuI | **L11** | 50 | 73 |
| 19 | $Cu(CH_3CN)_4BF_4$ | **L11** | 35 | 81 |

[a] The reaction were carried out with substrate **4a** (0.2 mmol), diethylzinc (0.3 mL of 1 M hexane solution, 1.5 eq), 5 mol% copper salt and 5 mol% chiral ligand in 2 mL $CH_2Cl_2$ at 0 °C for 48 hours.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralcel OD-H column.

**Table 8.** Solvent survey of the enantioselective 1,4-conjugate addition of dienone **4a**[a]



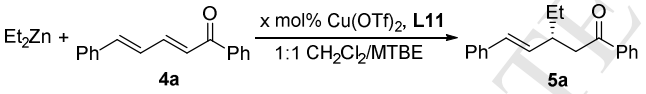
| Entry | Solvent | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | toluene | 24 | 62 | 87 |
| 2 | $CH_2Cl_2$ | 24 | 64 | 94 |
| 3 | $ClCH_2CH_2Cl$ | 24 | 70 | 90 |
| 4 | $Et_2O$ | 12 | 78 | 90 |
| 5 | MTBE | 12 | 84 | 87 |
| 6 | THF | 24 | 58 | 89 |
| 7 | EtOAc | 48 | 64 | 88 |
| 8 | $CH_3CN$ | 48 | trace | - |
| 9 | DMF | 48 | 47 | 82 |
| 10 | 1:1 $CH_2Cl_2$/MTBE | 24 | 80 | 90 |
| 11 | 2:1 $CH_2Cl_2$/MTBE | 24 | 80 | 89 |
| 12 | 4:1 $CH_2Cl_2$/MTBE | 24 | 82 | 88 |

[a] The reaction were carried out with substrate **4a** (0.2 mmol), diethylzinc (0.3 mL of 1 M hexane solution, 1.5 eq), 5 mol% $Cu(OTf)_2$ and 5 mol% chiral ligand **L11** in 2 mL solvent at 0 °C.
[b] Isolated yields.
[c] The ee values were determined by HPLC using a Chiralcel OD-H column.

The effect of copper salts on the conjugate addition between $Et_2Zn$ and dienone **4a** was summarized in Table 7 (entries 10 and 12-19). Different from chalcone as Michael acceptor, the copper precatalyst containing crystal water affected both the chemical yield and enantioselectivity (Table 7, entry 10 vs entry 12, entry 14 vs entry 15). When $Cu(OTf)_2$ was used as precatalyst, the 1,4-adduct **5a** was obtained in the highest chemical yield and enantioselectivity (64% yield with 94% ee, entry 16).

The solvent survey indicated that $CH_2Cl_2$ provided the highest enantioselectivity among the solvents screened (entry 2, Table 8), while MTBE gave the highest chemical yield (entry 5, Table 8). Therefore, a solvent mixture of $CH_2Cl_2$ and MTBE was examined. The results suggested that the volume ratio of $CH_2Cl_2$ to MTBE had a slight effect on the asymmetric conjugate addition (entries 10-12). Considering both the chemical yield and enantioselectivity, 1:1 $CH_2Cl_2$/MTBE was selected as the solvent for further optimization of the reaction conditions.

**Table 9.** Further optimization of the reaction conditions[a]



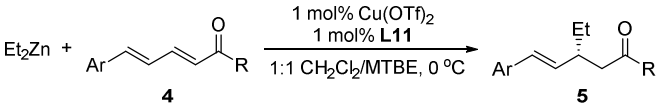

| Entry | x | Temp (°C) | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 5 | 25 | 6 | 62 | 92 |
| 2 | 5 | 0 | 24 | 80 | 90 |
| 3 | 5 | -20 | 72 | 61 | 75 |
| 4[d] | 5 | 0 | 24 | 80 | 90 |
| 5[e] | 5 | 0 | 24 | 81 | 89 |
| 6[f] | 5 | 0 | 24 | 61 | 90 |
| 7[g] | 5 | 0 | 24 | 80 | 90 |
| 8 | 2.5 | 0 | 24 | 82 | 94 |
| 9[h] | 1 | 0 | 24 | 84 | 94 |
| 10[h] | 0.5 | 0 | 36 | 83 | 91 |
| 11[i] | 0.1 | 0 | 120 | 45 | 87 |
| 12[h] | 5 | 0 | 24 | 83 | 90 |
| 13[h,j] | 1 | 0 | 24 | 84 | 93 |
| 14[h,k] | 1 | 0 | 18 | 78 | 93 |

[a] Unless stated otherwise, the reaction were carried out with substrate **4a** (0.2 mmol), diethylzinc (0.3 mL of 1 M hexane solution, 1.5 eq), x mol% $Cu(OTf)_2$ and x mol% chiral ligand **L11** in 2 mL 1:1 $CH_2Cl_2$/MTBE at 0 °C.
[b] Isolated yields.
[c] The *ee* values were determined by HPLC using a Chiralcel OD-H column.
[d] The amount of chiral ligand **L11** was 7.5 mol%.
[e] The amount of chiral ligand **L11** was 10 mol%.
[f] The amount of diethylzinc was 1.1 equivalent.
[g] The amount of diethylzinc was 2 equivalent.
[h] The reaction was performed in 0.5 mmol scale.
[i] The reaction was performed in 2.5 mmol scale.
[j] 4 mL 1:1 $CH_2Cl_2$/MTBE was used as solvent.
[k] 1 mL 1:1 $CH_2Cl_2$/MTBE was used as solvent.

