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# Copper-Catalyzed Enantioselective Intramolecular Conjugate Addition/Trapping Reactions: Synthesis of Cyclic Compounds with Multichiral Centers

**Kangying Li and Alexandre Alexakis*[a]**

**Abstract:** The Cu-catalyzed enantioselective conjugate addition of dialkylzinc to bis-α,β-unsaturated carbonyl compounds followed by the intramolecular trapping of the zinc enolate in the presence of chiral phosphoramidite ligands was investigated. Cyclic and heterocyclic compounds with multichiral centers were formed as a mixture of two diastereomers with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 94% *ee*, *ee* = enantiomeric excess). The stereochemistry was determined to be *trans*,*trans* for the major products and *trans*,*cis* for the minor products. The absolute configuration of the cyclic compounds was assigned by comparison with the analogous adduct derived from *trans*-3-nonen-2-one and $Et_2Zn$ or the adduct obtained through conjugate addition of $Me_2Zn$ to *trans*-1-phenyl-non-2-en-1-one. Further transformation of these cyclic products into more complex compounds is under investigation in our laboratory.

**Keywords:** copper · cyclization · enolates · Michael addition · selectivity

## Introduction

Asymmetric conjugate addition is recognized as one of the most attractive strategies for carbon–carbon bond formation and the construction of chiral building blocks.[1] During the last decade, the copper-catalyzed conjugate addition of organozinc reagents to α,β-unsaturated carbonyl compounds has been extensively studied.[2,7] More recently, organoaluminum reagents[3] have also been successfully applied for the conjugate addition of α,β-unsaturated substrates, particularly for the trisubstituted enones in which a new quaternary chiral center was created with excellent enantioselectivity. Other types of substrate, like cyclic or acyclic nitro olefins, α,β-unsaturated *N*-acyloxazolidinones, dione monoacetals, lactones or lactams, amides, and malonates, have also been developed for conjugate addition with the zinc reagent.[4,2e] Moreover, it is known that the in situ formed intermediate zinc enolates can easily be trapped by electrophilic reagents, such as aldehydes,[5] Pd–π-allyl,[5a,6] halides and tosylates,[7] oxocarbenium ions,[2e] or activated electrophiles[8] or they can be trapped as silyl enol ethers with trimethylsilyl trifluoromethanesulfonate (TMSOTf)[9] to build more functionalized chiral compounds. Recently we found that the halogenation, by using bromine, iodine, *N*-bromosuccinimide (NBS), or *N*-chlorosuccinimide (NCS), of the zinc enolate, derived through addition of diethyl zinc to α,β-unsaturated ketones in the presence of copper/chiral phosphoramidite ligands, proceeded cleanly and efficiently to produce the chiral α-bromo-β-alkylketones with excellent enantioselectivity and good yields of isolated product.[10] Krische and co-workers[11] disclosed that the conjugate addition of organozinc reagents to enones possessing appendant ketone, ester, and nitrile moieties in the presence of catalytic $Cu(OTf)_2/P(OEt)_3$ successfully provided the racemic cyclic products in good to high yields and diastereoselectivities. In a single example, they showed that the enantioselectivity with **L5** (L = ligand) was 80% but the diastereoselectivity decreased to 2.3:1 (down from 10:1). To the best of our knowledge, this is the only example reported so far for the construction of chiral cyclic compounds through the zinc enolate trapping process.

We herein present our results for the copper-catalyzed intramolecular enolate trapping reactions,[12] which provide a novel and promising pathway to construct cyclic compounds with multiple chiral centers.

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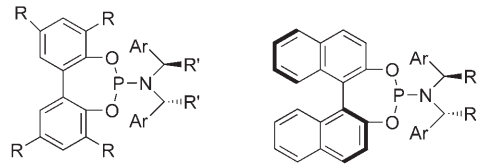
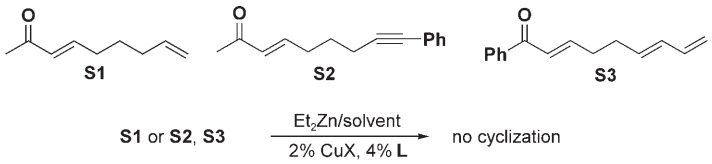
## Results and Discussion

The chiral phosphoramidite ligands **L1**–**L8** used in our experiments were easily prepared from biphenol or binaphthol and the corresponding chiral amines were synthesized according to the procedures we reported previously.[13]




In the literature, several groups have described the trapping of zinc enolate species by olefins through a carbometallation process. Normant and co-workers disclosed an efficient access to substituted tetrahydrofurans and polysubstituted pyrrolidines and piperidine derivatives through the intramolecular zinca ene-allene and zinc enolate cyclizations, as well amino zinc enolate carbocyclization reactions.[14] In 2004, Nakamura and co-workers reported the α-alkylation of ketones by addition of zinc enamides to unactivated olefins.[15] On the other hand, Parsons and co-workers revealed that the tributyltin hydride-mediated radical cyclization of carbonyl compounds conveniently gave functionalized oxygen and nitrogen heterocycles from the structurally similar substrates.[16] Houpis and Lee also reviewed the development of the nickel-catalyzed reactions of nucleophiles with unactivated and partially activated olefins.[17]

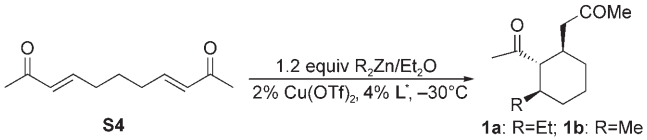
Our study began with the simple substrate **S1** with a terminal olefin. We hoped that the in situ formed zinc enolate, derived from the conjugate addition of diethyl zinc to substrate **S1**, could be intramolecularly trapped by the olefin to form the corresponding cyclic compound. In our experiment, however, only the normal 1,4-adduct was formed (Scheme 1). The enolate trapping by the terminal olefin did not happen at all, even with changed reaction conditions, such as the solvent, reaction temperature, or different additives (LiBr, $ZnBr_2$, Ni salts, etc.). We reasoned that this is probably because of the low activity of the terminal olefin. As modifications of the substrate, **S2** and **S3**, which were successfully applied in the nickel-catalyzed cyclization,[17] were prepared and subjected to the reaction under similar conditions.




