ChemPubSoc Europe

DOI: 10.1002/ejoc.201800476

EurJOC European Journal of Organic Chemistry

Full Paper

Asymmetric Catalysis

Cu^{I}-Catalysed Enantioselective Alkyl 1,4-Additions to (*E*)-Nitroalkenes and Cyclic Enones with Phosphino-Oxazoline Ligands

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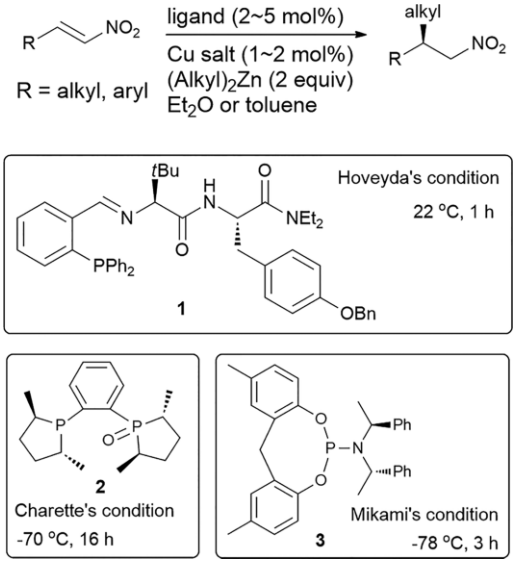
Abstract: Catalytic enantioselective conjugate additions of simple alkyl groups to nitroalkenes or cyclic enones that result in the formation of tertiary C–C bonds are described. For these stereoselective addition reactions, new chiral phosphino-oxazoline ligands were synthesized and used. The reactions were promoted by a Cu-based catalyst (2 mol-%), and gave the chiral products in up to 92 % yield with 95 % *ee*. A larger-scale synthesis was demonstrated, and the origin of the stereoselectivity was proposed based on DFT calculations.

Introduction

Amine-containing chiral molecules, such as Thalidomide®, show various kinds of biological activities that allow their commercialization as drugs to cure patients.[1] In contrast to the therapeutic (+)-enantiomer of Thalidomide®, which acts as a sedative drug, the (–)-enantiomer, if administered to pregnant women, results in birth defects in babies due to malformation of the embryos. This case drew attention to the need for the synthesis of chiral drugs with high enantiopurities.[1,2] The development of catalytic enantioselective C–C-bond-forming reactions is very important for the synthesis of nitrogen-containing optically active natural products and pharmaceuticals.[1,3,4] In particular, enantioselective conjugate additions to (*E*)-nitroalkenes under organocatalytic or transition-metal-catalysed conditions have played important roles in the preparation of amine-containing chiral compounds.[5,6]

Cu-catalysed enantioselective conjugate additions to nitroalkenes using organozinc reagents as the source of alkyl nucleophiles have been well investigated since first reports appeared.[7,8] Among the protocols that have been reported for the construction of tertiary carbon stereogenic centres, the representative examples shown in Scheme 1 give high stereoselectivities and have broad substrate scopes. Hoveyda and a co-worker developed the peptide-based ligand **1**, and found that the Cu complex formed from ligand **1** and a Cu salt gave efficient enantioselective conjugate additions to form nitroalkanes containing tertiary stereogenic centres. Surprisingly, a reaction time of 1 h at ambient temperature was enough for the successful conversion. The Hoveyda group also reported a protocol for the construction of quaternary carbon stereogenic centres through enantioselective conjugate additions to trisubstituted nitroalkenes with the same peptide ligand **1**.[9] Charette's group used Me-DuPHOS monoxide **2** as a source of chirality, and obtained the desired nitroalkenes in 70–91 % yield with 95–98 % *ee*. A copper complex of diphenylmethane-based phosphoramidite **3**, developed by Mikami's group, catalysed the enantioselective conjugate addition to aryl-substituted (*E*)-



Scheme 1. Examples of Cu-catalysed enantioselective conjugate additions to nitroalkenes with (alkyl)$_2$Zn reagents.

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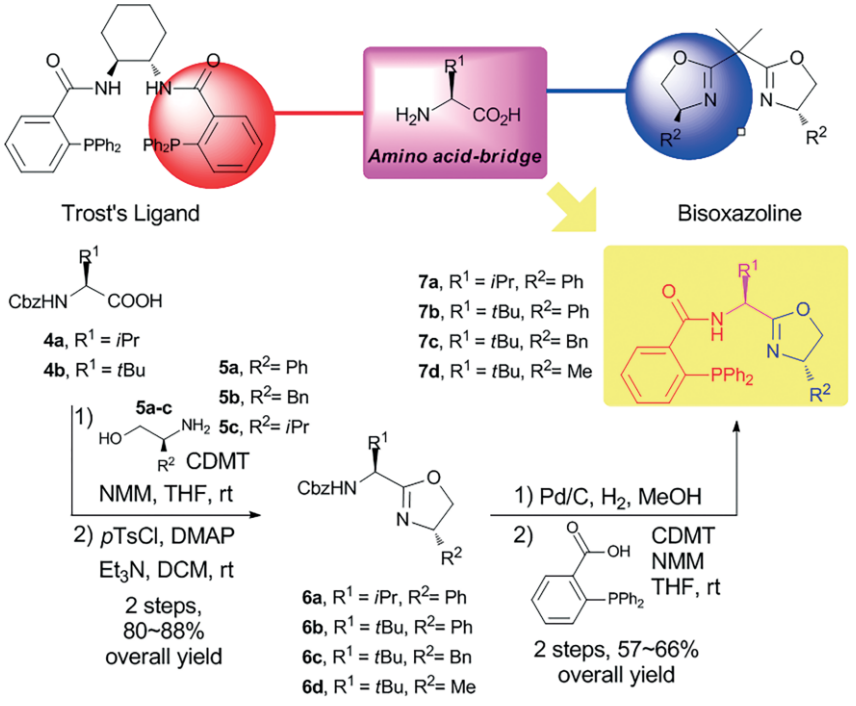
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800476.

nitroalkenes to give the ethyl-addition products with 91–99 % *ee*. Although these methods have broad substrate scopes and give excellent stereoselectivities, the necessity of cryogenic conditions for Charette's method (–70 °C) and Mikami's method (–78 °C) is hardly avoidable, and Mikami's protocol is not applicable to alkyl-substituted nitroalkenes. Moreover, despite the above-mentioned notable advances in catalytic enantioselective conjugate additions to nitroalkenes, the number of examples of asymmetric addition reactions of simple alkyl groups to nitroalkenes, especially those containing a small alkyl substituent at a prochiral centre, is still small. For this reason, it is still necessary to develop methods for Cu-catalysed enantioselective conjugate additions to nitroalkenes with new chiral ligands.