Reaction conditions including the loading amount of ligand, the reaction temperature, the molar ratio of chiral ligand to copper, the chiral catalyst, and the reaction concentration were further optimized (Table 9). At lower temperature, a longer reaction time was required for the conjugate reaction, and a temperature of 0 °C was showed to be optimal (entries 1-3). Increasing the molar ratio of ligand **L11** to $Cu(OTf)_2$ from 1:1 to 2:1 led to similar results (entries 2, 4 and 5). These results were different from that observed for chalcone with $Cu(OAc)_2 \cdot H_2O$/**L5** as chiral catalyst (Table 5). When the amount of $Et_2Zn$ was reduced to 1.1 equivalent, the chemical yield decreased dramatically (entry 6). Varying the chiral catalyst loading from 5 mol% to 0.5 mol% led to similar results (entries 8-10 vs entry 2). Further reducing the catalyst amount to 0.1 mol% compromised the conjugate addition since the reaction did not complete even after 5 days (entry 11). The change of substrate concentration had minimal influence on this reaction (entries 9, 13 and 14). Based on the results mentioned above, the optimal reaction condition was established to be 1 mol% $Cu(OTf)_2$ and 1 mol% **L11** in 1:1 $CH_2Cl_2$/MTBE (0.1 M concentration of unsaturated ketone respect to $CH_2Cl_2$/MTBE) at 0 °C (entries 9 and 13 in Table 9).

Under the optimized reaction conditions, the substrate scope of α,β,γ,δ-unsaturated ketones was investigated (Table 10). The asymmetric catalytic system tolerated a variety of substrate. The 1,4-adducts **5** were obtained in good yields (79-86%) for all the dienones examined. For all substrates except that shown in entry 8, excellent enantioselectivities were achieved (89-97% ee). The substituent at phenyl group of substrates **4** played an irregular role in the control of stereoselectivity.

**Table 10.** Substrate scope of the enantioselective 1,4-conjugate addition of α,β,γ,δ-unsaturated ketones[a]




| Entry | Ar | R | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 24 | 84 (**5a**) | 94 |
| 2 | 4-$BrC_6H_4$ | $C_6H_5$ | 24 | 79 (**5b**) | 92 |
| 3 | 4-$ClC_6H_4$ | $C_6H_5$ | 24 | 80 (**5c**) | 90 |
| 4 | 4-$FC_6H_4$ | $C_6H_5$ | 24 | 84 (**5d**) | 93 |
| 5 | 4-$MeC_6H_4$ | $C_6H_5$ | 24 | 82 (**5e**) | 89 |
| 6 | 4-$MeOC_6H_4$ | $C_6H_5$ | 24 | 81 (**5f**) | 93 |
| 7 | $C_6H_5$ | 4-$BrC_6H_4$ | 24 | 84 (**5g**) | 91 |
| 8 | $C_6H_5$ | 4-$ClC_6H_4$ | 24 | 85 (**5h**) | 78 |
| 9 | $C_6H_5$ | 4-$FC_6H_4$ | 24 | 86 (**5i**) | 93 |
| 10 | $C_6H_5$ | 4-$MeC_6H_4$ | 18 | 84 (**5j**) | 95 |
| 11 | $C_6H_5$ | 4-$MeOC_6H_4$ | 24 | 82 (**5k**) | 97 |

[a] The reactions were carried out with substrate **4** (0.5 mmol), diethylzinc (0.75 mL of 1 M hexane solution, 1.5 eq), 1 mol% $Cu(OTf)_2$ and 1 mol% chiral ligand **L11** in 5 mL 1:1 $CH_2Cl_2$/MTBE at 0 °C.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.

## 3. Conclusion

In conclusion, we have developed a Cu(II)-catalyzed enantioselective 1,4-conjugate addition of dialkylzinc reagent to enones and dienones. With 2 mol% of chiral amidophosphine ligand **L5** and $Cu(OAc)_2 \cdot H_2O$, 1,4-adducts of α-aryl enone, α-alkyl enones and dienes were obtained in excellent yields (up to

98%) with high enantioselectivities (up to 96% ee). Furthermore, a more efficient catalytic system was extended for the 1,4-conjugate addition of diethylzinc reagent to α,β,γ,δ-unsaturated ketones. With 1 mol% of chiral amidophosphine ligand **L11** and $Cu(OTf)_2$, the 1,4-adducts were afforded in good yields (79-86% yield) and excellent enantioselectivities (up to 97% ee).

## 4. Experimental

### *4.1. General methods*

All reactions were carried out under $N_2$ atmosphere using standard Schlenk techniques with magnetic stirring. Anhydrous solvents were distilled from $CaH_2$ (dichloromethane, chloroform, $ClCH_2CH_2Cl$, ethyl acetate, acetonitrile), sodium-benzophenone (hexane, toluene, ether, MTBE, THF). Anhydrous DMF was dried over $CaH_2$ and distilled under reduced pressure. Thin-layer chromatography (TLC) was performed on Silicycle 10-40 μm silica gel plates. Column chromatography was performed using silica gel (300-400 mesh) eluting with petroleum ether and ethyl acetate.

Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm). The NMR spectra were recorded on Bruker 400 spectrometer. The chemical shifts of $^1H$ NMR were referenced to tetramethylsilane (δ 0.00) using $CDCl_3$ as solvent, and the $^{13}C$ NMR spectra was referenced to solvent carbons (77.0 ppm for $CDCl_3$). High Resolution Mass spectra (HRMS) were recorded on Micromass GCT spectrometer with Electron Spray Ionization (ESI-TOF) resource. HPLC analysis was performed on Waters equipment using Daicel Chiralpak AD-H column, Chiralcel OD-H column and OJ-H column.