Scheme 1. Conjugate addition/cyclization of substrates **S1**–**S3**.

As with **S1**, only the uncyclized 1,4-adducts were obtained in both of these cases.

We next turned our attention to the dienone **S4**, which has been widely used for cyclization reactions.[18,16] The conjugate addition of diethyl zinc to **S4** worked well and the expected cyclic product was formed as two diastereomers (Scheme 2). In an attempt to evaluate the rate of the cyclization step, versus the rate of the Cu-catalyzed conjugate addition, an excess (4.0 equiv) of diethyl zinc was added. No second conjugate addition to the other enone moiety was observed; this result indicated that *the enolate trapping was faster than the conjugate addition of diethyl zinc to the enone*. The results presented in Table 1 show that the ligand structure has no significant influence on the diastereoselectivity. With regard to the enantioselectivities, in most cases moderate to good enantiomeric excesses were obtained. It was found that the ligands with a bulky group in the amino part, like **L4** and **L7** (Table 1, entries 4 and 7, respectively), gave better enantiomeric excess values. Ligand screening revealed that the best result was obtained with ligand **L7**, which gave *ee* values of 79 and 88% for the two isomers, respectively (entry 7). The use of CuTC as the copper salt caused a slight decrease in the *ee* value and the diastereo-




Scheme 2. Conjugate addition/cyclization of substrate **S4**.

Table 1. Conjugated addition/cyclization of substrate **S4**.

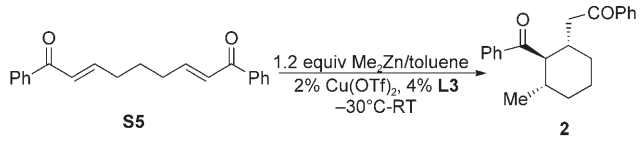
| Entry | Ligand | $R_2Zn$ | Conversion [%][a] | dr[a] | *ee* [%][b] | Configuration[c] |
|---|---|---|---|---|---|---|
| 1 | **L1** | $Et_2Zn$ | >99 | 80:20 | 53 (75) | (1*R*,2*S*,3*R*) |
| 2 | *ent*-**L2** | $Et_2Zn$ | >99 | 82:18 | 60 (79) | (1*S*,2*R*,3*S*) |
| 3 | **L3** | $Et_2Zn$ | >99 | 84:16 | 27 (65) | (1*R*,2*S*,3*R*) |
| 4 | **L4** | $Et_2Zn$ | >99 | 80:20 | 62 (83) | (1*R*,2*S*,3*R*) |
| 5 | *ent*-**L5** | $Et_2Zn$ | >99 | 79:21 | 67 (82) | (1*S*,2*R*,3*S*) |
| 6 | **L6** | $Et_2Zn$ | >99 | 80:20 | 58 (75) | (1*R*,2*S*,3*R*) |
| 7 | **L7** | $Et_2Zn$ | >99 | 80:20 | 79 (88) | (1*R*,2*S*,3*R*) |
| 8[d] | *ent*-**L7** | $Et_2Zn$ | >99 | 72:28 | 65 (76) | (1*S*,2*R*,3*S*) |
| 9[e] | **L7** | $Me_2Zn$ | >99 | 70:30 | 88 (94) | (1*R*,2*S*,3*R*) |
| 10[d] | *ent*-**L7** | $Me_2Zn$ | >99 | 60:40 | 33 (66) | (1*S*,2*R*,3*S*) |

[a] Determined by GCMS. [b] Measured by chiral GC. [c] Absolute configuration assigned by comparison with analogous adducts derived from *trans*-3-nonen-2-one and $Et_2Zn$.[19,3f] [d] With copper thiophene carboxylate (CuTC) as the copper salt. [e] With toluene as the solvent.

meric ratio (dr) (entry 8). The use of dimethyl zinc in toluene led to a slight decrease in the diastereoselectivity but the enantioselectivity increased to 94% (entry 9). Both the diastereoselectivity and enantioselectivity dropped a lot in diethyl ether with CuTC as the copper source (entry 10).

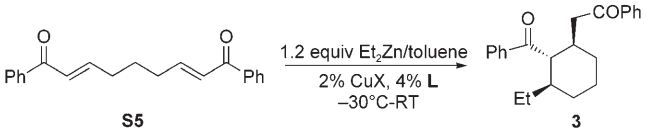
To determine the stereochemistry of the cyclic products, we ran the reaction in toluene with dimethyl zinc and substrate **S5** in the presence of $Cu(OTf)_2$ and **L3** (Scheme 3).




Scheme 3. Asymmetric conjugate addition/cyclization of substrate **S5**.

GCMS and NMR spectroscopic analysis suggested that only one isomer was formed. The NMR spectrum ($^1H$, $^{13}C$) is absolutely identical to that of the structurally determined diastereomer described by Krische and co-workers.[20] Therefore, the stereochemistry obtained by this conjugate addition/cyclization process can be determined as *trans,trans* for the major cyclic product and *trans,cis* for the minor diastereomer.