Results and Discussion

Our initial study focussed on the design of new chiral ligands. Our phosphino-oxazoline ligands were based on versatile chiral ligands, particularly Trost's ligand and bisoxazolines (Scheme 2).[10] The 2-diphenylphosphinobenzamide moiety was derived from Trost's ligand (red circle in Scheme 2), and the oxazoline part from bisoxazolines (blue circle in Scheme 2). An amino acid (violet box in Scheme 2) was used to connect the 2-diphenylphosphinobenzamide and oxazoline moieties.[11] The two stereogenic carbons in the chiral ligands originate from naturally abundant L-amino acids; the ligands were prepared from commercially available *N*-protected amino acids **4a** (valine) and **4b** (*tert*-leucine) in four steps. The synthesis began with an amide-forming reaction between *N*-Cbz-protected L-amino acids **4a** and **4b** and amino alcohols **5a**–**5c**, mediated by 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT).[12] Because of the poor solubility of the amide products in organic solvents such as ethyl acetate or dichloromethane, the amides were used directly in the following step, which involved tosylation and subsequent intramolecular cyclization under basic conditions. *N*-Cbz-protected monoxazolines **6a**–**6d** were obtained in 80–88 % overall yield. Heterogeneous Pd-catalysed hydrogenolysis of **6a**–**6d** gave the corresponding free primary amines. These were converted into the final P,N ligands **7a**–**7d** through CDMT-mediated peptide synthesis with diphenylphosphinobenzoic acid in 57–66 % yield.

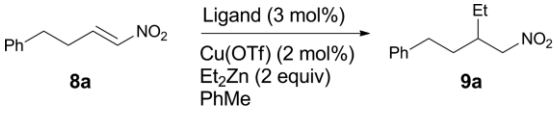
To evaluate the performance of the synthesized P,N ligands in Cu-catalysed enantioselective conjugate additions to (*E*)-nitroalkenes with dialkylzinc reagents, substrate **8a** was tested with Et_2Zn (Table 1). We found that Et_2Zn was not sufficiently nucleophilic for the conjugate addition; the desired 1,4-addition product **9a** was formed in <2 % yield (Table 1, entry 1). A complex of Trost's ligand and a Cu salt was similarly inefficient in this system. The addition of the Cu complex of (*R*,*R*)-Ph-bisoxazoline (3 mol-%) resulted in the efficient formation of **9a** in 84 % yield, but the optical purity of **9a** was low (10 % *ee*; Table 1, entry 3). In sharp contrast to the Trost ligand and Ph-bisoxazoline, the newly developed P,N ligand **7a** showed superior efficiency and enantioselectivity, and **9a** was formed in 90 % yield with 75 % *ee* (Table 1, entry 4). A complex of **7e**, a diastereomer of **7a**, with a Cu salt did not efficiently catalyse the enantioselective conjugate addition reaction (37 % yield and 6 % *ee*; Table 1, entry 5). A change from an *i*Pr group (**7a**) to a *t*Bu (**7b**) group in the P,N ligand gave a slight increase in the stereoselectivity for the formation of **9a** (Table 1, entry 6), but replacement of the phenyl group with a benzyl or methyl group resulted in a decrease in the optical purity of **9a** (Table 1, entries 6–8). A reaction carried out with **7b** at –50 °C was not efficient or stereoselective (Table 1, entry 9), but when the reac-



Scheme 2. Design and synthesis of phosphino-oxazoline ligands. DMAP = 4-dimethylaminopyridine; NMM = *N*-methylmorpholine.

tion temperature was raised to 0 °C, the reaction was complete within 2 h, and **9a** was formed in 91 % yield with 86 % *ee* (entry 10). When the same reaction was carried out at 22 °C, the reaction was complete within 10 min, and **9a** was obtained with a similar yield and *ee* (Table 1, entry 11). Increasing the loading of the **7b**–Cu(OTf) catalyst resulted in a decrease in the optical purity of **9a** to 76 % *ee* (Table 1, entry 12). However, changing the counterion from triflate (OTf) to thiophen-2-carboxylate (Tc) enhanced the performance of the catalyst, and **9a** was obtained in 92 % yield with 90 % *ee* (Table 1, entry 13). We observed that the background reaction with CuTc (2 mol-%) gave a significant amount of **9a** (14 % yield) within 2 h.

Table 1. Optimization of the Cu-catalysed enantioselective conjugate addition to **8a** with Et_2Zn.[a]



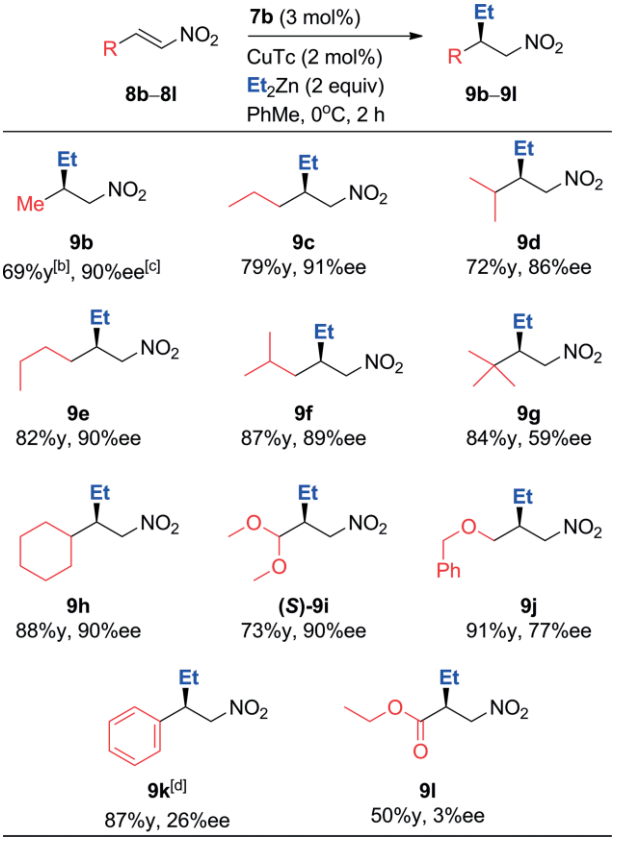
Entry	Ligand	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	No Cu/ligand	-35	6	<2%	N.A.[d]
2	Trost ligand	-35	6	4	N.A.
3	(*R*,*R*)-Ph-Box	-35	6	84	10
4	**7a** (α-Ph)	-35	6	90	75
5	**7e** (β-Ph)	-35	6	37	6
6	**7b**	-35	6	88	79
7	**7c**	-35	6	85	70
8	**7d**	-35	6	86	50
9	**7b**	-50	8	61	36
10	**7b**	0	2	91	86
11	**7b**	22	10 min	90	82
12[e]	**7b**	0	2	91	76
13[f]	**7b**	0	2	92	90
14	2 mol% CuTc No ligand	0	2	14	N.A.

[a] All reactions were carried out on a 0.2 mmol scale of **8a** in toluene (0.1 M) under a nitrogen atmosphere. [b] Yield of purified product. [c] Determined by GLC analysis. [d] N.A. = not applicable. [e] 5 mol-% of Cu and 6 mol-% of the ligand were used. [f] CuTc was used instead of Cu(OTf).

