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Regio- and Enantioselective Copper-Catalyzed 1,4-Conjugate Addition of Trimethylaluminium to Linear α,β,γ,δ-Unsaturated Alkyl Ketones

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Abstract: A regio- and enantioselective copper-catalyzed 1,4-conjugate addition of trimethylaluminium to linear δ-aryl-substituted α,β,γ,δ-unsaturated alkyl ketones was developed. A series of γ,δ-unsaturated alkyl ketones were obtained in good yields with high regio- and enantioselectivity (up to 88% *ee* and 96:4 *dr*). Expansion of the reaction scope to substrates containing aromatic heterocycles also afforded good yields and enantioselectivities (up to 91% *ee*) with very high regioselectivities, exclusively providing the single 1,4-products.

Keywords: asymmetric catalysis; 1,4-conjugate addition reaction; copper-catalyzed addition; linear α,β,γ,δ-unsaturated alkyl ketones; organoaluminium reagents

Introduction

In asymmetric conjugate additions (ACA), excellent regio- and stereoselectivities have been achieved in reactions involving transition metal-catalyzed α,β-unsaturated Michael acceptors, especially for copper-catalyzed systems.[1] However, the use of α,β,γ,δ-unsaturated Michael acceptors[2–12] in ACA remains challenging because of the difficulties encountered in controlling regioselectivity (preferential formation of 1,2-, 1,4-, and 1,6-products) and obtaining high enantioselectivity, especially for reactions involving linear α,β,γ,δ-unsaturated ketones. Since Hayashi's pioneering work in 2004,[4a] several successful examples of rhodium,[4] iridium,[5] and cobalt[6] catalyzed 1,6-ACA with aryl organometallic reagents have been reported. Copper-catalyzed 1,6-ACA with alkyl organometallic reagents or silane reagents have also been realized by Fillion,[7] Alexakis,[8] Feringa,[9] Hoveyda[10] and Campagne.[11]

The use of α,β,γ,δ-unsaturated Michael acceptors in 1,6-ACA reactions often leads to the formation of 1,6-adducts rather than the valuable 1,4-adducts. The chiral products resulting from 1,4-ACA, especially linear α,β,γ,δ-unsaturated ketones which contain a C=C double bond, are versatile building blocks that can be easily transformed into many other functional groups (Figure 1). Such chiral intermediates, particularly methyl-substituted derivatives, are often found in natural products and biologically active compounds (Figure 2).[13–15] Therefore the ACA of methyl organometallic reagents represents a particularly important synthetic methodology.[16] Due to the importance of this structural motif, significant resources have been directed towards the development of efficient regio- and enantioselective procedures.

However, only three examples of copper-catalyzed 1,4-ACA reactions have been reported by Alexakis[12a,b] and our group.[12c] These methodologies utilized linear nitrodienes and nitroenynes, α,β,γ,δ-unsa-

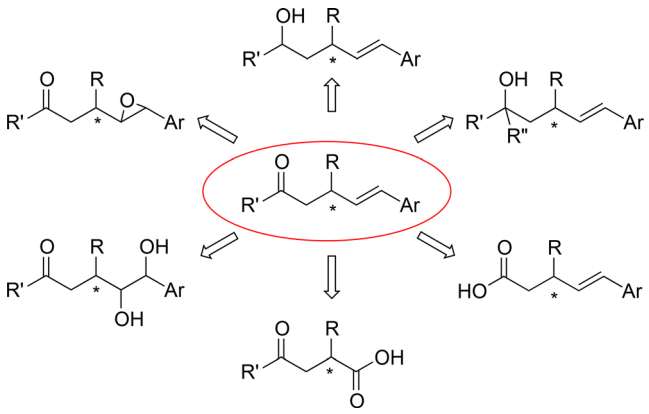

Figure 1. Transformations of γ,δ-unsaturated alkyl ketones.

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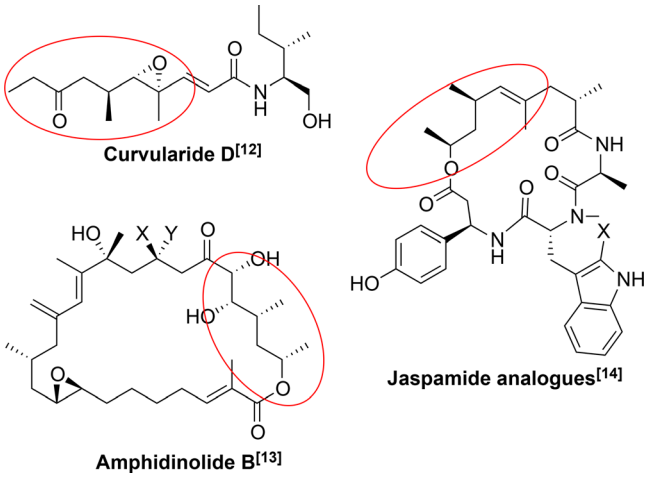


Figure 2. Representative chiral natural products and bioactive compounds.

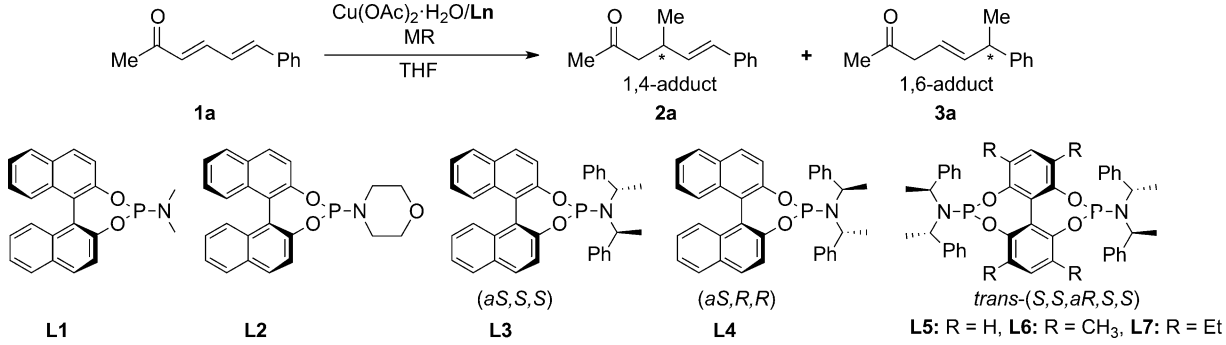
turated cyclic enones and linear α,β,γ,δ-unsaturated aryl ketones, all of which rely on specific structural features of the substrates.