Ligand screening has been performed for diethyl zinc addition to **S5** (Scheme 4). The results were summarized in Table 2. In all cases, the reactions proceeded with full conversion and excellent diastereoselectivities (dr = up to 99:1). In terms of enantioselectivities, the ligands with an ethyl group in the amino moiety gave the better enantiomeric




Scheme 4. Ligand screening for the conjugate addition/cyclization of substrate **S5**.

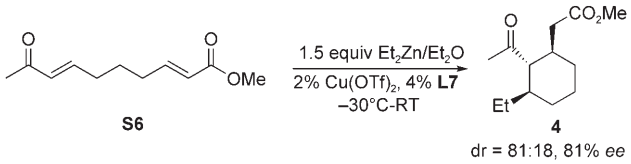
Table 2. Ligand screening for the conjugate addition/cyclization of substrate **S5**.

| Entry | Ligand | CuX | Conversion [%][a]/ (yield [%][b]) | dr[a] | *ee* [%][c] | Configuration[d] |
|---|---|---|---|---|---|---|
| 1 | **L1** | $Cu(OTf)_2$ | >99 | >99:1 | 62 | (1*S*,2*R*,3*S*) |
| 2 | **L2** | $Cu(OTf)_2$ | >99 | >99:1 | 66 | (1*S*,2*R*,3*S*) |
| 3 | **L3** | $Cu(OTf)_2$ | >99 (83) | >99:1 | 86 | (1*S*,2*R*,3*S*) |
| 4 | **L4** | $Cu(OTf)_2$ | >99 | >99:1 | 66 | (1*S*,2*R*,3*S*) |
| 5 | *ent*-**L5** | $Cu(OTf)_2$ | >99 (84) | >99:1 | 45 | (1*R*,2*S*,3*R*) |
| 6 | **L6** | $Cu(OTf)_2$ | >99 | >99:1 | 74 | (1*S*,2*R*,3*S*) |
| 7 | **L7** | $Cu(OTf)_2$ | >99 | >99:1 | 16 | (1*S*,2*R*,3*S*) |
| 8[e] | **L3** | $Cu(OTf)_2$ | >99(97) | >99:1 | 88 | (1*S*,2*R*,3*S*) |
| 9 | **L3** | CuTC | >99 | >99:1 | 79 | (1*S*,2*R*,3*S*) |
| 10 | **L3** | $Cu(OAc)_2{\cdot}H_2O$ | >99 | >99:1 | 79 | (1*S*,2*R*,3*S*) |
| 11[f] | **L3** | $Cu(OTf)_2$ | >99 (68) | >99:1 | 72 | (1*S*,2*R*,3*S*) |

[a] Determined by GCMS. [b] Yield of isolated product. [c] Determined by SFC. [d] Absolute configuration assigned by comparison with analogous adducts derived from (*E*)-1-phenylnon-2-en-1-one and $Me_2Zn$.[21] [e] $Et_2O$ as the solvent. [f] $Me_2Zn$ was used.

excess values. For example, 86% *ee* (Table 2, entry 3) was obtained with ligand **L3**, a value that is higher than those obtained with ligands **L1**, **L2**, or **L4** (entries 1, 2, and 4, respectively). Among the binaphthol-type ligands, **L6** afforded a higher *ee* value (74% *ee*; entry 6) than ligands **L5** and **L7** (45 and 16% *ee*, respectively; entries 5 and 7). For ligand **L3**, performance of the reaction in diethyl ether led to a slightly improved enantiomeric excess (88% *ee*; entry 8) and 97% yield of isolated product, but a small decrease was caused by using other copper salts, such as CuTC or $Cu(OAc)_2{\cdot}H_2O$ (entries 9 and 10).

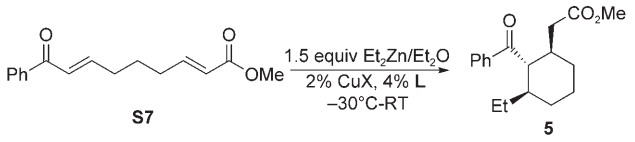
Next we synthesized other structurally different substrates like **S6** with two different α,β-unsaturated carbonyl groups (Scheme 5). It is known that the conjugate addition of diethyl zinc selectively occurs on the enone instead of the α,β-unsaturated ester moiety. So we hoped that the newly formed zinc enolate could be trapped by the terminal α,β-unsaturated ester through the intramolecular pathway. In fact, the reaction worked well under the catalytic conditions and went to completion after several hours. Ligand screening showed that ligand **L7** exhibited the best diastereoselectivity (81:18) and 81% enantiomeric excess for the major diastereomer. The other ligands gave low to moderate diastereoselectivities and enantioselectivities. When **L1** was used, moderate diastereoselectivity (74:26) was obtained which remained almost unchanged (76:24) after an attempted isomerization with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in MeOH.




Scheme 5. Conjugate addition/cyclization of substrate **S6**.

To examine the effect of substrate structure on the diastereoselectivity and enantioselectivity, we synthesized compound **S7** containing an aromatic group on the enone moiety. In comparison with substrate **S6**, the replacement of the methyl group with a phenyl moiety remarkably improved both the diastereomeric ratios and the enantioselectivities (Scheme 6, Table 3). This trend is also observed in the work of Krische and co-workers.[11] Similarly to the results described in Table 2, ligands **L3** and **L6** (Table 3, entries 3 and 6, respectively) with an ethyl group in the amino part proved to be more efficient for the improvement of diastereoselectivity and enantioselectivity under the




Scheme 6. Conjugate addition/cyclization of substrate **S7**.

Table 3. Conjugate addition/cyclization of substrate **S7**.