Chiral ligands were prepared according to literature procedures.[6a,6c,9]

### *4.2. General procedure for the enantioselective 1,4-conjugate addition of α,β-unsaturated ketones*

A flame-dried Schlenk tube was charged with chiral ligand **L5** (2 mol%, 0.01 mmol) in dry toluene (4 mL), $Cu(OAc)_2 \cdot H_2O$ (2 mol%, 0.01 mmol) was added and the mixture was stirred at 25 $^oC$ under $N_2$ atmosphere for 30 min. Then the mixture was cooled down to 0 °C. The α,β-unsaturated ketone **1** (0.5 mmol) was added at 0 °C, followed by adding diethylzinc (0.75 mL, 1 M in hexane, 1.5 eq) dropwise via a syringe. After the reaction was completed (monitored by TLC), 2 mL of 1 M HCl were added slowly. The resulting mixture was stirred for 0.5 hour, then extracted with ether (10 mL × 3). The combined organic phase was washed with saturated aqueous $Na_2CO_3$ and brine, respectively. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The resulting residue was purified by chromatography on silica gel to afford the desired product **2**. Chiral HPLC chromatography was used to determine the enantiomeric excesses.

*4.2.1 (R)-1,3-diphenylpentan-1-one (**2a**):* Yellow oil, 96% yield, 88% ee, $[\alpha]_D^{27}$-1.9 (*c* 2.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.82 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.23-7.09 (m, 5H), 3.25-3.13 (m, 3H), 1.76-1.67 (m, 1H), 1.60-1.52 (m, 1H), 0.73 (t, *J* = 7.6 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 9.48 min (minor), 11.12 min (major).

*4.2.2 (R)-1-phenyl-3-(4-(trifluoromethyl)phenyl)pentan-1-one (**2b**):* Yellow oil, 76% yield, 79% ee, $[\alpha]_D^{27}$+17.1 (*c* 0.81, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.90 (d, *J* = 7.6 Hz, 2H), 7.54-7.51 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.37-3.26 (m, 3H), 1.86-1.76 (m, 1H), 1.73-1.60 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 8.39 min (minor), 10.43 min (major).

*4.2.3 (R)-3-(4-bromophenyl)-1-phenylpentan-1-one (**2c**):* Yellow oil, 82% yield, 85% ee, $[\alpha]_D^{27}$+9.1 (*c* 0.91, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.89 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.44-7.38 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.27-3.18 (m, 3H), 1.82-1.72 (m, 1H), 1.65-1.54 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.35 min (minor), 13.78 min (major).

*4.2.4 (R)-3-(4-chlorophenyl)-1-phenylpentan-1-one (**2d**):* Yellow oil, 86% yield, 86% ee, $[\alpha]_D^{27}$+13.8 (*c* 0.79, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.81-7.79 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35-7.31 (m, 2H), 7.16-7.13 (m, 2H), 7.08-7.06 (m, 2H), 3.19-3.10 (m, 3H), 1.73-1.64 (m, 1H), 1.57-1.46 (m, 1H), 0.71 (t, *J* = 7.6 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.10 min (minor), 13.14 min (major).

*4.2.5 (R)-3-(3-chlorophenyl)-1-phenylpentan-1-one (**2e**):* Yellow oil, 81% yield, 78% ee, $[\alpha]_D^{27}$+18.5 (*c* 0.82, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.82-7.80 (m, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.13-7.02 (m, 4H), 3.20-3.11 (m, 3H), 1.74-1.64 (m, 1H), 1.58-1.47 (m, 1H), 0.72 (t, *J* = 7.6 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.02 min (minor), 11.02 min (major).

*4.2.6 (R)-3-(2-chlorophenyl)-1-phenylpentan-1-one (**2f**):* Yellow oil, 98% yield, 38% ee, $[\alpha]_D^{27}$+15.2 (*c* 0.88, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.85-7.83 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35-7.32 (m, 2H), 7.26 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.2 Hz, 1H), 7.17 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.6 Hz, 1H), 7.12 (td, $J_1$ = 8.0 Hz, $J_2$ = 1.2 Hz, 1H,), 7.02 (td, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz, 1H,), 3.82-3.75 (m, 1H), 3.23 (dd, $J_1$ = 16.8 Hz, $J_2$ = 6.0 Hz, 1H), 3.15 (dd, $J_1$ = 16.8 Hz, $J_2$ = 8.0 Hz, 1H), 1.78-1.68 (m, 1H), 1.66-1.55 (m, 1H), 0.73 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 9.60 min (minor), 11.57 min (major).

*4.2.7 (R)-3-(4-fluorophenyl)-1-phenylpentan-1-one (**2g**):* Yellow oil, 84% yield, 83% ee, $[\alpha]_D^{27}$+10.1 (*c* 0.80, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.80-7.78 (m, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.10-7.06 (m, 2H), 6.88-6.83 (m, 2H), 3.17-3.10 (m, 3H), 1.73-1.63 (m, 1H), 1.56-1.45 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.13 min (minor), 12.27 min (major).

*4.2.8 (R)-1-phenyl-3-(p-tolyl)pentan-1-one (**2h**):* Yellow oil, 93% yield, 88% ee, $[\alpha]_D^{27}$-5.1 (*c* 2.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.78 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.01-6.96 (m, 4H), 3.18-3.08 (m, 3H), 2.17 (s, 3H), 1.68-1.63 (m, 1H), 1.53-1.47 (m, 1H), 0.71-0.67 (m, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 9.04 min (minor), 11.59 min (major).