Using the optimized reaction conditions using the Cu–**7b** complex (2 mol-%; formed from CuTc) with Et_2Zn (2 equiv.) at 0 °C for 2 h, we examined a range of (*E*)-nitroalkenes (Table 2). Nitroalkenes with a small alkyl substituent such as Me, *n*Pr, or *n*Bu were converted into the respective 1,4-addition products **9b**, **9c**, and **9e** in 69–82 % yield with 90 % *ee*. The more sterically hindered substituents *i*Pr, *i*Bu, and cyclohexyl (Cy) did not adversely affect the stereoselectivity of the Cu-catalysed reaction, and the ethyl-addition products **9d**, **9f**, and **9h** were generated in 72–88 % yield with 86–90 % *ee*. However, the high steric hindrance of the *t*Bu group resulted in a drop in the optical purity of the corresponding product **9g** to 59 % *ee*, although the reactivity of **8g** was similar to those of **8b**–**8f** and **8h**. To evaluate the functional-group compatibilities of the Cu-catalysed reaction, acetal-containing (**8i**) and ether-containing (**8j**) nitroalkenes were used under the optimized conditions. The Cu catalyst did not interfere with the acetal moiety in **8i**, and the desired nitroalkane **9i** was obtained in 73 % yield with 90 % *ee*.

In contrast, $BnOCH_2$-substituted nitroalkene **8j** was converted into 1,4-addition product **9j** in 91 % yield, but the optical purity decreased to 77 % *ee*. To investigate the behaviour of highly activated nitroalkenes, phenyl-substituted (**8k**) and EtO_2C-substituted (**8l**) nitrostyrenes were examined. Disappointingly, the Cu-catalysed enantioselective conjugate additions to **8k** and **8l** were not stereoselective, and the corresponding products **9k** and **9l** were generated in 50–87 % yield with 3–26 % *ee*. We suspect that a planar substituent such as Ph- or EtO_2C- cannot generate enough steric hindrance in the transition state to give a significant difference between the $\Delta G^{\ddagger}$ values of the (*R*)-forming pathway and (*S*)-forming pathway.

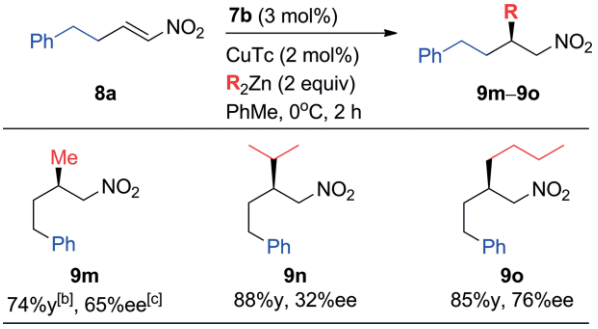
Table 2. Substrate scope.[a]



[a] All reactions were carried out on a 0.2 mmol scale of **8b**–**8l** in toluene (0.1 M) under a nitrogen atmosphere. [b] Yield of purified product. [c] Determined by GLC analysis. [d] The reaction was carried out at –45 °C for 16 h.

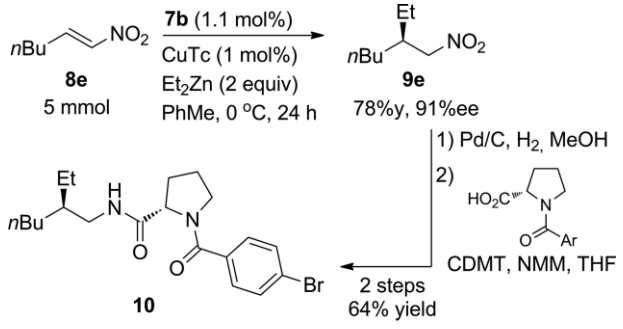
Next, we explored the range of dialkylzinc reagents that could be used in the Cu-catalysed enantioselective conjugate additions to nitroalkene **8a**. As shown in Table 3, the use of Me, *i*Pr, and *n*Bu as alternative alkyl groups resulted in significant decreases in the stereoselectivity of the reaction.[13] For comparison, ethyl-addition product **9a** was obtained in 92 % yield with 90 % *ee* (Table 1, entry 13), whereas methyl-addition product **9m** was generated in 74 % yield with 65 % *ee*. The Cu-catalysed reaction of **8a** with $(nBu)_2Zn$ resulted in the formation of **9o** in 85 % yield with 76 % *ee*. However, the sterically hindered $(iPr)_2Zn$ reagent showed relatively poor stereoselectivity in the addition reaction with **8a**, and compound **9n** was obtained with 32 % *ee*.[14]

Table 3. Scope of the reaction in terms of dialkyl zinc reagents.[a]



[a] All reactions were carried out on a 0.2 mmol scale of **8a** in toluene (0.1 M) under a nitrogen atmosphere. [b] Yield of purified product. [c] Determined by GLC analysis.

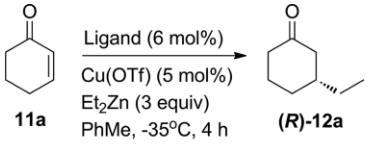
To examine the synthetic utility of the method, a reaction with (*E*)-nitroalkene **8e** was carried out on a 5 mmol scale (Scheme 3). A catalyst loading of the **7b**–CuTc complex of 1 mol-% resulted in the complete conversion of **8e** within a reaction time of 24 h, and nitroalkane **9e** was obtained in 78 % yield with 91 % *ee*. Reduction of the nitro group in **9e** through Pd/C-catalysed hydrogenation resulted in quantitative conversion into the amine. Because of the volatility of the amine, a CDMT-mediated amide-coupling reaction with *N*-(4-bromobenzoyl)proline was then carried out to generate amide **10** in 64 % yield.



Scheme 3. A larger-scale synthesis of **10**.

The synthetic utility of the complexes of the P,N ligands with Cu salts was examined further by testing Cu-catalysed enantioselective conjugate additions to cyclic enone **11a** with Et_2Zn (Table 4).[1,15] Ligand **7b** was found to be optimal in terms of reactivity for Cu-catalysed enantioselective conjugate additions to (*E*)-nitroalkenes, but was gave worse results than **7a** in terms of stereoselectivity for the formation of **12a** (Table 4, entries 1 and 2). In contrast to the enantioselective conjugate additions to nitroalkenes, the replacement of the phenyl group with Bn, Me, or *i*Pr did not influence the stereoselectivity in the formation of **12a** (Table 4, entries 2–5). The use of weakly coordinating Et_2O as a solvent resulted in a lower optical purity and lower yield of **12a** (32 % yield and 65 % *ee*; Table 4, entry 6). When CuTc was used instead of CuOTf, and the loading of **7a**–CuTc was decreased, the stereoselectivity of the formation of **12a** increased (77 % yield and 95 % *ee*). Some enantioselective conjugate additions to cyclic enones were explored under the optimized reaction conditions using the Cu complex of **7a** and CuTc (2 mol-%) with dialkylzinc (3 equiv.) at –35 °C for 4 h.