Due to the importance of the methyl group in natural products and the importance of the structural skeleton of the 1,4-adducts, we herein report a copper-catalyzed 1,4-ACA of trimethylaluminium to linear α,β,γ,δ-unsaturated alkyl ketones with high regio- and enantioselectivity, utilizing ligands bearing a D_2-symmetric biphenyl backbone previously developed by our group.[17]

Results and Discussion

In our previous research, a new highly regio- and enantioselective copper-catalyzed asymmetric 1,4-conjugate addition of Grignard reagents to δ-aryl-substituted α,β,γ,δ-unsaturated aryl ketones was developed, utilizing 1,2-disubstituted planar ligands.[12c] However, when linear δ-aryl-substituted α,β,γ,δ-unsaturated alkyl ketones were subjected to our reaction conditions, only the 1,2-addition products were obtained, and none of the desired 1,4-adducts were detected. Based on previous reports and our research, it has been shown that the chiral catalyst affects not only enantioselectivity but also regioselectivity. Firstly, 1,4-conjugate additions of trimethylaluminium reagent and dimethylzinc reagent (for comparison with

Table 1. Ligand and organometallic reagent screening.[a]



Entry	Ln	MR	Temperature [°C]	Conversion [%]	1,4/1,6[b]	*ee* [%][c]
1	**L1**	$AlMe_3$	−30	100	trace[d]	5
2	**L2**	$AlMe_3$	−30	100	trace[d]	5
3	**L3**	$AlMe_3$	−30	10	trace	−42
4	**L4**	$AlMe_3$	−30	89	88/12	−68
5	**L5**	$AlMe_3$	−30	100	88/12	78
6	**L6**	$AlMe_3$	−30	100	96/4	87
7	**L7**	$AlMe_3$	−30	100	87/13	−77
8	**L6**	$AlEt_3$	−30	48	82/18	2
9	**L6**	$ZnMe_2$	r.t.	trace	0/100	n.d.
10[e]	**L6**	MeMgBr	−80	100	1,2-adduct	–
11[e,f]	–	MeMgBr	−80	100	1,2-adduct	–

[a] The reaction of **1a** (0.200 mmol) with MR (1.2 equiv.) was performed in THF for 12 h in the presence of the chiral complex formed *in situ* from $Cu(OAc)_2·H_2O$ (0.005 mmol, 2.5 mol%) and ligand (0.010 mmol, 5.0 mol%).
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC analysis.
[d] Unknown components.
[e] The reaction was performed in dichloromethane (DCM) for 15 h.
[f] In the absence of $Cu(OAc)_2·H_2O$.

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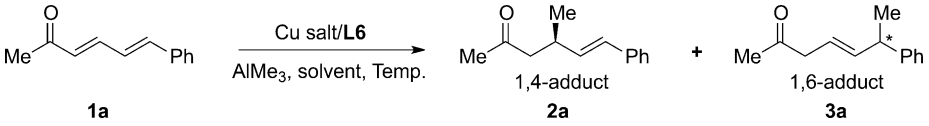
Grignard reagents) to linear α,β,γ,δ-unsaturated alkyl ketones were screened using different chiral ligands (Table 1).

Phosphoramidite ligands **L1** and **L2** possessing only axial chirality were first used with trimethylaluminium as nucleophile. The reaction proceeded to completion, however only trace amounts of racemic 1,4- or/and 1,6-conjugate addition products were obtained (Table 1, entries 1 and 2). BINOL phosphoramidite ligands **L3** and **L4** bearing chiral amine substituents were next examined (entries 3 and 4). **L4** provided the desired 1,4-adduct as the main product with moderate enantioselectivity (entry 4). Ligands (**L5**–**L7**) bearing a D_2-symmetric biphenyl backbone were also employed because they could be easily modified at the 3,3′,5,5′-positions, and because of their excellent performance in previous 1,4-ACA reactions as reported by our group (entries 5–7).[17] The substituents at the 3,3′,5,5′-positions had an obvious effect on both regio- and enantioselectivity.[18] To our delight, the 1,4-adduct was obtained with excellent regioselectivity (96:4) and good enantioselectivity (87% *ee*) when **L6** was used (entry 6). Then, triethylaluminium was tested under these conditions, the 1,4-adduct was obtained with good regioselectivity (82:18) but almost no enantioselectivity (2% *ee*) (entry 8). Subsequently, other organometallic reagents were investigated with this asymmetric catalytic system. Dimethylzinc gave its corresponding 1,6-adduct with lower reactivity (entry 9) and methylmagnesium bromide afforded only the 1,2-adduct with complete conversion (entries 9 and 10).

Optimization of this regio- and enantioselective reaction was thus carried out using **L6** as chiral ligand. The influence of copper salts on the reaction was examined (Table 2, entries 1–4). $Cu(OAc)_2{\cdot}H_2O$ provided the most satisfactory result considering regio- and enantioselectivity as well as yield (entry 4). A careful screening of the solvent showed that THF was effective and gave the best result (entries 4–6). Besides the copper salt and solvent, the optimal reaction temperature was next investigated (entries 4 and 7–9). Excellent results were maintained when the temperature was increased from −30 °C to −5 °C or room temperature (1,4:1,6 = 95:5) but enantioselectivity decreased (entry 4 *vs.* 7 and 8). Additionally, reducing the reaction temperature to −50 °C, was detrimental to the reaction, which provided decreased regio- and enantioselectivity with much lower reactivity (entry 4 *vs.* 9). Taking these factors into account, we chose −30 °C as the optimal reaction temperature.