*4.2.9 (R)-1-phenyl-3-(m-tolyl)pentan-1-one (**2i**):* Yellow oil, 92% yield, 85% ee, $[\alpha]_D^{27}$-0.6 (*c* 1.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): *δ* 7.82 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.95-6.89 (m, 3H), 3.19-3.08 (m, 3H), 2.23 (s, 3H), 1.73-1.62 (m, 1H), 1.59-1.48 (m, 1H), 0.71 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ =

240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 11.08 min (minor), 12.36 min (major).

*4.2.10 (R)-1-phenyl-3-(o-tolyl)pentan-1-one (**2j**):* Yellow oil, 81% yield, 62% ee, $[\alpha]_D^{27}$+31.7 (*c* 0.66, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.83-7.81 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.36-7.32 (m, 2H), 7.13-6.97 (m, 4H), 3.55-3.47 (m, 1H), 3.22-3.12 (m, 2H), 2.30 (s, 3H), 1.75-1.65 (m, 1H), 1.62-1.51 (m, 1H), 0.73 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.60 min (minor), 12.46 min (major).

*4.2.11 (R)-3-(4-methoxyphenyl)-1-phenylpentan-1-one (**2k**):* Yellow oil, 72% yield, 72% ee, $[\alpha]_D^{27}$-4.5 (*c* 2.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.81-7.79 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.06-7.03 (m, 2H), 6.75-6.71 (m, 2H), 3.66 (s, 3H), 3.17-3.06 (m, 3H), 1.72-1.62 (m, 1H), 1.56-1.45 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 12.15 min (minor), 16.82 min (major).

*4.2.12 (R)-3-(naphthalen-1-yl)-1-phenylpentan-1-one (**2l**):* Yellow oil, 93% yield, 65% ee, $[\alpha]_D^{27}$+60.7 (*c* 0.99, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.14 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.61-7.56 (m, 1H), 7.39-7.24 (m, 7H), 4.23-4.09 (m, 1H), 3.32-3.19 (m, 2H), 1.87-1.69 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 14.61 min (minor), 16.16 min (major).

*4.2.13 (R)-3-(naphthalen-2-yl)-1-phenylpentan-1-one (**2m**):* Yellow oil, 82% yield, 87% ee, $[\alpha]_D^{27}$+15.8 (*c* 0.95, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.87 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 3H), 7.65 (s, 1H), 7.45-7.32 (m, 6H), 3.45-3.25 (m, 3H), 1.89-1.79 (m, 1H), 1.77-1.66 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 12.00 min (minor), 14.22 min (major).

*4.2.14 (R)-1-(4-chlorophenyl)-3-phenylpentan-1-one (**2n**):* Yellow oil, 88% yield, 73% ee, $[\alpha]_D^{27}$+12.0 (*c* 0.65, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.71 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.19-7.07 (m, 5H), 3.16-3.08 (m, 3H), 1.73-1.63 (m, 1H), 1.59-1.49 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 11.35 min (minor), 13.91 min (major).

*4.2.15 (R)-3-phenyl-1-(p-tolyl)pentan-1-one (**2o**):* Yellow oil, 92% yield, 89% ee, $[\alpha]_D^{27}$+12.9 (*c* 0.78, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.70 (d, *J* = 8.0 Hz, 2H), 7.19-7.05 (m, 7H), 3.16-3.09 (m, 3H), 2.26 (s, 3H), 1.74-1.62 (m, 1H), 1.58-1.48 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 11.67 min (minor), 16.03 min (major).

*4.2.16 (R)-1-(4-methoxyphenyl)-3-phenylpentan-1-one (**2p**):* Yellow oil, 70% yield, 91% ee, $[\alpha]_D^{27}$+4.9 (*c* 2.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.91-7.87 (m, 2H), 7.30-7.26 (m, 2H), 7.24-7.16 (m, 3H), 6.92-6.88 (m, 2H), 3.85 (s, 3H), 3.26-3.15 (m, 3H), 1.81-1.73 (m, 1H), 1.69-1.60 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 18.79 min (minor), 28.76 min (major).

*4.2.17 (R)-1,3-di-p-tolylpentan-1-one (**2q**):* Yellow oil, 92% yield, 90% ee, $[\alpha]_D^{27}$+9.7 (*c* 0.94, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.70 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.02-6.96 (m, 4H), 3.13-3.06 (m, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.71-1.61 (m, 1H), 1.55-1.44 (m, 1H), 0.69 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 11.44 min (minor), 18.20 min (major).

*4.2.18 (R)-3-phenyl-1-(thiophen-2-yl)pentan-1-one (**2r**):* Yellow oil, 66% yield, 91% ee, $[\alpha]_D^{27}$-11.2 (*c* 2.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.54 (dd, $J_1$ = 3.6 Hz, $J_2$ = 0.8 Hz, 1H), 7.47 (dd, $J_1$ = 5.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.21-7.07 (m, 5H), 6.97 (dd, $J_1$ = 4.8 Hz, $J_2$ = 3.6 Hz, 1H), 3.18-3.03 (m, 3H), 1.75-1.65 (m, 1H), 1.62-1.51 (m, 1H), 0.71 (t, *J* = 7.2 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 10.15 min (minor), 12.11 min (major).

*4.2.19 (R)-4-phenylhexan-2-one (**2s**):* Yellow oil, 72% yield, 92% ee, $[\alpha]_D^{27}$-26.1 (*c* 1.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.23-7.18 (m, 2H), 7.13-7.08 (m, 3H), 2.99-2.92 (m, 1H), 2.65 (d, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.65-1.55 (m, 1H), 1.54 -1.43 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (OJ-H column, λ = 220 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 13.03 min (minor), 14.55 min (major).