Table 4. Optimization of the Cu-catalysed enantioselective conjugate addition to **11a** with Et_2Zn.[a]



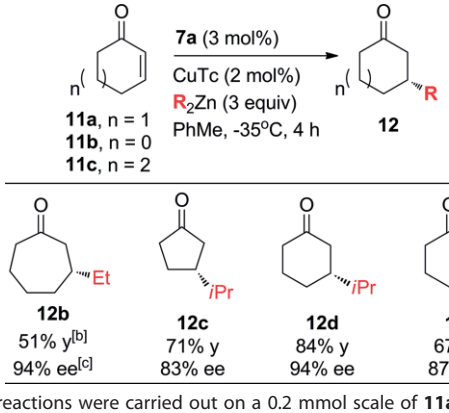
Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**7b**	84	88
2	**7a**	67	93
3	**7f** (R^1=*i*Pr, R^2=Bn)	82	86
4	**7g** (R^1=*i*Pr, R^2=Me)	68	91
5	**7h** (R^1=*i*Pr, R^2=*i*Pr)	76	91
6[d]	**7a**	32	65
7[e]	**7a**	79	94
8[f]	**7a**	77	95

[a] All reactions were carried out on a 0.2 mmol scale of **11a** in toluene (0.1 M) under a nitrogen atmosphere. [b] Yield of purified product. [c] Determined by GLC analysis. [d] The reaction was carried out in Et_2O. [e] CuTc was used instead of Cu(OTf). [f] 3 mol-% of **7a** and 2 mol-% of CuTc were used.

As shown in Table 5, the Cu-catalysed 1,4-addition of an ethyl group to 2-cycloheptenone (**11c**) proceeded less efficiently than for 2-cyclohexeneone (**11a**); compound **12b** was obtained in 51 % yield, but with a high optical purity of 94 % *ee*. Cu-catalysed enantioselective conjugate additions to **11a** and **11b** with $(iPr)_2Zn$ proceeded smoothly, and the corresponding products **12c** and **12d** were obtained in 71–84 % yield with 83–94 % *ee*. Thus, there is a remarkable contrast between the Cu-catalysed enantioselective conjugate additions to (*E*)-nitroalkenes and those to cyclic enones. The addition of an *i*Pr group to nitroalkene **8a** gave the desired product with 32 % *ee*, but the addition of an *i*Pr group to cyclic enone **11a** gave **12d** with 94 % *ee*. The stereoselective addition of $(nBu)_2Zn$ to cyclic enone **11b** proceeded successfully to generate **12e** in 67 % yield with 87 % *ee*.

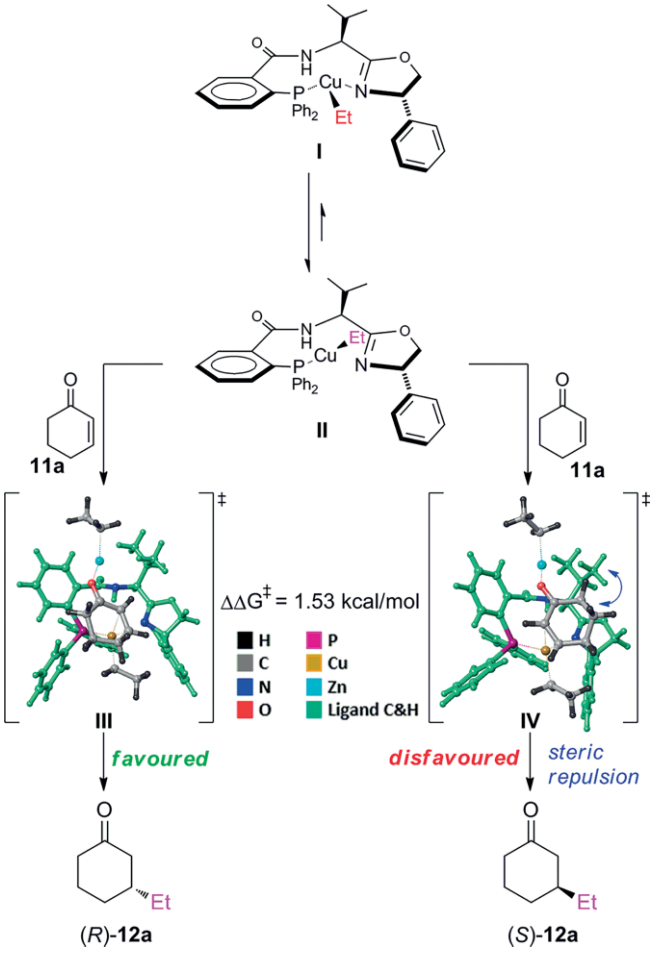
The stereoselectivity observed in the formation of **12a** can be rationalized by the stereochemical model shown in

Table 5. Substrate scope.[a]



[a] All reactions were carried out on a 0.2 mmol scale of **11a**–**11c** in toluene (0.1 M) under a nitrogen atmosphere. [b] Yield of purified product. [c] Determined by GLC analysis.

Scheme 4. This model is supported by density functional theory (DFT; M06/LACVP**) calculations carried out in toluene at 253 K using Jaguar v8.8.[16] The calculations showed that monodentate Cu species **II** was more prone than bidentate Cu species **I** to interact with the π* orbital of **11a**. A similar trend of bidentate vs. monodentate ligand–metal complexes for allylic substitutions with NHC–Cu (NHC = N-heterocyclic carbene) complexes was also reported by Hoveyda and co-workers.[17] They proposed that it was the monodentate NHC–Cu complex, rather than the bidentate form, that was involved in the addition step of a Cu catalyst to an allylic phosphate, as supported by computational studies. Transition states **III** and **IV** of the enantioselective conjugate addition of Cu complex **II** are shown in Scheme 4. Computations suggest that the energy level of transition state **III** is lower than that of transition state **IV** as a result of steric repulsion between the *i*Pr group and **11a** ($\Delta\Delta G^{\ddagger}_{253}$ = 1.53 kcal/mol); this is consistent with the experimental results. This stereochemical model also clarifies why the substituents on the chiral centre in the oxazoline moiety of P,N ligands, such as Me, *i*Pr, Ph, or Bn, are not crucial for the stereoselectivity in the formation of **12a** (Table 4, entries 2–5). As shown in Scheme 4, the substituent in question is well removed from the Cu centre, so it is unlikely to influence the enantioselectivity. The role of the substituent is presumably to block the bottom-face approach of **11a** to Cu complex **II**. Moreover, this hypothesis can explain why valine-based ligand **7a** is better than *tert*-leucine-based ligand **7b** for enantioselective conjugate additions to cyclic enones. The alkyl substituent — *i*Pr or *t*Bu — in the bridging moiety is relatively close to **11a** during the reaction, and steric repulsion would be expected between the *t*Bu group and **11a** in transition state **III**.



Scheme 4. Stereochemical model.

Conclusions

We have demonstrated Cu-catalysed enantioselective conjugate additions to nitroalkenes and cyclic enones with simple alkylzinc reagents. To facilitate these reactions, new phosphino-oxazoline ligands **7a**–**7h** were synthesized. We found that the **7a**–CuTc complex was optimal for enantioselective conjugate additions to cyclic enones, and that the **7b**–CuTc complex was optimal for enantioselective conjugate additions to nitroalkenes. Even a 1 mol-% catalyst loading of **7b**–CuTc facilitated the desired reactions in good yield with high stereoselectivity. Further investigations will focus on computational studies to determine the origin of the high stereoselectivity in the formation of the chiral nitroalkanes. In addition, the expansion of the substrate scope, especially to aryl-substituted (*E*)-nitroalkenes, will be investigated further.