After the optimized conditions were identified, the scope of the 1,4-ACA for linear α,β,γ,δ-unsaturated alkyl ketones was then examined. The substrates can be easily prepared *via* an aldol reaction of commercially available unsaturated aldehydes with alkyl ketones.[20] The reaction proceeded smoothly with a wide range of substrates (Scheme 1). The influence of the R^1 group was first investigated. Increasing the size of the R^1 group (**1a**–**c**), led to a reduction in both enantioselectivity and regioselectivity, and yield. When compound **1c** was used, a sharp drop in reactivity was observed. When R^1 was changed to a CF_3 group, the 1,4-adduct **2d** was obtained exclusively in 71% yield but with much lower enantioselectivity (10% *ee*). When R^1 was a methyl group, and R^2 was either a phenyl or substituted phenyl (**1e**–**l**), excellent regioselectivities (1,4:1,6 = 93:7–95:5), good enantioselectivities (81–88% *ee*) and moderate to good yields (63–74%) were obtained (**2e**–**l**), irrespective of the

Table 2. Copper salts and temperature screening.[a]



1a **2a** **3a**

Entry	Cu salt	Solvent	Temperature [°C]	Conversion [%]	1,4/1,6[b]	*ee* [%][c,d]
1	CuTC	THF	−30	100	93/7	87
2	$Cu(OTf)_2$	THF	−30	100	86/14	80
3	$Cu(OAc)_2$	THF	−30	75	95/5	82
4	$Cu(OAc)_2{\cdot}H_2O$	THF	−30	100	96/4	87
5	$Cu(OAc)_2{\cdot}H_2O$	toluene	−30	100	92/8	45
6	$Cu(OAc)_2{\cdot}H_2O$	DCM	−30	100	87/13	64
7	$Cu(OAc)_2{\cdot}H_2O$	THF	r.t.	100	95/5	63
8	$Cu(OAc)_2{\cdot}H_2O$	THF	−5	100	95/5	76
9	$Cu(OAc)_2{\cdot}H_2O$	THF	−50	26	82/18	76

[a] The reaction of **1a** (0.200 mmol) with $AlMe_3$ (1.2 equiv.) was performed for 12 h in the presence of the chiral complex formed *in situ* from CuX (0.005 mmol, 2.5 mol%) and **L6** (0.010 mmol, 5.0 mol%).
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC analysis.
[d] The absolute configuration of **2a** was determined as *R* according to ref.[19].

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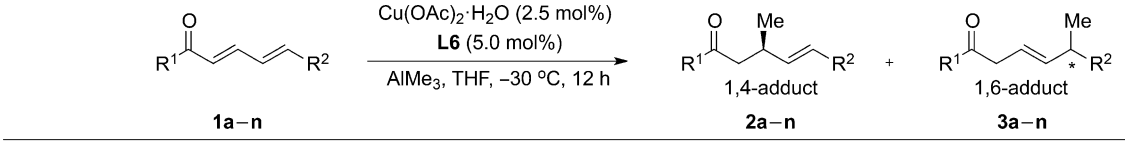
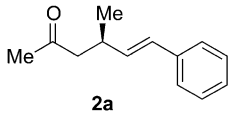
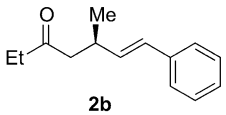
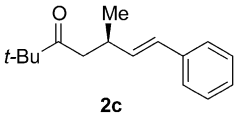




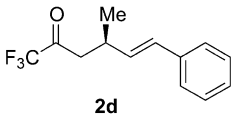
2a
65% yield[a], 87% *ee*[b,c]
1,4/1,6 : 96/4[d]



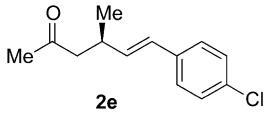
2b
67% yield, 82% *ee*,
1,4/1,6 : 89/11



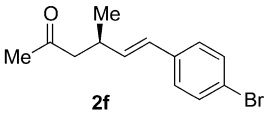
2c
40% yield, 52% *ee*,
1,4/1,6 : 95/5



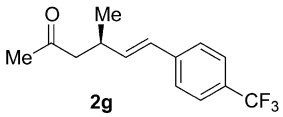
2d
71% yield, 10% *ee*,
1,4/1,6 : 100/0



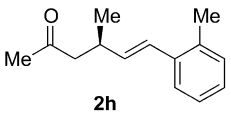
2e
64% yield, 83% *ee*,
1,4/1,6 : 93/7



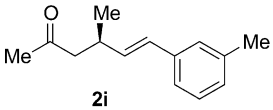
2f
65% yield, 84% *ee*,
1,4/1,6 : 93/7



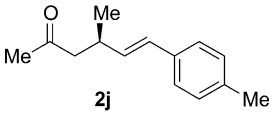
2g
70% yield, 81% *ee*,
1,4/1,6 : 94/6



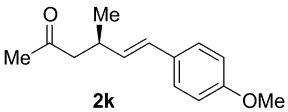
2h
63% yield, 81% *ee*,
1,4/1,6 : 95/5



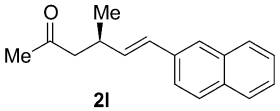
2i
67% yield, 86% *ee*,
1,4/1,6 : 94/6



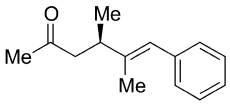
2j
70% yield, 87% *ee*,
1,4/1,6 : 93/7



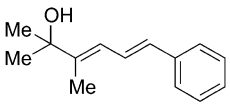
2k
73% yield, 84% *ee*,
1,4/1,6 : 94/6



2l
74% yield, 88% *ee*,
1,4/1,6 : 93/7



2m
73% yield, 63% *ee*,
1,4/1,6 : >99/1



2n
25% conv.,1,2-adduct

[a] Yield of products (**2a**–**m**) isolated after chromatography.
[d] Determined by HPLC analysis.
[c] The absolute configuration of **2a** was determined as *R* according to ref.[19]
[e] Determined by ^{1}H NMR spectroscopy.