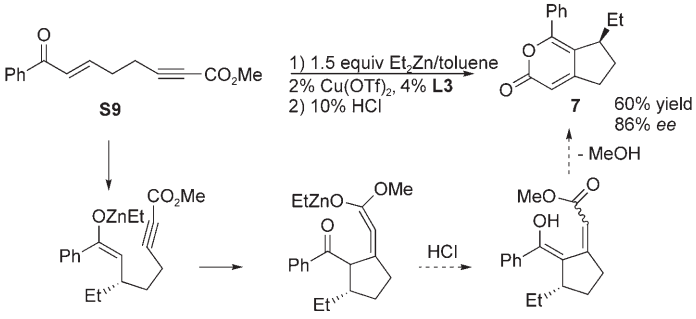
| Entry | Ligand | CuX | Conversion [%][a]/ (yield [%]) | dr[a] | *ee* [%][b] | Configuration[e] |
|---|---|---|---|---|---|---|
| 1 | **L1** | $Cu(OTf)_2$ | >99 | 91:9 | 47 (62) | (1*S*,2*R*,3*S*) |
| 2 | **L2** | $Cu(OTf)_2$ | >99 | 78:22 | 54 (48) | (1*S*,2*R*,3*S*) |
| 3 | *ent*-**L3** | $Cu(OTf)_2$ | >99 | 81:19 | 88 (90) | (1*R*,2*S*,3*R*) |
| 4 | **L4** | $Cu(OTf)_2$ | >99 | 65:35 | 45 (43) | (1*S*,2*R*,3*S*) |
| 5 | **L5** | $Cu(OTf)_2$ | >99 | 76:24 | 7 (49) | (1*S*,2*R*,3*S*) |
| 6 | **L6** | $Cu(OTf)_2$ | >99 | 80:20 | 72 (51) | (1*S*,2*R*,3*S*) |
| 7 | **L7** | $Cu(OTf)_2$ | >99 | 69:31[d] | 45 (2) | (1*S*,2*R*,3*S*) |
| 8 | *ent*-**L3** | CuTC | >99 | 92:8 | 91 (90) | (1*R*,2*S*,3*R*) |
| 9 | *ent*-**L3** | $Cu(OAc)_2 \cdot H_2O$ | >99 | 90:10 | 92 (87) | (1*R*,2*S*,3*R*) |
| 10[c] | **L3** | CuTC | >99(43) | 93:7 | 92(86) | (1*S*,2*R*,3S) |

[a] Determined by GCMS. [b] Measured by SFC. [c] Toluene used as the solvent. [d] 70:30 ratio after isomerization with DBU in MeOH. [e] Absolute configuration assigned by comparison with analogous adduct derived from (*E*)-1-phenylnon-2-en-1-one and $Me_2Zn$.[21]

same conditions. An *ee* value of 90%, for instance, was obtained by using **L3** (Table 3, entry 3) whereas the levels of enantiomeric excess obtained from **L1**, **L2**, and **L4** (entries 1, 2, and 4, respectively) were below 60%. Ligand **L6** produced the corresponding product with 72% *ee* and with a dr of 80:20 (entry 6), which was better than the results with ligands **L5** and **L7** (entries 5 and 7, respectively). In the case of ligand **L3**, further investigation into the copper salt effect was performed. CuTC (entry 8) and $Cu(OAc)_2 \cdot H_2O$ (entry 9) seemed to be beneficial to get slightly higher diastereomic ratios and enantiomeric excesses. Toluene was also found to be a good choice for this reaction; with this solvent, the ratio increased to 93:7 and the *ee* value remained high (entry 10). As expected, isomerization of the product by using DBU (entry 7) did not change the ratio.

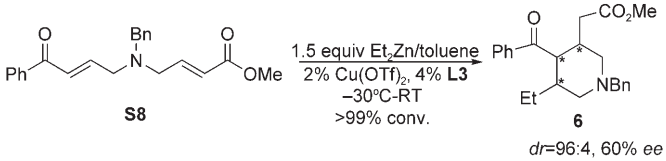
To examine the application of this strategy for the synthesis of chiral heterocyclic compounds, we synthesized substrate **S8** from readily available materials. The conjugate addition/cyclization of diethyl zinc to **S8** proceeded smoothly and went to completion within several hours (Scheme 7). The products were formed with good to excellent diastereomic ratios (up to 96:4) which were completely dependent upon the ligand used. As compared to the results obtained with substrate **S7**, a great drop in enantioselectivity was observed; this is presumably because of the coordination between the amino group in substrate **S8** and the Lewis acid $Et_2Zn$. The highest enantiomeric excess was only 60% and resulted with ligand **L3**.

We then tested substrate **S9**, which was easily synthesized from readily available starting materials in several steps. In this molecule, there are two possible reactive positions. It could be anticipated that the expected product will be formed without enantioselectivity if the conjugate addition first takes place at the α,β-saturated triple-bond moiety. In fact, 86% *ee* was achieved when the conjugate addition was performed in toluene with the optimized ligand **L3** and $Cu(OTf)_2$ (Scheme 8), a result indicating that the reaction preferentially occurred at the α,β-unsaturated ketone part. The other ligands exhibited lower enantioselectivities. NMR spectroscopic analysis showed the formation of the bicyclic lactone which was probably obtained by the pathway shown in Scheme 8.

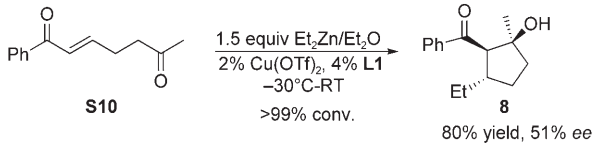



Scheme 8. Conjugate addition/cyclization of substrate **S9**.