Experimental Section

General Remarks: Melting points of solid compounds were measured with a Metler Toledo MP50 instrument. ^{1}H NMR spectra were recorded with a Bruker Avance III 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance as an internal standard ($CDCl_3$: δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. s = broad singlet, m = multiplet), coupling constant [Hz], and integration. ^{13}C NMR spectra were recorded with a Bruker Avance III 400 (100 MHz) spectrometer with complete broadband decoupling. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance as an internal standard ($CDCl_3$: δ = 77.16 ppm). High-resolution mass spectrometry was carried out with a Bruker Daltonics 7 T SolariX XR instrument in positive mode at the department of Chemistry, Kyungpook National University. Unless otherwise stated, all reactions were carried out under an atmosphere of dry N_2 in oven-dried (100 °C) glassware using vacuum-line techniques. Distilled solvents, including CH_2Cl_2, Et_2O, tetrahydrofuran, benzene, toluene, and dimethylformamide, were purchased from Sigma–Aldrich sealed with Sure/Seal™, and used directly. All work-up and purification procedures were carried out with reagent-grade solvents (purchased from Daejung Chemicals & Metals Co., Ltd) in air. Enantiomeric ratios were determined by GLC analysis [Alltech Associated lipodex E column (30 m × 0.25 mm), γ-dex column (30 m × 0.25 mm)], or HPLC analysis [Chiral Technologies Chiralpak® OJ-H column (250 × 4.6 mm)] in comparison with authentic racemic materials. Specific rotations were measured with a Kruss P3000 automatic polarimeter.

Representative Procedure for the Synthesis of P,N Ligands: An oven-dried round-bottomed flask (250 mL) equipped with a magnetic stirrer bar was sealed with a septum and evacuated using a Schlenk line. The reaction vessel was filled with inert N_2 gas using an N_2 balloon. Cbz-protected valine (2.51 g, 10 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT; 1.93 g, 11 mmol), and THF (50 mL) were added to the flask. *N*-Methylmorpholine (NMM; 3.3 mL, 30 mmol) was added by syringe, and the mixture was stirred at

22 °C for 2 h. (*S*)-Phenylglycinol (1.38 g, 10 mmol) was added, and the resulting solution was stirred at 22 °C for 10 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (30 mL). The solution was diluted with ethyl acetate (EtOAc), and the organic layer was transferred into a beaker (200 mL) by using a separatory funnel. The aqueous layer was washed with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was used directly in the next step without further purification.

The crude product was dissolved in CH_2Cl_2 (100 mL) in a round-bottomed flask (250 mL) equipped with a magnetic stirrer bar. 4-(Dimethylamino)pyridine (DMAP; 122 mg, 1 mmol), *p*-toluenesulfonyl chloride (2.09 g, 11 mmol), and triethylamine (4.18 mL, 30 mmol) were added sequentially. The mixture was stirred at 22 °C for 24 h, and then the reaction was quenched with a saturated aqueous solution of ammonium chloride (30 mL). The organic layer was transferred into a beaker (200 mL) by using a separatory funnel, and the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2/acetone, 95:5; note the products are less soluble in an EtOAc/hexanes eluent system) to give Cbz-protected mono-oxazoline **6a** (3.10 g, 8.8 mmol, 88 %).

N-Cbz-protected mono-oxazoline **6a** (700 mg, 1.98 mmol), Pd/C (10 %; 70 mg, 10 wt.-%), and anhydrous methanol (5 mL) were added to an oven-dried round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. The flask was evacuated and then filled with H_2 gas using an H_2 balloon. The solution was stirred at 22 °C for 3 h, and then the balloon was removed. The hydrogenolysis reaction was quenched by passing the mixture through a short plug of Celite, which was then washed with methanol (3 × 2 mL). The filtrate was concentrated in vacuo to give the amino-oxazoline, which was used directly in the next step without further purification.

2-Diphenylphosphinobenzoic acid (606 mg, 1.98 mmol), CDMT (382 mg, 2.18 mmol), and THF (5 mL) were added to an oven-dried round-bottomed flask (25 mL) equipped with a magnetic stirrer bar. NMM (0.65 mL, 5.94 mmol) was added by syringe, and the mixture was stirred at 22 °C for 1 h. A solution of the amino-oxazoline in THF (3 mL) was added by cannula, and the resulting solution was stirred at 22 °C for 12 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (8 mL). The solution was diluted with EtOAc, and the organic layer was transferred into a beaker (50 mL) by using a separatory funnel. The aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/hexanes, 1:3) to give ligand **7a** (590 mg, 1.16 mmol, 59 %) as a white solid.

The ^1H and ^{13}C NMR spectroscopic data of **6a–6c**[12] and **6d**–**6e**[18] were consistent with those reported in the literature.

2-(Diphenylphosphanyl)-*N*-{(*S*)-2-methyl-1-[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]propyl}benzamide (7a): White solid (59 %). M.p. 105 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2 H), 7.35–7.24 (m, 16 H), 6.96 (qd, *J* = 4.0, 0.8 Hz, 1 H), 6.72 (d, *J* = 8.8 Hz, 1 H), 5.17 (dd, *J* = 10.0, 8.4 Hz, 1 H), 4.86 (dd, *J* = 8.8, 4.8 Hz, 1 H), 4.64 (dd, *J* = 10.0, 8.4 Hz, 1 H), 4.16–4.09 (m, 1 H), 2.19–2.1 (m, 1 H), 0.94 (dd, *J* = 6.8, 2.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 167.7, 141.9, 137.4, 136.3, 134.5, 133.9, 133.7, 130.2, 128.8, 128.6, 128.5, 128.4, 127.7, 126.7, 75.4, 69.2, 53.0, 31.6, 18.7, 18.0 ppm. $[\alpha]_D^{23}$ = +6.54 (*c* = 0.31, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{32}H_{31}N_2NaO_2P$ $[M + Na]^+$ 529.2021; found 529.2015.

N-{(S)-2,2-Dimethyl-1-[(S)-4-phenyl-4,5-dihydrooxazol-2-yl]propyl}-2-(diphenylphosphanyl)benzamide (7b): White solid (64 %). M.p. 98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (qd, *J* = 3.6. 1.2 Hz, 1 H), 7.37–7.26 (m, 17 H), 7.00 (qd, *J* = 3.6. 1.2 Hz, 1 H), 6.74 (d, *J* = 9.6 Hz, 1 H), 5.21 (dd, *J* = 10.2, 8.2 Hz, 1 H), 4.84 (d, *J* = 9.6 Hz, 1 H), 4.63 (dd, *J* = 10.0, 8.4 Hz, 1 H), 4.16 (t, *J* = 8.2 Hz, 1 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 142.0, 134.6, 133.9, 133.7, 130.3, 128.8, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 127.7, 127.5, 126.7, 75.0, 69.4, 55.9, 35.2, 26.7 ppm. $[\alpha]_D^{23}$ = –12.3 (*c* = 0.16, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{33}H_{33}N_2NaO_2P$ $[M + Na]^+$ 543.2177; found 543.2171.