Scheme 1. Substrate scope. The reactions of **1a**–**n** (0.200 mmol) with $AlMe_3$ (1.2 equiv.) were performed in THF at −30 °C for 12 h in the presence of the chiral complex formed *in situ* from $Cu(OAc)_2{\cdot}H_2O$ (0.005 mmol, 2.5 mol%) and **L6** (0.010 mmol, 5.0 mol%).

electronic properties or substitution pattern of the aromatic ring. However, when R^2 was changed to an *n*-propyl group, a mixture of 1,2-, 1,4-, 1,6-adducts and unidentified products was obtained. Finally, the effect of steric-hindrance on regio- and enantioselectivity was investigated (**1m** and **1n**). As expected, the presence of a methyl group at the γ-position provided **2m** with improved excellent regioselectivity (1,4:1,6 > 99:1) and 63% *ee*. A substrate bearing a methyl group at the α-position provided only the 1,2-addition product (**2n**) with low reactivity. This result is similar to copper-catalyzed 1,2-additions of Grignard reagents to α-methy-substituted α,β-unsaturated ketones[21].

In addition, the reaction scope was expanded to include substrates bearing aromatic heterocycles such as thienyl and furyl rings systems (Scheme 2). The desired products were obtained with good to excellent enantioselectivities (88–91% *ee*) and in good yields (70–78%). To our delight, no 1,6-adducts were detected.

To demonstrate the potential utility of these chiral 1,4-adducts, linear α,β,γ,δ-unsaturated ketones containing a C=C double bond, transformations of **2a** were carried out (Scheme 3): **2a** could be reduced into alcohol **4a** with $NaBH_4$ in 98% yield with 89% *ee* and 1.2:1 *dr* and **2a** could also be oxidized to epoxide **5a** by *m*-CPBA in 78% yield with high diasteroselectivity (25:1). These examples show the possible applications of chiral 1,4-adducts.

Conclusions

In summary, a copper-catalyzed 1,4-conjugate addition of trimethylaluminium reagent to linear δ-aryl-substituted α,β,γ,δ-unsaturated alkyl ketones with high regio- and enantioselectivies (up to 88% *ee* and up to 96/4 for 1,4/1,6) has been developed. The reaction conditions were also suitable for substrates bearing heterocyclic ring systems, such as thienyl and furyl

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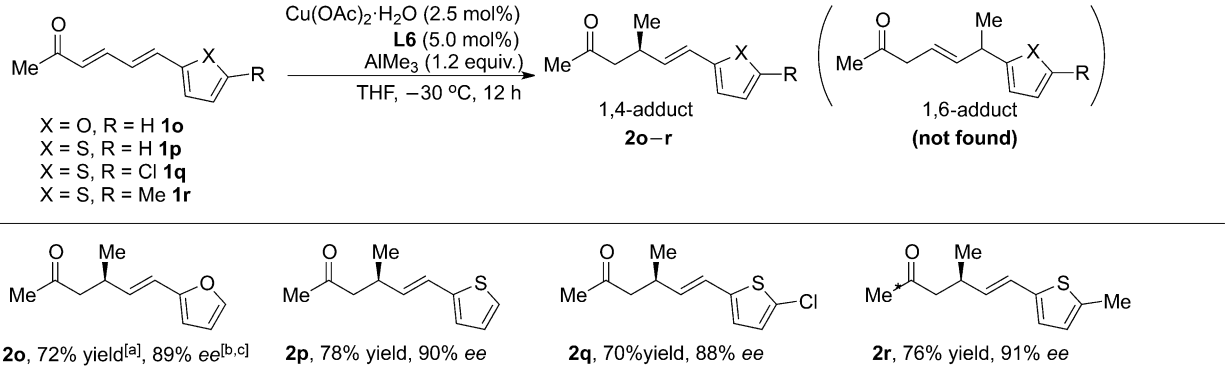
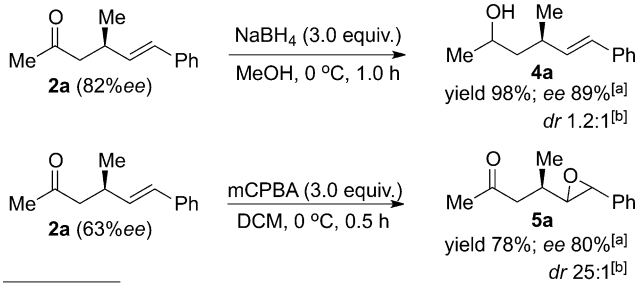


[a] Yield of products **2o−r** isolated after chromatography.
[b] Determined by HPLC analysis.
[c] The absolute configuration of **2** was determined as *R* according to ref.[19]

Scheme 2. Expansion of the reaction scope for aromatic heterocycles. The reactions of **1o–r** (0.200 mmol) with $AlMe_3$ (1.2 equiv.) were performed at −30 °C for 12 h in the presence of the chiral complex formed *in situ* from $Cu(OAc)_2{\cdot}H_2O$ (0.005 mmol, 2.5 mol%) and **L6** (0.010 mmol, 5.0 mol%).



[a] Determined by HPLC analysis.
[b] Determined by HPLC analysis.

Scheme 3. Transformations of **2a**.

groups, giving the corresponding 1,4-adducts exclusively in good yields (70–78%) and enantioselectivities (88–91% *ee*).