Compound **S10** with a terminal ketone moiety was recently used as substrate in the Cu-catalyzed nonasymmetric tandem conjugate addition/electrophilic trapping by Krische and co-workers.[11] Up to 95:5 diastereoselectivity and a good yield of isolated product were achieved. In our asymmetric version of the reaction, we got 98:2 diastereoselectivity and 80% chemical yield (Scheme 9). With regard to the enantiomeric excesses, poor to moderate *ee* values were attained in all cases. Generally, the biphenol-type ligands **L1**–




Scheme 7. Conjugate addition/cyclization of substrate **S8**.




Scheme 9. Conjugate addition/cyclization of substrate **S10**.

**L4** were better (27–51 % *ee*) than the ligands with a binaphthol framework (4–32 % *ee*).

## Conclusion

We have developed an efficient asymmetric conjugate addition/trapping reaction for the synthesis of cyclic and heterocyclic compounds with multiple chiral centers. In all cases, only two diastereomers were formed with full conversion and moderate to high enantiomeric excesses. The stereochemistry of this process and the absolute configurations of the products were determined. The application of this strategy for the synthesis of more elaborate natural compounds is still in progress in our laboratory.

## Experimental Section

**General procedures**: $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in $CDCl_3$ and chemical shifts ($\delta$) are given in ppm relative to residual $CHCl_3$. The evolution of each reaction was followed with by GCMS with a Hewlett–Packard (EI mode) HP6890-5973 instrument. Enantiomeric excesses were determined by chiral GC (capillary column, 10 psi $H_2$) or chiral SFC with the stated column. Temperature programs are described as follows: initial temperature (°C)–initial time (min)–temperature gradient (°C min$^{-1}$)–final temperature (°C); retention times ($t_R$) are given in min.

Flash chromatography were performed by using silica gel 32–63 μm with cyclohexane/ethyl acetate as the eluent. All reactions were conducted under an argon atmosphere. Diethyl ether and dichloromethane were distilled from sodium benzophenone ketyl under nitrogen. Substrates **S1**[22] and **S10**[23] were synthesized according to the procedures reported previously.

**Substrate S2**: The Swern oxidation of 6-phenylhex-5-yn-1-ol[24] (15 mmol, 2.61 g) under standard conditions with oxalyl chloride (23.6 mmol, 2 mL), dimethylsulfoxide (DMSO; 59.6 mmol, 4.2 mL), and triethyl amine (74.6 mmol, 10.4 mL) in $CH_2Cl_2$ gave quantitatively the corresponding aldehyde 6-phenylhex-5-ynal, which is used directly without further purification. A mixture of the 6-phenylhex-5-ynal and 1-triphenylphosphoranylidene-2-propanone (19.5 mmol, 6.20 g) in $CH_2Cl_2$ (40 mL) was stirred at room temperature for 60 h under argon. After removal of the solvent, the residue was purified by flash chromatography to give the pure product **S2** (2.58 g, 81 % yield) as a light yellow oil. $^1$H NMR: $\delta$ = 1.81–1.88 (m, 2H; $CH_2$), 2.30 (s, 3H; Me), 2.44–2.53 (m, 4H; 2$CH_2$), 6.16–6.21 (d, 1H; CH), 6.85–6.92 (m, 1H; CH), 7.31–7.34 (m, 3H; PhH), 7.43–7.45 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 18.97, 26.96, 27.11, 31.51, 81.51, 89.08, 123.74, 127.75, 128.28, 131.56, 131.86, 147.24, 198.58 ppm.

**Substrate S3**: A mixture of 4,6-heptadienal[25] (17 mmol, 1.87 g) and (benzoylmethylene)triphenylphosphorane (20 mmol, 7.6 g) in $CH_2Cl_2$ (20 mL) was stirred at room temperature for 48 h. The solvent was evaporated and the residue was purified by flash chromatography to give the product **S3** (2.28 g, 63 % yield) as a light yellow oil. $^1$H NMR: $\delta$ = 2.27–2.45 (m, 4H; 2$CH_2$), 4.98–5.15 (dd, 2H; =$CH_2$), 5.65–5.75 (m, 1H; =CH), 6.06–6.14 (m, 1H; =CH), 6.24–6.37 (m, 1H; =CH), 6.85–6.91 (d, 1H; =CH), 6.99–7.08 (m, 1H; =CH), 7.42–7.51 (m, 3H; PhH), 7.90–7.92 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 10.85, 26.39, 29.84, 33.09, 35.33, 42.91, 113.89, 128.13, 128.61, 131.08, 132.92, 135.12, 137.27, 200.55 ppm.

**Substrate S4**:[24] Glutaric dialdehyde (2 mmol, 0.35 mL) was added to a solution of 1-triphenylphosphoranylidene-2-propanone (5 mmol, 1.59 g) in $CH_2Cl_2$ (10 mL). The resulting solution was stirred at room temperature for 70 h and was then washed with water and dried over $MgSO_4$. The crude product was purified by chromatography. The pure product was obtained as a yellow oil in 65 % yield. $^1$H NMR: $\delta$ = 1.64–1.73 (m, 2H), 2.29–2.36 (m, 9H), 5.92–5.95 (d, 2H), 6.74–6.85 ppm (m, 2H); $^{13}$C NMR: $\delta$ = 26.24, 26.73, 31.40, 131.55, 147.01, 198.17 ppm.