N-{(S)-1-[(S)-4-Benzyl-4,5-dihydrooxazol-2-yl]-2,2-dimethylpropyl}-2-(diphenylphosphanyl)benzamide (7c): White solid (66 %). M.p. 90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (qd, *J* = 4.0, 1.2 Hz, 1 H), 7.42 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.37–7.21 (m, 16 H), 7.01 (qd, *J* = 4.0, 0.8 Hz, 1 H), 6.70 (d, *J* = 9.6 Hz, 1 H), 4.70 (d, *J* = 9.6 Hz, 1 H), 4.42–4.35 (m, 1 H), 4.18 (t, *J* = 9.0 Hz, 1 H), 4.06–3.98 (m, 1 H), 3.07 (dd, *J* = 13.6, 5.6 Hz, 1 H), 2.65 (dd, *J* = 13.8, 8.6 Hz, 1 H), 0.96 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 166.6, 141.5, 137.9, 137.4, 136.7, 134.6, 133.9, 133.9, 133.7, 133.7, 130.3, 129.2, 128.8, 128.6, 128.6, 128.5, 128.4, 127.7, 127.6, 126.6, 71.9, 67.0, 55.9, 41.9, 35.2, 26.7 ppm. $[\alpha]_D^{23}$ = –12.0 (*c* = 0.17, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{34}H_{35}N_2NaO_2P$ $[M + Na]^+$ 557.2334; found 557.2329.

N-{(S)-2,2-Dimethyl-1-[(S)-4-methyl-4,5-dihydrooxazol-2-yl]propyl}-2-(diphenylphosphanyl)benzamide (7d): White solid (57 %). M.p. 109 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (qd, *J* = 3.6. 1.2 Hz, 1 H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.36–7.25 (m, 11 H), 7.00 (qd, *J* = 4.0, 0.8 Hz, 1 H), 6.67 (d, *J* = 9.6 Hz, 1 H), 4.70 (d, *J* = 9.6 Hz, 1 H), 4.31 (dd, *J* = 9.2, 8.0 Hz, 1 H, 1 H), 4.2–4.14 (m, 1 H), 3.84 (dd, *J* = 8.0, 6.8 Hz, 1 H), 1.26 (d, *J* = 6.4 Hz, 3 H), 0.96 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 165.7, 141.5, 137.6, 137.5, 137.4, 134.5, 134.0, 133.9, 133.8, 133.7, 130.3, 128.7, 128.6, 128.5, 128.5, 128.4, 127.7, 127.6, 73.9, 61.2, 55.8, 35.3, 26.6, 21.6 ppm. $[\alpha]_D^{23}$ = –27.3 (*c* = 0.11, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{28}H_{31}N_2NaO_2P$ $[M + Na]^+$ 481.2021; found 481.2018.

2-(Diphenylphosphanyl)-N-{(S)-2-methyl-1-[(R)-4-phenyl-4,5-dihydrooxazol-2-yl]propyl}benzamide (7e): White solid (62 %). M.p. 111 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 1 H), 7.37–7.21 (m, 16 H), 6.96 (qd, *J* = 4.0, 0.8 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 5.17 (t, *J* = 10.4 Hz, 1 H), 4.81 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1 H), 4.67 (dd, *J* = 10.4, 8.4 Hz, 1 H), 4.10–4.00 (m, 1 H), 2.21–2.14 (m, 1 H), 0.96 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 167.7, 141.9, 137.5, 134.5, 134.0, 133.9, 133.8, 130.3, 128.8, 128.7, 128.5, 127.8, 126.8, 75.4, 69.5, 53.1, 31.8, 18.8 ppm. $[\alpha]_D^{23}$ = +4.25 (*c* = 0.23, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{32}H_{31}N_2NaO_2P$ $[M + Na]^+$ 529.2021; found 529.2016.

N-{(S)-1-[(S)-4-Benzyl-4,5-dihydrooxazol-2-yl]-2-methylpropyl}-2-(diphenylphosphanyl)benzamide (7f): White solid (64 %). M.p. 97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (ddd, *J* = 7.6, 3.6, 1.2 Hz, 1 H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.32–7.26 (m, 13 H), 7.20 (t, *J* = 5.2 Hz, 2 H), 6.97 (ddd, *J* = 7.6, 3.6, 0.8 Hz, 1 H), 6.63 (d, *J* = 8.8 Hz, 1 H), 4.71 (dd, *J* = 8.8, 4.4 Hz, 1 H), 4.39–4.31 (m, 1 H), 4.20 (t, *J* = 8.8 Hz, 1 H), 4.01–3.99 (m, 1 H), 3.00 (dd, *J* = 13.8, 5.6 Hz, 1 H), 2.66 (dd, *J* = 13.8, 8.0 Hz, 1 H), 2.10–2.02 (m, 1 H), 0.85 (t, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 166.7, 141.4, 141.2, 137.8, 137.6, 137.4, 136.4, 134.5, 133.9, 133.8, 130.3, 129.3, 128.7, 128.6, 128.5, 128.4, 127.7, 126.6, 72.6, 67.1 53.0, 41.8, 31.5, 18.6, 17.9 ppm. $[\alpha]_D^{23}$ = –20.5 (*c* = 0.39, $CHCl_3$). HRMS (ESI^+): calcd. for $C_{33}H_{33}N_2NaO_2P$ $[M + Na]^+$ 543.2177; found 543.2172.

2-(Diphenylphosphanyl)-N-{(S)-2-methyl-1-[(S)-4-methyl-4,5-dihydrooxazol-2-yl]propyl}benzamide (7g): White solid (58 %). M.p.

132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (qd, J = 8.0. 1.2 Hz, 1 H), 7.41 (td, J = 7.6, 1.2 Hz, 1 H), 7.35–7.27 (m, 11 H), 6.99 (qd, J = 4.0, 1.2 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H), 4.73 (dd, J = 8.6, 4.6 Hz, 1 H), 4.35 (dd, J = 9.2, 8.0 Hz, 1 H), 4.20–4.14 (m, 1 H), 3.84 (dd, J = 8.0, 7.6 Hz, 1 H), 2.10 (quintet of doublets, J = 6.8, 4.8 Hz, 1 H), 1.26 (d, J = 6.8 Hz, 3 H), 0.89 (dd, J = 7.2, 4.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 165.9, 137.5, 137.4, 134.4, 133.9, 133.8, 130.3, 128.7, 128.7, 128.6, 128.5, 128.4, 127.7, 127.7, 74.4, 61.1, 52.9, 31.6, 21.5, 18.6, 18.1 ppm. $[\alpha]_D^{23}$ = –18.5 (c = 0.11, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{27}H_{29}N_2NaO_2P$ [M + Na]$^+$ 467.1864; found 467.1858.