Experimental Section

General

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. HR-MS was performed at the Analysis Center of Shanghai Jiao Tong University. Enantioselectivity was measured by a high performance liquid chromatography (HPLC) using Daicel Chiralcel OD-H and AD-H columns with *n*-hexane/*i*-PrOH as an eluent. Column chromatography was performed using 100–200 mesh silica gel. Melting points were measured with SGW X-4 micro melting point apparatus.

Preparation of the Substrates 1

Dienones **1a** (cas: 4173-44-8), **1b** (cas: 75391-05-8), **1c** (cas: 1654-02-0), **1d** (cas: 17510-46-2), **1e** (cas: 168211-22-1), **1f** (cas: 113388-19-5), **1k** (cas:76594-51-9), **1l** (cas: 76594-52-0), **1m** (cas: 29622-02-4), **1n** (cas: 19520-38-8), **1o** (cas:113388-26-4), **1p** (cas: 90843–14–4).

(3*E*,5*E*)-6-(4-Bromophenyl)hexa-3,5-dien-2-one (1f): 72% yield; yellow solid; mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.30–7.21 (m, 1H), 6.89–6.84 (m, 2H), 6.27 (d, $J = 15.2$ Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.5$, 143.1, 139.9, 135.0, 132.2, 131.1, 128.8, 127.4, 123.4, 27.3; HR-MS (ESI): $m/z = 251.0077$, calcd. for $C_{12}H_{11}BrO$ $[M+H]^+$: 251.0072.

(3*E*,5*E*)-6-[4-(trifluoromethyl)phenyl]hexa-3,5-dien-2-one (1g): 69% yield; yellow solid; mp 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$ (dd, $J = 8.4$, 20.0 Hz, 4H), 7.31–7.24 (m, 1H), 6.97–6.92 (m, 2H), 6.31 (d, $J = 15.6$ Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.4$, 142.6, 139.5, 139.3, 131.9, 130.8 (q, $J = 32.6$ Hz), 129.2, 127.5, 125.9 (d, $J = 3.0$ Hz), 122.8, 27.7; ^{19}F NMR(376 MHz, $CDCl_3$): $\delta = -62.72$; HR-MS (ESI): $m/z = 241.0845$, calcd. for $C_{13}H_{11}F_3O$ $[M+H]^+$: 241.0840.

(3*E*,5*E*)-6-(2-Methylphenyl)hexa-3,5-dien-2-one (1h): 71% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 6.8$ Hz, 1H), 7.32 (dd, $J = 10.8$, 15.6 Hz, 1H), 7.26–7.15 (m, 4H), 6.81 (dd, $J = 10.8$, 15.6 Hz, 1H), 6.26 (d, $J = 15.6$ Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.7$, 144.0, 139.0, 136.8, 134.9, 130.9, 130.5, 129.3, 127.8, 126.5, 125.8, 27.6, 20.0; HR-MS (ESI): $m/z = 187.1121$, calcd. for $C_{13}H_{14}O$ $[M+H]^+$: 187.1123.

(3*E*,5*E*)-6-(3-Methylphenyl)hexa-3,5-dien-2-one (1i): 75% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32–7.22$ (m, 4H), 7.14 (d, $J = 6.8$ Hz, 1H), 6.95–6.83 (m, 2H), 6.24 (d, $J = 15.6$ Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.6$, 143.8, 141.7, 138.6, 136.3, 130.5, 130.3, 128.9, 128.1, 126.6, 124.7, 27.5, 21.6; HR-MS (ESI): $m/z = 187.1125$, calcd. for $C_{13}H_{14}O$ $[M+H]^+$: 187.1123.

(3*E*,5*E*)-6-(2-Naphthyl)hexa-3,5-dien-2-one (1l): 46% yield; yellow solid; mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.86–7.79$ (m, 4H), 7.66 (dd, $J = 1.6$, 8.4 Hz,

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1H), 7.54–7.46 (m, 2H), 7.35 (dd, J=10.8, 15.6 Hz, 1H), 7.12 (d, J=15.6 Hz, 1H), 7.01 (dd, J=10.8, 15.6 Hz, 1H), 6.30 (d, J=15.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.6, 143.7, 141.6, 133.9, 133.7, 130.7, 128.8, 128.5, 128.0, 127.2, 127.0, 126.9, 123.6, 27.6; HR-MS (ESI): m/z=223.1124, calcd. for $C_{16}H_{14}O$ $[M+H]^+$: 223.1123.

(3*E*,5*E*)-6-(5-Chloro-2-thienyl)hexa-3,5-dien-2-one (1q): 51% yield; yellow solid; mp 29–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (dd, J=11.2, 15.6 Hz, 1H), 6.94–6.82 (m, 3H), 6.53 (dd, J=11.2, 15.6 Hz, 1H), 6.22 (d, J=15.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.3, 142.6, 140.4, 133.1, 131.8, 130.5, 128.3, 127.4, 126.3, 27.8; HR-MS (ESI): m/z=213.0146, calcd. for $C_{10}H_9ClOS$ $[M+H]^+$: 213.0141.

(3*E*,5*E*)-6-(5-Methyl-2-thienyl)hexa-3,5-dien-2-one (1r): 45% yield; yellow solid; mp 25–27 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.21 (dd, J=10.8, 15.6 Hz, 1H), 6.98 (d, J=15.2 Hz, 1H), 6.92 (d, J=3.6 Hz, 1H), 6.89–6.66 (m, 1H), 6.54 (dd, J=10.8, 15.6 Hz, 1H), 6.19 (d, J=15.2 Hz, 1H), 2.49 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.5, 143.6, 142.7, 139.7, 134.4, 129.5, 129.4, 126.6, 125.1, 27.6, 16.0; HR-MS (ESI): m/z=193.0688, calcd. for $C_{11}H_{12}OS$ $[M+H]^+$: 193.0687.