**Substrate S5**: A mixture of glutaric dialdehyde (10 mmol, 1.8 mL) and (benzoylmethylene)triphenylphosphorane (25 mmol, 9.51 g) in $CH_2Cl_2$ (20 mL) was stirred at room temperature for 48 h. Removal of the solvent gave the crude product which was purified by flash chromatography to afford the pure product (2.4 g, 79 % yield) as a yellow oil. $^1$H NMR: $\delta$ = 1.75–1.79 (m, 2H; $CH_2$), 2.36–2.40 (m, 4H; 2$CH_2$), 6.90–6.94 (d, 2H; 2CH), 7.44–7.94 ppm (m, 10H; 2PhH); $^{13}$C NMR: $\delta$ = 26.88, 32.40, 126.66, 128.51, 128.67, 128.77, 128.81, 130.35, 133.01, 138.01, 148.91, 190.93 ppm. The NMR spectrum is identical to those reported before.[26]

**Substrate S6**:[18a] A mixture of 7-oxo-5-octenal (10 mmol, 1.45 g) and methyl (triphenylphosphoranylidene)acetate (20 mmol, 6.69 g) in $CHCl_3$ (20 mL) was stirred at room temperature for 60 h under argon. The solvent was evaporated and the residue was purified by flash chromatography to give the pure product (1.07 g, 55 % yield) as a light yellow oil. $^1$H NMR: $\delta$ = 1.63–1.70 (m, 2H), 2.25–2.35 (m, 7H), 3.74 (s, 3H), 5.83–5.87 (d, 1H), 6.07–6.11 (d, 1H), 6.75–6.81 (m, 1H), 6.91–6.99 ppm (m, 1H); $^{13}$C NMR: $\delta$ = 26.38, 26.94, 31.54, 51.46, 121.63, 131.74, 147.06, 148.27, 166.90, 198.44 ppm.

**Substrate S7**:[18c] A solution of (*E*)-7-phenyl-7-oxohept-5-enal[27] (22 mmol, 4.46 g) in $CH_2Cl_2$ (20 mL) was added to a mixture of methyl (triphenylphosphoranylidene)acetate (44 mmol, 14.75 g) and $CH_2Cl_2$ (110 mL). The resulting solution was stirred at room temperature for 40 h. The solvent was evaporated and the residue was purified by chromatography to give the pure product (2.86 g, 50 % yield) as a light yellow oil. $^1$H NMR: $\delta$ = 1.68–1.79 (m, 2H), 2.27–2.42 (m, 4H), 3.77 (s, 3H), 5.85–5.92 (d, 1H), 6.92–7.07 (m, 3H), 7.49–7.62 (m, 3H), 7.96–7.98 ppm (d, 2H); $^{13}$C NMR: $\delta$ = 26.52, 31.59, 32.09, 51.51, 121.65, 126.44, 128.54, 132.77, 137.86, 148.41, 148.54, 166.98, 190.64 ppm.

**Substrate S8**: A mixture of methyl (*E*)-5-aza-5-benzyl-7-oxohept-2-enoate[28] (15 mmol, 3.71 g) and (benzoylmethylene)triphenylphosphorane (7.6 g, 20 mmol) in $CH_2Cl_2$ (20 mL) was allowed to stir at room temperature for 16 h. The solvent was removed to give the crude product which was purified by flash chromatography. The pure product was isolated in 65 % yield (4.54 g). $^1$H NMR: $\delta$ = 3.339–3.346 (d, 2H, $CH_2$), 3.403–3.41 (d, 2H, $CH_2$), 3.72 (s, 2H, $CH_2$), 3.80 (s, 3H, MeO), 6.12–6.16 (d, 1H, =CH), 7.08–7.15 (m, 3H, 3=CH), 7.30–7.51 (m, 5H, PhH), 7.53–7.95 ppm (m, 5H, PhH); $^{13}$C NMR: $\delta$ = 51.64, 54.73, 55.13, 58.61, 122.77, 127.24, 127.40, 137.71, 146.01, 166.66, 190.43 ppm; MS (ESI): *m*/*z* (%): 349 (13), 245 (16), 244 (73), 204 (20), 158 (16), 144 (12), 105 (51), 91 (100); HRMS: calcd for $C_{22}H_{23}NO_3$: 350.1756 [*M*+1]; found: 350.1759.

**Substrate S9**: This compound was obtained from 6-hydroxy-hex-2-ynoic acid methyl ester[29] (2.843 g, 20 mmol) and (benzoylmethylene)triphenylphosphorane (9.50 g, 25 mmol) through typical Swern oxidation procedures and with classical Wittig reaction conditions in $CH_2Cl_2$. Pure product was isolated through flash chromatography in 68 % yield (3.28 g). $^1$H NMR: $\delta$ = 2.56–2.58 (t, 4H; 2$CH_2$), 3.73 (s, 3H; MeO), 6.96 (m, 2H; CH=CH), 7.43–7.52 (m, 3H; PhH), 7.54 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 17.78, 30.52, 52.69, 73.85, 87.58, 127.44, 129.00, 132.93, 137.62, 145.28, 153.90, 190.40 ppm; MS (ESI): *m*/*z* (%): 242 (8), 227 (22), 183 (22), 155 (22), 117 (47), 105 (100), 91 (30), 77 (92), 51 (66); HRMS: calcd for $C_{15}H_{14}O_3$: 243.1021 $[M+1]^+$; found: 243.1014.

**Typical procedure for the asymmetric conjugate addition/trapping (for 0.5 mmol of substrate)**: Dry diethyl ether (2 mL) was added to a mixture of $Cu(OTf)_2$ (0.02 equiv) and ligand (0.04 equiv) under nitrogen. The solution was allowed to stir at room temperature for 30 min and was then cooled to −30 °C. Diethyl zinc (1.5 equiv, 0.75 mL, 1 M in hexane) was added dropwise while the temperature was maintained below −30 °C. The solution was stirred for 5 min, and a solution of the substrate (0.5 mmol) in diethyl ether (0.5 mL) was added dropwise. The reaction mixture was stirred at −30 °C for 2 h and was then warmed to room temperature until all of the starting material was consumed. The solution was diluted with diethyl ether (20 mL) and washed successively with 2 N HCl and brine. The organic layer was dried over sodium sulfate. Removal of the solvent gave the crude product which underwent to GC and *ee* analysis or NMR spectroscopy measurements after flash chromatography.