*4.2.20 (R)-5-phenylheptan-3-one (**2t**):* Yellow oil, 62% yield, 90% ee, $[\alpha]_D^{27}$+11.1 (*c* 0.76, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.21-7.18 (m, 2H), 7.11-7.08 (m, 3H), 3.00-2.93 (m, 1H), 2.61 (d, *J* = 7.2 Hz, 2H), 2.29-2.08 (m, 2H), 1.64-1.43 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); HPLC (OJ-H column, λ = 220 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.05 min (minor), 8.34 min (major).

*4.2.21 (R)-2-methyl-5-phenylheptan-3-one (**2u**):* Yellow oil, 56% yield, 78% ee, $[\alpha]_D^{27}$-10.5 (*c* 0.80, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.21-7.18 (m, 2H), 7.11-7.08 (m, 3H), 3.03-2.96 (m, 1H), 2.71-2.60 (m, 2H), 2.41-2.31 (m, 1H), 1.63-1.45 (m, 2H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H); HPLC (OJ-H column, λ = 220 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 8.02 min (minor), 9.00 min (major).

*4.2.22 (R)-1,3-diphenylbutan-1-one (**3**):* Dimethylzinc was used instead of diethylzinc. 33% yield, 96% ee, $[\alpha]_D^{27}$-2.8 (*c* 1.00, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.85 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.24-7.17 (m, 4H), 7.14-7.11 (m, 1H), 3.47-3.39 (m, 1H), 3.22 (dd, $J_1$ = 16.4 Hz, $J_2$ = 5.6 Hz, 1H), 3.11 (dd, $J_1$ = 16.4 Hz, $J_2$ = 8.4 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H); HPLC (AD-H column, λ = 240 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.6 mL/min): $t_R$ = 9.65 min (minor), 10.78 min (major).

### *4.3. General procedure for the enantioselective 1,4-conjugate addition of α,β,γ,δ-unsaturated ketones*

To a flame-dried Schlenk tube charged with chiral ligand **L11** (1 mol%, 0.005 mmol) and 5 mL $CH_2Cl_2$/MTBE (1:1 v/v), $Cu(OTf)_2$ (1 mol%, 0.005 mmol) was added and the mixture was stirred at 25 °C under $N_2$ atmosphere for an hour. Then mixture was cooled to 0 °C. The α,β,γ,δ-unsaturated ketone **4** (0.5 mmol) was added at 0 °C, followed by adding diethylzinc (0.75 mL, 1 M in hexane, 1.5 eq) dropwise via a syringe. After the reaction was completed (monitored by TLC), 5 mL of an aqueous solution of $NH_4Cl$ were added slowly. The resulting mixture was stirred for 15 minutes, then extracted with dichloromethane (10 mL × 3) and washed with brine. The organic phase was dried over anhydrous sodium sulfate, and then concentrated. The resulting residue was purified by chromatography on silica gel to afford the desired product **5**. Chiral HPLC chromatography was used to determine the enantiomeric excesses.

*4.3.1 (R,E)-3-ethyl-1,5-diphenylpent-4-en-1-one (**5a**):* White solid, 84% yield, 94% ee, mp 86.0-87.7 °C, $[\alpha]_D^{25}$-93.7 (*c* 0.48,

MeOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.95 (d, $J$ = 7.6 Hz, 2H), 7.55 (t, $J$ = 7.2 Hz, 1H), 7.46 (t, $J$ = 7.6 Hz, 2H), 7.32 - 7.26 (m, 4H), 7.18 (t, $J$ = 7.2 Hz, 1H), 6.39 (d, $J$ = 16.0 Hz, 1H), 6.07 (dd, $J$ = 16.0, 8.4 Hz, 1H), 3.08 (d, $J$ = 6.4 Hz, 2H), 2.89 - 2.80 (m, 1H), 1.66 - 1.58 (m, 1H), 1.52 - 1.41 (m, 1H), 0.94 (t, $J$ = 7.6 Hz, 3H); HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.48 min (minor), 8.99 min (major).

*4.3.2 (R,E)-5-(4-bromophenyl)-3-ethyl-1-phenylpent-4-en-1-one (**5b**):* Colorless oil, 79% yield, 92% ee, $[\alpha]_D^{20}$-40.8 (*c* 3.65, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.94 - 7.92 (m, 2H), 7.55 - 7.51 (m, 1H), 7.44 (t, $J$ = 7.6 Hz, 2H), 7.37 (dt, $J$ = 8.4, 1.2 Hz, 2H), 7.17 - 7.14 (m, 2H), 6.32 (d, $J$ = 16.0 Hz, 1H), 6.05 (dd, $J$ = 15.6, 8.4 Hz, 1H), 3.06 (d, $J$ = 6.8 Hz, 2H), 2.87 - 2.78 (m, 1H), 1.66 - 1.56 (m, 1H), 1.52 - 1.41 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.1, 137.2, 136.3, 134.1, 132.9, 131.4, 129.2, 128.5, 128.0, 127.6, 120.6, 43.7, 40.6, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3029 2964, 2926, 1684, 1596, 1491, 1447, 1367, 1217, 1130, 1068, 1012, 969, 776, 689; HRMS (ESI) calcd for $C_{19}H_{19}BrNaO$ ($[M+Na]^+$): 365.0511, found 365.0517. HPLC (AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 8.56 min (minor), 9.56 min (major).