General Procedure for Copper-Catalyzed Enantioselective Conjugate Addition

A flame-dried Schlenk tube was charged with $Cu(II)(OAc)_2{\cdot}H_2O$ (0.005 mmol, 2.5 mol%) and 2.0 equivalents of ligand (0.010 mmol) under nitrogen, and the mixture was dissolved in dry THF (2.0 mL), resulting in a blue solution. The solution was stirred at room temperature for 2 h and then cooled to −30 °C. The substrate **1** (0.200 mmol dissolved in 0.5 mL dry THF) was then added dropwise over 3 min. The solution was stirred for 5 min at −30 °C and gradually turned to a light yellow color. $AlMe_3$ (0.24 mmol, 0.24 mL of 1 M solution in hexane) was added dropwise over 3 min. The reaction mixture was stirred at −30 °C for 12 h and monitored by TLC until full conversion to the product was observed. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with ethyl acetate (5.0 mL×3). The organic extracts were combined, concentrated and the residue was purified by silica gel column chromatography to afford the product. Enantiomeric excess was determined by chiral HPLC.

(4*R*,5*E*)-1,1,1-Trifluoro-4-methyl-6-phenyl-5-hexaen-2-one (2d): 71% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.19 (m, 5H), 6.44 (d, J=16.0 Hz, 1H), 6.11 (dd, J=7.6, 16.0 Hz, 1H), 3.08–2.95 (m, 1H), 2.88 (dd, J=6.5, 18.0 Hz, 1H), 2.76 (dd, J=7.2, 18.0 Hz, 1H), 1.19 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.4 (q, J=34.0 Hz), 137.19, 133.0, 130.0, 128.8, 127.6, 126.4, 115.7 (q, J=291 Hz), 43.5, 32.2, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−79.55; HR-MS (ESI): m/z=243.0914, calcd. for $C_{13}H_{13}F_3O$ $[M+H]^+$: 243.0844; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH=98:2, UV=210 nm, flow rate=0.8 mL min^{-1}): t_{R1}=6.16 min (minor) and t_{R2}=38.85 min (major); *ee*=10%; $[\alpha]_D^{20}$: −0.9 (*c* 0.42, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(4-chlorophenyl)-5-hexaen-2-one (2e): 64% yield (93/7, 1,4/1.6 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25 (s, 4H), 6.30 (dd, J=1.2, 16.0 Hz, 1H), 6.10 (dd, J=7.2, 16.0 Hz, 1H), 2.94–2.82 (m, 1H), 2.57 (dd, J=6.8, 16.0 Hz, 1H), 2.46 (dd, J=7.2, 16.4 Hz, 1H), 2.14 (s, 3H), 1.11 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.9, 136.1, 135.4, 132.8, 128.8, 127.7, 127.5, 50.7, 33.0, 30.8, 20.3; HR-MS (ESI): m/z=223.0975, calcd. for $C_{13}H_{15}ClO$ $[M+H]^+$: 223.0890; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH=99:1, UV=254 nm, flow rate=0.8 mL min^{-1}): t_{R1}=15.56 min (minor) and t_{R2}=18.28 min (major); *ee*=83%; $[\alpha]_D^{20}$: −29.5 (*c* 0.16, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(4-bromophenyl)-5-hexaen-2-one (2f): 65% yield (93/7, 1,4/1.6 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 6.31 (d, J=16.0 Hz, 1H), 6.12 (dd, J=7.6, 16.0 Hz, 1H), 2.94–2.82 (m, 1H), 2.56 (dd, J=6.8, 16.0 Hz, 1H), 2.46 (dd, J=7.2, 16.4 Hz, 1H), 2.14 (s, 3H), 1.11 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.9, 136.5, 135.6, 131.8, 127.9, 127.8, 121.0, 50.7, 33.0, 30.8, 20.3; HR-MS (ESI): m/z=267.0365, calcd. for $C_{13}H_{15}BrO$ $[M+H]^+$: 267.0293; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH=99:1, UV=254 nm, flow rate=0.8 mL min^{-1}): t_{R1}=17.05 min (minor) and t_{R2}=19.56 min (major); *ee*=84%; $[\alpha]_D^{20}$: −18.5 (*c* 0.28, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(2-methylphenyl)-5-hexaen-2-one (2h): 63% yield (94/6, 1,4/1.6 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.35 (m, 1H), 7.18–7.10 (m, 3H), 6.58 (d, J=15.6 Hz, 1H), 5.98 (dd, J=7.6, 16.0 Hz, 1H), 2.98–2.85 (m, 1H), 2.57 (dd, J=6.8, 15.6 Hz, 1H), 2.47 (dd, J=7.2, 16.0 Hz, 1H), 2.32 (s, 3H), 2.15(s, 3H), 1.13 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=208.1, 138.2, 137.6, 134.6, 128.9, 128.6, 128.1, 127.0, 123.5, 51.0, 33.2, 30.8, 21.6, 20.5; HR-MS (ESI): m/z=203.1443, calcd. for $C_{14}H_{18}O$ $[M+H]^+$: 203.1436; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH=98:2, UV=254 nm, flow rate=0.8 mL min^{-1}): t_{R1}=8.89 min (minor) and t_{R2}=9.99 min (major); *ee*=81%; $[\alpha]_D^{20}$: −18.3 (*c* 0.24, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(3-methylphenyl)-5-hexaen-2-one (2i): 67% yield (94/6, 1,4/1.6 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.21–7.10 (m, 3H), 7.02 (d, J=6.8 Hz, 1H), 6.35 (d, J=16.0 Hz, 1H), 6.12 (dd, J=7.6, 16.0 Hz, 1H), 2.90–2.82 (m, 1H), 2.56 (dd, J=6.8, 16.0 Hz, 1H), 2.46 (dd, J=7.2, 16.0 Hz, 1H), 2.33 (s, 3H), 2.14 (s, 3H), 1.12 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=208.1, 136.8, 136.2, 135.3, 130.4, 127.3, 126.9, 126.2, 125.7, 51.0, 33.5, 30.1, 20.7, 20.0; HR-MS (ESI): m/z=203.1445, calcd. for $C_{14}H_{18}O$ $[M+H]^+$: 203.1447; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH=98:2, UV=254 nm, flow rate=0.8 mL min^{-1}): t_{R1}=8.52 min (minor) and t_{R2}=10.24 min (major); *ee*=86%; $[\alpha]_D^{20}$: −33.6 (*c* 0.24, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(4-methylphenyl)-5-hexaen-2-one (2j): 70% yield (93/7, 1,4/1.6 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.0 Hz, 2H), 7.10 (d, J=8.0 Hz, 2H), 6.35 (d, J=15.6 Hz, 1H), 6.07 (dd, J=7.6, 16.0 Hz, 1H), 2.94–2.81 (m, 1H), 2.56 (dd, J=6.8, 16.0 Hz, 1H), 2.45 (dd, J=7.2, 16.0 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 3H), 1.11 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=208.3, 137.1, 134.8, 133.7, 129.4, 128.7, 126.2, 51.0, 33.2, 30.8, 21.4, 20.5; HR-MS (ESI): m/z=203.1437, calcd. for $C_{14}H_{18}O$ $[M+H]^+$: 203.1447; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH=98:2, UV=254 nm, flow rate=0.8 mL min^{-1}): t_{R1}=8.08 min (minor) and t_{R2}=9.15 min (major); *ee*=87%; $[\alpha]_D^{20}$: −38.6 (*c* 0.24, $CHCl_3$).