**Compound 1a**: dr = 72:28; $^1$H NMR: $\delta$ = 0.82–1.06 (m, 5H), 1.21–1.46 (m, 3H), 1.49–1.62 (m, 2H), 1.70–1.91 (m, 3H), 2.06–2.11 (m, 6H), 2.19–2.67 ppm (m, 2H); $^{13}$C NMR: $\delta$ = 10.79, 11.08, 20.58, 25.28, 26.34, 26.81, 27.21, 29.42, 29.62, 29.88, 30.56, 31.22, 31.36, 32.14, 33.76, 34.57, 35.21, 35.38, 41.09, 43.19, 48.35, 48.71, 57.70, 63.52, 207.75, 207.86, 212.66, 213.96 ppm; MS (ESI): *m*/*z* (%): 210 (11), 181 (27), 153 (56), 109 (100), 81 (60), 67 (52), 55 (24); HRMS: calcd for $C_{13}H_{22}O_2$: 210.1619 $[M]^+$; found: 210.1619; chiral GC (hydrodex-B-3P, 60–0–1–17–10, 30 cm s$^{-1}$): $t_{R1}$ = 78.33, $t_{R2}$ = 79.48, $t_{R3}$ = 85.48, $t_{R4}$ = 86.27 min.

**Compound 1b**: $^1$H NMR: $\delta$ = 0.82–0.83 (d, 3H; $CH_3$), 1.30–1.44 (m, 2H; $CH_2$), 1.63–1.84 (m, 6H; 2CH, $2CH_2$), 2.084 (m, 3H; $CH_3$), 2.087 (m, 3H; $CH_3$), 2.11–2.28 ppm (m, 3H; $CH_2$, CH); $^{13}$C NMR: $\delta$ = 20.55, 25.38, 28.92, 30.54, 31.91, 34.33, 34.96, 35.26, 48.68, 65.07, 207.76, 213.76 ppm; MS (ESI): *m*/*z* (%): 196 (3), 178 (37), 163 (19), 139 (27), 122 (32), 109 (100), 95 (72), 82 (70), 67 (21), 55 (20); HRMS: calcd for $C_{12}H_{20}O_2$: 196.1463 $[M]^+$; found: 196.1469; chiral GC (hydrodex-B-3P, 60–0–1–17–10, 50 cm s$^{-1}$): $t_{R1}$ = 66.07, $t_{R2}$ = 69.22, $t_{R3}$ = 72.13, $t_{R4}$ = 73.50 min.

**Compound 2**:[20] $^1$H NMR: $\delta$ = 0.77–0.79 (d, 3H; $CH_3$), 1.02–1.23 (m, 2H; $CH_2$), 1.32–1.42 (m, 1H; CH), 1.63–1.88 (m, 4H; $2CH_2$), 2.38–2.51 (m, 2H; $CH_2$), 2.82–2.92 (q, 1H; CH), 3.06–3.15 (t, 1H; CH), 7.39–7.58 (m, 6H; PhH), 7.77–7.79 (d, 2H; PhH), 7.99–8.30 ppm (d, 2H; PhH); $^{13}$C NMR: $\delta$ = 21.10, 25.38, 31.46, 34.99, 37.03, 38.38, 44.14, 56.59, 128.26, 128.29, 128.83, 132.99, 133.28, 136.77, 139.34, 199.44, 206.33 ppm; SFC (Chiral AD, 2–2–1–15%, 2 mL min$^{-1}$, 200 bar, 30 °C): $t_{R1}$ = 8.48, $t_{R2}$ = 9.07 min.

**Compound 3**: $^1$H NMR: $\delta$ = 0.75–0.77 (t, 3H; Me), 0.94–1.07 (m, 2H; $CH_2$), 1.15–1.39 (m, 4H; $2CH_2$), 1.73–1.82 (m, 2H; $CH_2$), 1.94–1.98 (m, 1H; CH), 2.43–2.52 (m, 2H; $CH_2$), 2.83–2.91 (q, 1H; CH), 3.18–3.23 (t, 1H; CH), 7.38–7.77 (m, 6H; PhH), 7.78–7.80 (d, 2H; PhH), 8.02–8.04 ppm (d, 2H; PhH); $^{13}$C NMR: $\delta$ = 11.27, 25.27, 27.72, 30.54, 31.69, 38.84, 43.35, 44.22, 55.16, 128.24, 128.27, 128.58, 128.84, 132.98, 133.29, 136.75, 139.38, 199.42, 206.66 ppm; MS (ESI): *m*/*z* (%): 334 (6), 224 (20), 215 (69), 109 (38), 105 (100), 77 (73); HRMS: calcd for $C_{23}H_{26}O_2$: 335.2011 $[M+1]^+$; found: 335.2001; SFC (Chiral AD, 2–2–1–15%, 2 mL min$^{-1}$, 200 bar, 30 °C): $t_{R1}$ = 4.90, $t_{R2}$ = 6.49 min.

**Compound 4**: dr = 95:5; $^1$H NMR: $\delta$ = 0.83–0.87 (m, 3H; $CH_3$), 0.97–1.11 (m, 2H; $CH_2$), 1.25–1.37 (m, 2H; $CH_2$), 1.46–1.57 (m, 1H; CH), 1.74–1.90 (m; 4H), 2.06 (s, 3H; $CH_3$), 1.95–2.36 (m, 4H; $CH_2$, 2CH), 3.63–3.64 ppm (d, 2.85H, 0.15H; $CH_3$); $^{13}$C NMR: $\delta$ = 10.80, 25.22, 26.94, 27.12, 29.88, 31.73, 36.82, 39.31, 41.37, 51.56, 62.73, 172.73, 213.69 ppm; MS (ESI): *m*/*z* (%): 226 (7), 194 (16), 165 (32), 151 (16), 136 (36), 109 (100), 81 (45), 74 (59); HRMS: calcd for $C_{13}H_{22}O_3$: 249.1466 $[M+Na]^+$; found: 249.1476; chiral GC (hydrodex-B-3P, 60–0–1–170–10, 40 cm s$^{-1}$): $t_{R1}$ = 72.39, $t_{R2}$ = 72.84, $t_{R3}$ = 76.86, $t_{R4}$ = 77.32 min.