*4.3.3 (R,E)-5-(4-chlorophenyl)-3-ethyl-1-phenylpent-4-en-1-one (**5c**):* Colorless oil, 80% yield, 90% ee, $[\alpha]_D^{20}$-46.3 (*c* 3.21, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.94-7.92 (m, 2H), 7.55 -7.51 (m, 1H), 7.46 -7.42 (m, 2H), 7.21 (s, 4H), 6.34 (d, $J$ = 16.0 Hz, 1H), 6.04 (dd, $J$ = 16.0, 8.8 Hz, 1H), 3.06 (d, $J$ = 6.4 Hz, 2H), 2.88 - 2.79 (m, 1H), 1.67 - 1.56 (m, 1H), 1.52 - 1.41 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.2, 137.2, 135.9, 133.9, 132.9, 132.5, 129.1, 128.5, 128.5, 128.0, 127.2, 43.7, 40.6, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3028, 2969, 2926, 1683, 1591, 1491, 1447, 1367, 1273, 1217, 1137, 1094, 963, 771, 689; HRMS (ESI) calcd for $C_{19}H_{20}ClO$ ($[M+H]^+$): 299.1197, found 299.1204. HPLC (AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.99 min (minor), 8.97 min (major).

*4.3.4 (R,E)-3-ethyl-5-(4-fluorophenyl)-1-phenylpent-4-en-1-one (**5d**):* Colorless oil, 84% yield, 93% ee, $[\alpha]_D^{20}$-39.9 (*c* 2.97, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.95-7.93 (m, 2H), 7.53 (t, $J$ = 7.2 Hz, 1H), 7.44 (t, $J$ = 8.0 Hz, 2H), 7.28 - 7.23 (m, 2H), 6.97 - 6.91 (m, 2H), 6.35 (d, $J$ = 16.0 Hz, 1H), 5 (dd, $J$ = 16.0, 8.8 Hz, 1H), 3.06 (d, $J$ = 6.4 Hz, 2H), 2.87 - 2.78 (m, 1H), 1.66 - 1.56 (m, 1H), 1.52 - 1.40 (m, 1H), 0.94 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.3, 161.9 (d, $J$ = 245.0 Hz), 137.3, 133.6 (d, $J$ = 2.9 Hz), 132.9 (d, $J$ = 2.2 Hz), 132.9, 129.1, 128.5, 128.0, 127.5 (d, $J$ = 8.0 Hz), 115.2 (d, $J$ = 21.2 Hz), 43.9, 40.6, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3027, 3043, 2963, 1683, 1596, 1447, 1360, 1217, 1155, 1086, 969, 856, 814, 771, 696; HRMS (ESI) calcd for $C_{19}H_{20}FO$ ($[M+H]^+$): 283.1493, found 283.1488. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.30 min (minor), 8.28 min (major).

*4.3.5 (R,E)-3-ethyl-1-phenyl-5-(p-tolyl)pent-4-en-1-one (**5e**):* Semi-solid, 82% yield, 89% ee, $[\alpha]_D^{20}$-39.5 (*c* 3.97, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.94 - 7.91 (m, 2H), 7.53 - 7.49 (m, 1H), 7.42 (t, $J$ = 8.0 Hz, 2H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.06 (d, $J$ = 8.0 Hz, 2H), 6.35 (d, $J$ = 15.6 Hz, 1H), 6.00 (dd, $J$ = 16.0, 8.8 Hz, 1H), 3.04 (d, $J$ = 6.0 Hz, 2H), 2.86 - 2.77 (m, 1H), 2.29 (s, 3H), 1.66 - 1.55 (m, 1H), 1.50 - 1.39 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.4, 137.3, 136.6, 134.6, 132.8, 132.1, 130.1, 129.0, 128.5, 128.0, 125.9, 44.0, 40.7, 27.8, 21.0, 11.7; IR (KBr, $cm^{-1}$): ν 3025, 3022, 2966, 1687, 1594, 1506, 1446, 1361, 1268, 1224, 1070, 968, 771, 684, 608; HRMS (ESI) calcd for $C_{20}H_{23}O$ ($[M+H]^+$): 279.1743, found 279.1738. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 6.13 min (minor), 6.91 min (major).

*4.3.6 (R,E)-3-ethyl-5-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (**5f**):* Semi-solid, 81% yield, 93% ee, $[\alpha]_D^{20}$-54.3 (*c* 2.75, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.95 - 7.92 (m, 2H), 7.55 - 7.51 (m, 1H), 7.46 -7.42 (m, 2H), 7.24 (dt, $J$ = 8.8, 2.0 Hz, 2H), 6.81 (dt, $J$ = 8.8, 2.0 Hz, 2H), 6.33 (d, $J$ = 16.0 Hz, 1H), 5.92 (dd, $J$ = 16.0, 8.8 Hz, 1H), 3.77 (s, 3H), 3.05 (d, $J$ = 7.6 Hz. 2H), 2.85 - 2.76 (m, 1H), 1.64 - 1.55 (m, 1H), 1.50 -1.39 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.5, 158.7, 137.4, 132.8, 131.0, 130.3, 129.6, 128.5, 128.1 127.1, 113.8, 55.2, 44.1, 40.7, 27.9, 11.7; IR (KBr, $cm^{-1}$): ν 3026, 2962, 2927, 1686, 1601, 1515, 1446, 1250, 1172, 1035, 967, 822, 753, 685, 608; HRMS (ESI) calcd for $C_{20}H_{23}O_2$ ($[M+H]^+$): 295.1693, found 295.1690. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 8.94 min (major), 10.49 min (minor).