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(4*R*,5*E*)-4-Methyl-6-(2-naphthyl)-5-hexaen-2-one (2l): 74% yield (94/6, 1,4/1.6 mixture); yellow solid; mp 47–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (t, J = 8.4 Hz, 3H), 7.71 (s, 1H), 7.59 (dd, J = 1.6, 8.4 Hz, 1H), 7.50–7.40 (m, 2H), 6.58 (d, J = 16.0 Hz, 1H), 6.29 (dd, J = 7.6, 16.0 Hz, 1H), 3.03–2.93 (m, 1H), 2.64 (dd, J = 6.8, 16.0 Hz, 1H), 2.53 (dd, J = 6.8, 16.0 Hz, 1H), 2.19 (s, 3H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 135.0, 134.8, 133.6, 132.7, 128.8, 128.1, 127.8, 127.6, 126.2, 125.7, 125.6, 123.5, 50.7, 33.0, 30.6, 20.3; HR-MS (ESI): m/z = 239.1430, calcd. for $C_{17}H_{18}O$ $[M+H]^+$: 239.1436; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 98:2, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 15.26 min (minor) and t_{R2} = 17.59 min (major); *ee* = 88%; $[\alpha]_D^{20}$: −24.4 (*c* 0.48, $CHCl_3$).

(4*R*,5*E*)-4-methyl-6-(2-furyl)-5-hexaen-2-one (2o): 72% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 1.2 Hz, 1H), 6.34 (dd, J = 1.6, 3.2 Hz, 1H), 6.21 (d, J = 16.0 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 6.07 (dd, J = 7.6, 16.0 Hz, 1H), 2.91–2.80 (m, 1H), 2.55 (dd, J = 6.8, 16.4 Hz, 1H), 2.44 (dd, J = 7.2, 16.4 Hz, 1H), 2.14 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 153.0, 141.7, 133.6, 117.6, 111.4, 107.0, 50.8, 32.8, 30.9, 20.3; HR-MS (ESI): m/z = 179.1072, calcd, for $C_{11}H_{14}O_2$ $[M+H]^+$: 179.1072; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 98:2, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 8.35 min (minor) and t_{R2} = 8.94 min (major); *ee* = 89%; $[\alpha]_D^{20}$: −42.7 (*c* 0.22, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(2-thienyl)-5-hexaen-2-one (2p): 78% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, J = 5.2 Hz, 1H), 6.93 (dd, J = 3.6, 4.8 Hz, 1H), 6.88 (d, J = 3.2 Hz, 1H), 6.88 (d, J = 15.2 Hz, 1H), 5.97 (dd, J = 7.2, 15.6 Hz, 1H), 2.91–2.80 (m, 1H), 2.56 (dd, J = 6.8, 16.4 Hz, 1H), 2.44 (dd, J = 7.2, 16.4 Hz, 1H), 2.14 (s, 3H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 142.8, 134.6, 127.5, 125.1, 123.7, 122.2, 50.7, 32.9, 30.9, 20.3; HR-MS (ESI): m/z = 217.0687, calcd. for $C_{11}H_{14}OS$ $[M+H]^+$: 217.0677; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 98:2, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 10.51 min (minor) and t_{R2} = 12.17 min (major); *ee* = 90%; $[\alpha]_D^{20}$: −35.0 (*c* 0.52, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(5-chloro-2-thienyl)-5-hexaen-2-one (2q): 70% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, J = 4.0 Hz, 1H), 6.62 (d, J = 4.0 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 5.84 (dd, J = 8.0, 16.0 Hz, 1H), 2.89–2.77 (m, 1H), 2.53 (dd, J = 8.0, 16.0 Hz, 1H), 2.43 (dd, J = 8.0, 16.0 Hz, 1H), 2.13 (s, 3H), 1.08 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 207.6, 141.6, 134.9, 128.0, 126.5, 124.3, 122.0, 50.6, 32.8, 30.8, 20.2; HR-MS (ESI): m/z = 229.0458, calcd. for $C_{11}H_{13}ClOS$ $[M+H]^+$: 229.0454; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH = 98:2, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 8.43 min (minor) and t_{R2} = 11.02 min (major); *ee* = 88%; $[\alpha]_D^{20}$: −37.5 (*c* 0.48, $CHCl_3$).