**Compound 5**: $^1$H NMR: $\delta$ = 0.85–0.89 (t, 3H; $CH_3$), 1.07–1.21 (m, 2H; $CH_2$), 1.46–1.66 (m, 4H; $2CH_2$), 1.80–1.91 (m, 3H; $CH_2$, CH), 2.39–2.41 (m, 2H; $CH_2$), 2.55 (m, 1H; CH), 3.44–3.48 (dd, 1H; CH), 3.56 (s, 3H; $CH_3O$), 7.44–7.48 (m, 3H; PhH), 7.94–7.99 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 11.27, 20.09, 26.84, 29.15, 29.99, 32.42, 33.99, 35.03, 51.41, 128.11, 128.69, 132.91, 137.46, 173.58, 202.90 ppm; MS (ESI): *m*/*z* (%): 288 (31), 256 (23), 214 (12), 161 (39), 136 (32), 109 (55), 105 (100), 77 (71); HRMS: calcd for $C_{18}H_{24}O_3$: 289.1803 $[M+1]^+$; found: 289.1813; SFC (Chiral OD-H, 5–6–1–15%, 2 mL min$^{-1}$, 130 bar, 10 °C): $t_{R1}$ = 3.91, $t_{R2}$ = 4.11, $t_{R3}$ = 4.48, $t_{R4}$ = 4.80 min.

**Compound 6**: $^1$H NMR: $\delta$ = 0.82–0.85 (t, 3H; $CH_3$), 1.07 (m, 1H; $CH_2$), 1.38–1.43 (m, 1H; $CH_2$), 1.80–1.86 (t, 1H), 2.20–2.29 (m, 2H), 2.29–2.34 (dd, 1H), 2.52–2.53 (m, 1H), 2.77–2.83 (m, 2H), 3.05–3.07 (d, 1H), 3.36–3.39 (m, 2H), 3.46 (s, 3H; $OCH_3$), 3.62–3.65 (d, 1H), 7.23–7.31 (m, 5H; PhH), 7.44–7.48 (t, 2H; PhH), 7.54–7.57 (t, 1H; Ph-H), 7.92–7.94 ppm (d, 2H; PhH); $^{13}$C NMR: $\delta$ = 11.35, 25.33, 32.55, 33.64, 34.48, 51.36, 57.08, 58.35, 62.92, 126.95, 128.78, 133.14, 137.12, 138.69, 173.62, 202.00 ppm; MS (ESI): *m*/*z* (%): 379 (15), 219 (21), 218 (90), 174 (82), 105 (26), 91 (100); HRMS: calcd for $C_{24}H_{29}NO_3$: 380.2225 $[M+1]^+$; found: 380.2227; SFC (Chiral OJ, 2–2–1–15%, 200 bar, 2 mL min$^{-1}$, 30 °C): $t_{R1}$ = 4.41, $t_{R2}$ = 5.61 min.

**Compound 7**: $^1$H NMR: $\delta$ = 0.88–0.92 (t, 3H; $CH_3$), 1.30–1.36 (m, 2H; $CH_2$), 1.53–1.59 (m, 1H; $CH_2$), 1.90–2.00 (m, 1H; $CH_2$), 2.17–2.25 (m, 1H; $CH_2$), 2.79–2.88 (m, 2H; $CH_2$), 3.38–3.42 (m, 1H; CH), 6.18 (s, 1H; CH), 7.46–7.51 (m, 3H; PhH), 7.78–7.79 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 12.04, 25.93, 29.90, 30.42, 42.60, 107.56, 124.27, 127.55, 128.65, 129.97, 132.52, 154.19, 163.11, 166.48 ppm; MS (ESI): *m*/*z* (%): 240 (45), 212 (38), 211 (100), 184 (9), 156 (14), 105 (71), 77 (73), 51 (24); HRMS: calcd for $C_{16}H_{16}O_2$: 241.1228 $[M+1]^+$; found: 241.1225; SFC (Chiral OD-H, 5–2–1–15%, 200 bar, 2 mL min$^{-1}$, 30 °C): $t_{R1}$ = 8.19, $t_{R2}$ = 8.87 min.

**Compound 8**:[11] $^1$H NMR: $\delta$ = 0.82–0.86 (t, 3H; $CH_3$), 1.32 (s, 3H; $CH_3$), 1.33–1.48 (m, 3H; $CH_2$, CH), 1.80–1.86 (m, 1H; CH*H*), 1.93–2.00 (m, 1H; C*H*H), 2.18–2.27 (m, 1H; C*H*H), 2.59–2.65 (m, 1H; CH*H*), 3.45–3.48 (d, 1H; CH), 3.84 (s, 1H; OH), 7.52–7.65 (m, 3H; PhH), 8.00–8.02 ppm (m, 2H; PhH); $^{13}$C NMR: $\delta$ = 12.71, 27.40, 28.61, 29.04, 40.99, 46.62, 60.22, 81.99, 128.47, 128.80, 133.66, 138.49, 206.36 ppm; SFC (Chiral AD, 5–2–1–15%–3, 200 bar, 2 mL min$^{-1}$, 30 °C): $t_{R1}$ = 5.13, $t_{R2}$ = 6.85 min.

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