*4.3.7 (R,E)-1-(4-bromophenyl)-3-ethyl-5-phenylpent-4-en-1-one (**5g**):* Colorless oil, 84% yield, 91% ee, $[\alpha]_D^{20}$-38.1 (*c* 5.52, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.78 (dt, $J$ = 8.8, 2.0 Hz, 2H), 7.56 (dt, $J$ = 8.4, 2.0 Hz, 2H), 7.31 - 7.24 (m, 4H), 7.20 - 7.15 (m, 1H), 6.38 (d, $J$ = 15.6 Hz, 1H), 6.04 (dd, $J$ = 15.6, 8.8 Hz, 1H), 3.01 (d, $J$ = 6.8 Hz, 2H), 2.85 - 2.76 (m, 1H), 1.65 - 1.55 (m, 1H), 1.50 - 1.39 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 198.2, 137.2, 135.9, 132.9, 131.8, 130.4, 129.6, 128.4, 128.0, 127.0, 126.0, 43.8, 40.6, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3012, 3022, 2966, 1687, 1584, 1497, 1394, 1260, 1070, 1008, 962, 813, 773, 690, 495; HRMS (ESI) calcd for $C_{19}H_{19}BrKO$ ($[M+K]^+$): 381.0251, found 381.0254. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.96 min (minor), 17.83 min (major).

*4.3.8 (R,E)-1-(4-chlorophenyl)-3-ethyl-5-phenylpent-4-en-1-one (**5h**):* Colorless oil, 85% yield, 78% ee, $[\alpha]_D^{20}$-35.0 (*c* 4.43, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.86 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.8 Hz, 2H), 7.32 - 7.23 (m, 4H), 7.18 (t, $J$ = 7.2 Hz, 1H), 6.38 (d, $J$ = 16.0 Hz, 1H), 6.04 (dd, $J$ = 15.6, 8.8 Hz, 1H), 3.02 (d, $J$ = 6.8 Hz, 2H), 2.86 - 2.77 (m, 1H), 1.66 - 1.55 (m, 1H), 1.51 - 1.40 (m, 1H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 198.0, 139.3, 137.3, 135.6, 132.9, 130.4, 129.5, 128.8, 128.4, 127.0, 126.0, 43.9, 40.7, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3011, 3028, 2962, 1687, 1590, 1492, 1399, 1266, 1090, 1008, 962, 813, 746, 695, 525; HRMS (ESI) calcd for $C_{19}H_{20}ClO$ ($[M+H]^+$): 299.1197, found 299.1182. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 7.31 min (minor), 14.65 min (major).

*4.3.9 (R,E)-3-ethyl-1-(4-fluorophenyl)-5-phenylpent-4-en-1-one (**5i**):* Colorless oil, 86% yield, 93% ee, $[\alpha]_D^{20}$-49.0 (*c* 4.76, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.98 - 7.93 (m, 2H), 7.32 - 7.30 (m, 2H), 7.28 - 7.22 (m, 2H), 7.19 - 7.15 (m, 1H), 7.12 - 7.06 (m, 2H), 6.39 (d, $J$ = 16.0 Hz, 1H), 6.05 (dd, $J$ = 16.0, 8.4 Hz, 1H), 3.03 (d, $J$ = 6.0 Hz, 1H), 2.86 - 2.77 (m, 1H), 1.66 - 1.56 (m, 1H), 1.51 - 1.40 (m, 1H), 0.94 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 197.6, 165.5 (d, $J$ = 252.3 Hz), 137.3, 133.7 (d, $J$ = 2.9 Hz), 133.0, 130.7 (d, $J$ = 8.8 Hz), 130.4, 128.4, 127.0, 126.0, 115.5 (d, $J$ = 21.2 Hz), 43.8, 40.7, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3002, 3028, 2961, 1687, 1594, 1507, 1410, 1235, 1157, 968, 833, 773, 690, 598, 489; HRMS (ESI) calcd for $C_{19}H_{20}FO$ ($[M+H]^+$): 283.1493, found 283.1491. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 6.72 min (minor), 10.97 min (major).

*4.3.10 (R,E)-3-ethyl-5-phenyl-1-(p-tolyl)pent-4-en-1-one (**5j**):* Semi-solid, 84% yield, 95% ee, $[\alpha]_D^{20}$-52.5 (*c* 4.24, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, $J$ = 8.0 Hz, 2H), 7.32 - 7.22

(m, 6H), 7.19 - 7.15 (m, 1H), 6.39 (d, $J$ = 16.0 Hz, 1H), 6.06 (dd, $J$ = 16.0, 8.4 Hz, 1H), 3.03 (d, $J$ = 6.8 Hz, 2H), 2.87 - 2.78 (m, 1H), 2.39 (s, 3H), 1.66 - 1.56 (m, 1H), 1.51 - 1.39 (m, 1H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 199.0, 143.6, 137.5, 134.9, 133.3, 130.2, 129.2, 128.4, 128.2, 126.9, 126.0, 43.8, 40.7, 27.8, 21.5, 11.7; IR (KBr, $cm^{-1}$): ν 3003, 3022, 2962, 1681, 1610, 1450, 1266, 1183, 1019, 968, 803, 746, 690, 571, 464; HRMS (ESI) calcd for $C_{20}H_{22}O$ ([M+H]$^+$): 279.1743, found 279.1740. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 6.36 min (minor), 8.44 min (major).