(4*R*,5*E*)-4-Methyl-6-(5-methyl-2-thienyl)-5-hexaen-2-one (2r): 76% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, J = 4.0 Hz, 1H), 6.56 (d, J = 4.0 Hz, 1H), 6.41 (d, J = 16.0 Hz, 1H), 5.83 (dd, J = 8.0, 16.0 Hz, 1H), 2.87–2.78 (m, 1H), 2.53 (dd, J = 4.0, 16.0 Hz, 1H), 2.42 (dd, J = 8.0, 16.0 Hz, 1H), 2.43 (s, 3H), 2.13 (s, 3H), 1.08 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 140.5, 138.2, 133.1, 125.3, 125.0, 122.4, 50.6, 32.7, 30.6, 20.2, 15.5; HR-MS (ESI): m/z = 209.1002, calcd. for $C_{12}H_{16}OS$ $[M+H]^+$: 209.1000; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 98:2, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 7.80 min (minor) and t_{R2} = 8.52 min (major); *ee* = 91%; $[\alpha]_D^{20}$: −25.0 (*c* 0.40, $CHCl_3$).

Transformations of 2a

A flame-dried flask equipped with a stir bar was backfilled with N_2 and **2a** (0.1 mmol, 1.0 equiv., 82% *ee*) in anhydrous MeOH (0.5 mL, 0.2 M) was added before placing the flask in an ice bath. $NaBH_4$ (0.3 mmol, 3.0 equiv.) was added portion-wise to control the evolution of H_2 from the reaction flask and the reaction mixture was allowed to stir at 0 °C for 1.0 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM (3 × 10 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography to afford the product. The enantiomeric excess was determined by chiral HPLC.

(4*R*,5*E*)-4-Methyl-6-phenyl-5-hexen-2-ol (4a): 98% yield (18.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 4H), 7.30–7.26 (m, 4H), 7.22–7.16 (m,2H), 6.40 (d, J = 15.6 Hz, 1H), 6.38 (d, J = 16.0 Hz, 1H), 6.12 (dd, J = 16.0, 8.4 Hz, 1H), 6.05 (dd, J = 16.0, 8.4 Hz, 1H), 3.92–3.79 (m, 2H), 2.61–2.50 (m, 1H), 2.49–2.39 (m, 1H), 1.78 (s, 2H), 1.65–1.52 (m, 2H), 1.48–1.42 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 2.0 Hz, 3H), 1.09 (d, J = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (d, J = 6.2 Hz), 136.4 (d, J = 51.6 Hz), 129.08 (s), 128.6 (d, J = 18.2 Hz), 127.25 (s), 126.26 (s), 66.52 (d, J = 54.9 Hz), 46.77 (s), 34.82 (d, J = 59.3 Hz), 24.12 (d, J = 45.8 Hz), 21.40 (d, J = 56.3 Hz); HR-MS (ESI): m/z = 191.1433, calcd. for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95:5, UV = 254 nm, flow rate = 0.9 mL min^{-1}): t_{R2} = 12.13 min (minor) and t_{R4} = 13.56 min (major), *ee* = 89%; *dr* = 1.2:1.

2a (0.1 mmol, 1.0 equiv., 63% *ee*) was dissolved in dry CH_2Cl_2 (0.4 mL, 0.3 M), and mCPBA (0.3 mmol, 3.0 equiv., 75%), was added in small portions at 0 °C while stirring. After 5 min, the mixture was allowed to warm to room temperature and was stirred for another 0.5 h until complete conversion as monitored by TLC. After addition of saturated. aqueous $Na_2S_2O_3$ (1.5 mL) and $NaHCO_3$ (1.5 mL), the mixture was stirred for 15 min. Then the mixture was extracted with DCM (3 × 5 mL), dried with $MgSO_4$, and the solvent was removed on a rotary evaporator. The purification of product was achieved using column chromatography.

(4*S*)-4-Methyl-5,6-epoxy-6-phenyl-2-hexanone (5a): 78% yield (15.9 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 3H), 7.26–7.22 (m, 2H), 3.66 (d, J = 2.0 Hz, 1H), 2.83 (dd, J = 7.2, 2.0 Hz, 1H), 2.74 (dd, J = 16.8, 4.8 Hz, 1H), 2.43 (dd, J = 16.8, 8.4 Hz, 1H), 2.18 (s, 3H), 2.13–2.06 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.7, 137.7, 128.7, 128.4, 125.7, 66.6, 58.5, 47.5, 32.5, 30.7, 16.4; HR-MS (ESI): m/z = 205.1223, calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1223; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH = 95:5, UV = 210 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 11.130 min (minor) and t_{R2} = 14.184 min (major), *ee* = 80%; *dr* = 25:1.

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10 Regio- and Enantioselective Copper-Catalyzed 1,4-Conjugate Addition of Trimethylaluminium to Linear α,β,γ,δ-Unsaturated Alkyl Ketones

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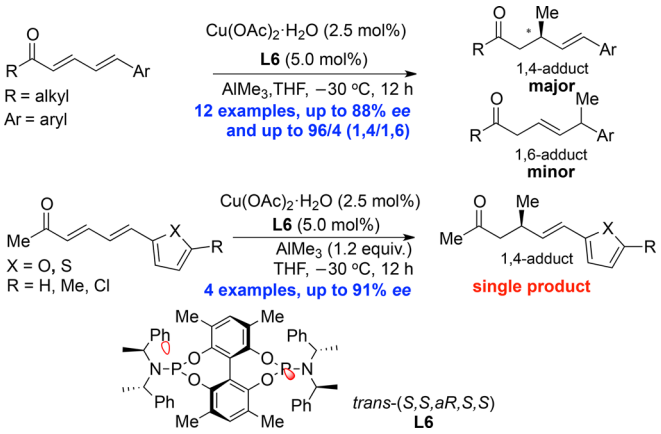

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