2-(Diphenylphosphanyl)-*N*-{(*S*)-1-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]-2-methylpropyl}benzamide (7h): White solid (61 %). M.p. 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (qd, J = 8.0. 1.2 Hz, 1 H), 7.38 (td, J = 7.6, 1.2 Hz, 1 H), 7.33–7.25 (m, 10 H), 6.98 (qd, J = 4.0, 1.2 Hz, 1 H), 6.66 (d, J = 8.4 Hz, 1 H), 4.72 (dd, J = 8.8, 4.8 Hz, 1 H), 4.25 (dt, J = 8.8, 1.2 Hz, 1 H), 4.00 (t, J = 8.0 Hz, 1 H), 3.89–3.84 (m, 1 H), 2.11–2.04 (m, 1 H), 1.72 (septet, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 6 H), 0.87 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 166.0, 141.6, 141.3, 137.6, 137.5, 137.4, 136.7, 136.4, 134.4, 134.0, 133.9, 133.7, 130.2, 128.7, 128.6, 128.5, 128.4, 127.6, 127.5, 71.6, 70.7, 53.0, 32.7, 31.5, 18.8, 18.6, 18.3, 18.0 ppm. $[\alpha]_D^{23}$ = –22.7 (c = 0.66, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{29}H_{33}N_2NaO_2P$ [M + Na]$^+$ 495.2177; found 495.2171.

Representative Procedure for the Cu-Catalysed Enantioselective Conjugate Addition to (*E*)-Nitroalkenes with R_2Zn Reagents: An oven-dried round-bottomed flask (10 mL) equipped with a magnetic stirrer bar was sealed with a septum, and evacuated using a Schlenk line. The reaction vessel was filled with inert N_2 gas using an N_2 balloon. Compound **7b** (3.1 mg, 6 μmol), copper(I) thiophene-2-carboxylate (CuTc; 0.77 mg, 4 μmol), and toluene (1.6 mL) were then added. The mixture was stirred for 1 h at 22 °C, then it was cooled to 0 °C in an ice bath, and Et_2Zn (1.0 M in hexanes; 0.4 mL, 0.4 mmol) was added slowly by syringe. Compound **8a** (35.4 mg, 0.2 mmol) was then added by microsyringe, and the solution was stirred at 0 °C for 2 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (4 mL). The solution was diluted with Et_2O, and the organic layer was separated by using a pipette with a bulb. The aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (Et_2O/hexanes, 1:30) to give [3-(nitromethyl)pentyl]benzene (**9a**; 38.1 mg, 0.18 mmol, 92 %) as a colourless oil.

[3-(Nitromethyl)pentyl]benzene (9a): Colourless oil (92 % yield); 90 % *ee* determined by HPLC [Daicel Chiralcel OJ-H column (250 × 4.6 mm), *n*-hexane/*i*PrOH, 95:5, 1.0 mL min^{-1}, 225 nm; t_{minor} = 8.768 min, t_{major} = 9.156 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 2 H), 7.24–7.20 (m, 3 H), 4.40 (dd, J = 6.6, 1.4 Hz, 2 H), 2.69 (td, J = 8.0, 2.0 Hz, 2 H), 2.27–2.20 (m, 1 H), 1.77–1.70 (m, 2 H), 1.59–1.48 (m, 2 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 128.5, 128.3, 126.1, 79.0, 38.5, 32.7, 32.6, 23.9, 10.4 ppm. $[\alpha]_D^{23}$ = –6.17 (c = 0.33, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{12}H_{17}NNaO_2$ [M + Na]$^+$ 230.1157; found 230.1152.

2-Methyl-1-nitrobutane (9b): Colourless oil (69 % yield); 90 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 65 °C, FID; t_{major} = 23.280 min, t_{minor} = 27.935 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[19] $[\alpha]_D^{23}$ = +6.06 (c = 0.18, $CHCl_3$).

3-(Nitromethyl)hexane (9c): Colourless oil (79 % yield); 91 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 80 °C, FID; t_{minor} = 31.191 min, t_{major} = 32.346 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (d, J = 6.8 Hz, 2 H), 2.19–2.13 (m, 1 H), 1.44–1.29 (m, 6 H), 0.95–0.92 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.5, 38.8, 33.2, 24.1, 19.6, 14.2, 10.6 ppm. $[\alpha]_D^{23}$ = +3.83 (c = 0.27, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_7H_{15}NNaO_2$ [M + Na]$^+$ 168.1000; found 168.0995.

2-Methyl-3-(nitromethyl)pentane (9d): Colourless oil (72 % yield); 86 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 70 °C, FID; t_{minor} = 59.186 min, t_{major} = 61.336 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[20] $[\alpha]_D^{23}$ = +3.11 (c = 0.24, $CHCl_3$).

3-(Nitromethyl)heptane (9e): Colourless oil (82 % yield); 90 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 70 °C, FID; t_{minor} = 94.872 min, t_{major} = 96.787 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (d, J = 6.8 Hz, 2 H), 2.17–2.11 (m, 1 H), 1.44–1.37 (m, 2 H), 1.35–1.27 (m, 6 H), 0.94–0.88 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.4, 38.3, 30.4, 28.4, 23.9, 22.7, 13.9, 10.4 ppm. $[\alpha]_D^{23}$ = +5.56 (c = 0.18, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_8H_{17}NNaO_2$ [M + Na]$^+$ 182.1157; found 182.1151.

2-Methyl-4-(nitromethyl)hexane (9f): Colourless oil (87 % yield); 89 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 90 °C, FID; t_{minor} = 18.627 min, t_{major} = 21.315 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (dd, J = 6.6, 3.0 Hz, 2 H), 2.42–2.18 (m, 1 H), 1.67–1.60 (m, 1 H), 1.46–1.37 (m, 2 H), 1.30–1.22 (m, 1 H), 1.16–1.11 (m, 1 H), 0.92–0.87 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.7, 40.5, 36.8, 25.2, 24.4, 22.8, 22.6, 10.4 ppm. $[\alpha]_D^{23}$ = +3.70 (c = 0.27, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_8H_{17}NNaO_2$ [M + Na]$^+$ 182.1157; found 182.1152.

2,2-Dimethyl-3-(nitromethyl)pentane (9g): Colourless oil (84 % yield); 59 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 80 °C, FID; t_{major} = 31.831 min, t_{minor} = 33.242 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (dd, J = 12.8, 5.2 Hz, 1 H), 4.18 (dd, J = 12.8, 7.0 Hz, 1 H), 2.00–1.95 (m, 1 H), 1.67 (ddd, J = 14.4, 7.6, 3.6 Hz, 1 H), 1.25–1.13 (m, 1 H), 0.96 (t, J = 7.2 Hz, 3 H), 0.92 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.8, 49.4, 33.7, 28.7, 27.6, 22.1, 13.3 ppm. HRMS (ESI$^+$): calcd. for $C_8H_{17}NNaO_2$ [M + Na]$^+$ 182.1157; found 182.1151.

(1-Nitrobutan-2yl)cyclohexane (9h): Colourless oil (88 % yield); 90 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 120 °C, FID; t_{minor} = 23.265 min, t_{major} = 23.998 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[7e] $[\alpha]_D^{23}$ = +6.47 (c = 0.29, $CHCl_3$).