*4.3.11 (R,E)-3-ethyl-1-(4-methoxyphenyl)-5-phenylpent-4-en-1-one (**5k**):* Semi-solid, 82% yield, 97% ee, $[\alpha]_D^{20}$-48.3 (*c* 4.19, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.93 (dt, $J$ = 9.2, 2.4 Hz, 2H), 7.31 (d, $J$ = 7.2 Hz, 2H), 7.26 (t, $J$ = 7.6 Hz, 2H), 7.19 - 7.14 (m, 1H), 6.91 (dt, $J$ = 8.8, 2.0 Hz, 2H), 6.39 (d, $J$ = 16.0 Hz, 1H), 6.07 (dd, $J$ = 15.6, 8.4 Hz, 1H), 3.82 (s, 3H), 3.01 (d, $J$ = 7.2 Hz, 2H), 2.87 - 2.78 (m, 1H), 1.66 - 1.56 (m, 1H), 1.50 - 1.39 (m, 1H), 0.93 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 197.9, 163.3, 137.4, 133.3, 130.4, 130.3, 130.1, 128.4, 126.9, 126.0, 113.6, 55.3, 43.6, 40.8, 27.8, 11.7; IR (KBr, $cm^{-1}$): ν 3013, 3028, 2956, 1677, 1599, 1512, 1255, 1168, 1029, 962, 829, 746, 695, 602, 510; HRMS (ESI) calcd for $C_{20}H_{23}O_2$ ([M+H]$^+$): 295.1693, found 295.1691. HPLC (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R$ = 9.67 min (minor), 17.71 min (major).

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## References

1. For reviews, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033-8061. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236; (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rossle, M. *Synthesis* **2007**, 1279-1300; (d) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796-2823. (e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824-2852. (f) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S.; Palais, L.; Hénon, H.; Hawner, C. *Chimia* **2008**, *62*, 461-464; (g) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039-1075. (h) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295-7306. (i) Yu, Y.; Shan, F.; Li, Z.; Jiang, L. *Chin. J. Org. Chem.* **2011**, *31*, 443-452; (j) Tang, F.; Ye, J. *Chin. J. Org. Chem.* **2015**, *35*, 1414-1427; (k) Hayashi, M.; Matsubara, R. *Tetrahedron Lett.* **2017**, *58*, 1793-1805.
2. For early work on the asymmetric conjugate addition of organometallic reagents, see: (a) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427-2430; (b) de Vries, A. H. M; Meetsma, A.; Feringa, B. L. *Angew Chem Int Ed.* **1996**, *35*, 2374-2376.
3. For review, see: (a) Csaky, A. G.; Herran, G. D. L.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080-4102; (b) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109-3128; (c) Schmid, T. E.; Drissi-Amraoui, S.; Crévisy, C.; Baslé, O.; Mauduit, M. *Beilstein J. Org. Chem.* **2015**, *11*, 2418-2434.
4. For examples, see: (a) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3518-3521; (b) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4* , 3699-3702; (c) Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* **2003**, *68*, 4542-4545; (d) Liang, Y.-X.; Gao, S.; Wan, H.-H.; Hu, Y.-C.; Chen, H.-L.; Zheng, Z.; Hu, X.-Q. *Tetrahedron: Asymmetry* **2003**, *14*, 3211-3217; (e) Liu, L.-T.; Wang, M.-C.; Zhao, W.-X.; Zhou, Y.-L.; Wang, X.-D. *Tetrahedron: Asymmetry* **2006**, *17*, 136-141; (f) Roma, A. D.; Ruffo, F.; Woodward, S. *Chem. Commun.* **2008**, 5384-5386; (g) Xie, Y.-J.; Huang, H.-M.; Mo, W.-M.; Fan, X.-Q.; Shen, Z.-Q.; Shen, Z.-L.; Sun, N.; Hu, B.-X.; Hu, X.-Q. *Tetrahedron: Asymmetry* **2009**, *20*, 1425-1432; (h) Magrez, M.; Wencel-Delord, J.; Crevisy, C.; Mauduit, M. *Tetrahedron* **2012**, *68*, 3507-3511; (i) Lega, M.; Margalef, J.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron: Asymmetry* **2013**, *24*, 995-1000; (j) Endo, K.; Takayama, R.; Shibata, T. B. *Synlett* **2013**, *24*, 1155-1159.
5. For copper-catalyzed enantioselective 1,4-conjugate addition of organozinc reagents to α,β,γ,δ-unsaturated carbonyl compounds, see: (a) Magrez-Chiquet,M.; Morin, M. S. T. ; Wencel-Delord, J.; Amraoui, S. D.; Baslé, O.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Chem. Eur. J.* **2013**, *19*, 13663-13667; (b) Morin, M. S. T.; Vives, T.; Baslé, O.; Crévisy, C.; Ratovelomanana-Vidal, V.; Mauduit, M. *Synthesis* **2015**, *47*, 2570-2577; (c) Drissi-Amraoui, S.; Morin, M. S. T; Crévisy, C.; Baslé, O.; de Figueiredo, R. M.; Mauduit, M.; Campagne, J.-M. *Angew. Chem. Int. Ed.* **2015**, *54*, 11830-11834.
6. (a) Rexiti, R.; Lu, J.; Wang, G.; Sha, F.; Wu, X.-Y. *Tetrahedron: Asymmetry* **2016**, *27*, 923-929; (b) Xu, N.; Gu, D.-W.; Zi, J.; Wu, X.-Y.; Guo, X.-X. *Org. Lett.* **2016**, *18*, 2439-2442; (c) Rexiti, R.; Zhang, Z.-G.; Lu, J.; Sha, F.; Wu, X.-Y. *J. Org. Chem.* DOI: 10.1021/acs.joc.8b02798.
7. Zhang, L.; Yang, G.; Shen, C.; Arghib, S.; Zhang, W. *Tetrahedron Lett.* **2011**, *52*, 2375-2378.
8. Ma, Z.; Xie, F.; Yu, H.; Zhang, Y.; Wu, X.; Zhang, W. *Chem. Commun.* **2013**, *49*, 5292-5294.
9. Kang, T.-C.; Wu, L.-P.; Yu, Q.-W.; Wu, X.-Y. *Chem. Eur. J.* **2017**, *23*, 6509-6513.

## Supplementary data

Copies of HPLC spectra and NMR spectra associated with this article can be found in the Supporting Information.