(*R*)-1,1-Dimethoxy-2-(nitromethyl)butane (9i): Colourless oil (73 % yield); 90 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 100 °C, FID; t_{minor} = 24.562 min, t_{major} = 27.148 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[7e] $[\alpha]_D^{23}$ = –4.72 (c = 0.26, $CHCl_3$); lit.[7e] value for the (*S*) enantiomer $[\alpha]_D^{23}$ = +4.44 (c = 0.54, $CHCl_3$).[7e]

{[2-(Nitromethyl)butoxy]methyl}benzene (9j): Colourless oil (91 % yield); 77 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 120 °C, FID; t_{major} = 129.759 min, t_{minor} = 132.681 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 4.58–4.46 (m, 3 H), 4.38 (dd, J = 12.2, 6.6 Hz, 1 H), 3.52 (dd, J = 9.6, 4.4 Hz, 1 H), 3.43 (dd, J = 9.6, 6.8 Hz, 1 H), 2.42 (ddd, J = 14.0, 6.4, 4.4 Hz, 1 H), 1.54–1.40 (m, 2 H), 0.95 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 128.6, 127.9, 127.7, 77.4, 73.4, 69.6, 39.9, 22.0, 11.2 ppm. $[\alpha]_D^{23}$ = –12.3 (c = 0.24, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{12}H_{17}NNaO_3$ [M + Na]$^+$ 246.1106; found 246.1102.

(1-Nitrobutan-2yl)benzene (9k): Colourless oil (87 % yield); 26 % *ee* determined by HPLC [Daicel Chiralcel OJ-H column

(250 × 4.6 mm), *n*-hexane/*i*PrOH, 95:5, 1.0 mL min^{-1}, 225 nm; t_{minor} = 10.014 min, t_{major} = 10.861 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[7c]

Ethyl 2-(Nitromethyl)butanoate (9l): Colourless oil (50 % yield); 3 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 100 °C, FID; t_{major} = 42.328 min, t_{minor} = 43.328 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (dd, *J* = 14.4, 9.2 Hz, 1 H), 4.42 (dd, *J* = 14.4, 5.0 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3.17–3.10 (m, 1 H), 1.77–1.64 (m, 2 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 75.1, 61.5, 44.4, 22.7, 14.3, 11.1 ppm. HRMS (ESI$^+$): calcd. for $C_7H_{13}NNaO_4$ [M + Na]$^+$ 198.0742; found 198.0737.

(3-Methyl-4-nitrobutyl)benzene (9m): Colourless oil (74 % yield); 65 % *ee* determined by HPLC [Daicel Chiralcel OJ-H column (250 × 4.6 mm), *n*-hexane/*i*PrOH, 95:5, 1.0 mL min^{-1}, 225 nm; t_{minor} = 10.998 min, t_{major} = 11.860 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[21] $[\alpha]_D^{23}$ = +16.4 (*c* = 0.31, $CHCl_3$).

[4-Methyl-3-(nitromethyl)pentyl]benzene (9n): Colourless oil (88 % yield); 32 % *ee* determined by HPLC [Daicel Chiralcel OJ-H column (250 × 4.6 mm), *n*-hexane/*i*PrOH, 95:5, 1.0 mL min^{-1}, 225 nm; t_{minor} = 8.246 min, t_{major} = 8.795 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H), 7.22–7.19 (m, 3 H), 4.45 (dd, *J* = 12.0, 6.8 Hz, 1 H), 4.35 (dd, *J* = 12.0, 7.2 Hz, 1 H), 2.67 (t, *J* = 8.2 Hz, 2 H), 2.25–2.22 (m, 1 H), 1.88–1.75 (m, 2 H), 1.66–1.57 (m, 1 H), 0.96 (dd, *J* = 13.2, 8.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 128.5, 128.3, 126.1, 77.7, 42.9, 33.3, 30.5, 28.5, 18.9, 18.7 ppm. $[\alpha]_D^{23}$ = +2.07 (*c* = 0.29, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{13}H_{19}NNaO_2$ [M + Na]$^+$ 244.1313; found 244.1307.

[3-(Nitromethyl)heptyl]benzene (9o): Colourless oil (85 % yield); 76 % *ee* determined by HPLC [Daicel Chiralcel OJ-H column (250 × 4.6 mm), *n*-hexane/*i*PrOH, 95:5, 1.0 mL min^{-1}, 225 nm; t_{minor} = 6.974 min, t_{major} = 7.495 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2 H), 7.22–7.16 (m, 3 H), 4.36 (d, *J* = 6.8 Hz, 2 H), 2.65 (t, *J* = 8.0 Hz, 2 H), 2.28–2.21 (m, 1 H), 1.73–1.68 (m, 2 H), 1.45–1.38 (m, 2 H), 1.33–1.29 (m, 4 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 128.5, 128.3, 126.1, 79.4, 37.1, 33.2, 32.6, 30.9, 28.3, 22.7, 13.9 ppm. $[\alpha]_D^{23}$ = +4.24 (*c* = 0.24, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{14}H_{21}NNaO_2$ [M + Na]$^+$ 258.1470; found 258.1464.

Larger-Scale Synthesis and Preparation of Amide 10: An oven-dried round-bottomed flask (100 mL) equipped with a magnetic stirrer bar was sealed with a septum, and evacuated using a Schlenk line. The reaction vessel was filled with inert N_2 gas using an N_2 balloon. Ligand **6b** (28.6 mg, 55 μmol), copper(I) thiophene-2-carboxylate (CuTc; 9.53 mg, 50 μmol), and toluene (10 mL) were added to the flask. The mixture was stirred for 2 h at 22 °C, then additional toluene (30 mL) was added. The mixture was cooled to 0 °C in an ice bath. Et_2Zn (1.0 M in hexanes; 10 mL, 10 mmol) was added slowly by syringe. (*E*)-1-Nitrohex-1-ene (**8e**; 645.8 mg, 5 mmol) was added by syringe, and the solution was left in a fridge for 24 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (30 mL). The solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (Et_2O/petroleum ether, 1:30) to give 3-(nitromethyl)heptane (**9e**; 620 mg, 3.90 mmol, 78 %).

Compound **9e** (500 mg, 3.14 mmol), Pd/C (10 %; 50 mg, 10wt.-%), and anhydrous methanol (10 mL) were added to an oven-dried round-bottomed flask (25 mL) equipped with a magnetic stirrer bar. The flask was evacuated and filled with H_2 gas by using an H_2 balloon. The solution was stirred at 22 °C for 12 h, and then the balloon was removed. The hydrogenolysis reaction was quenched by passing the mixture through a short plug of Celite, which was then washed with methanol (3 × 5 mL). The filtrate was concentrated in vacuo to give the corresponding amine, which was used directly in the next step without further purification.

N-(4-Bromobenzoyl)-L-proline (936 mg, 3.14 mmol), CDMT (551 mg, 3.14 mmol), and THF (10 mL) were added to an oven-dried round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. NMM (1.03 mL, 9.42 mmol) was added by syringe, and the mixture was stirred at 22 °C for 2 h. A solution of the amine in THF (8 mL) was added by cannula, and the resulting solution was stirred at 22 °C for 12 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (15 mL). The solution was diluted with EtOAc, and the organic layer was transferred into a beaker (50 mL) by using a separatory funnel. The aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/hexanes) to give amide **10** (823 mg, 2.01 mmol, 64 % over two steps) as a white solid.

(2*S*)-1-(4-Bromobenzoyl)-*N*-(2-ethylhexyl)pyrrolidine-2-carboxamide (10): White solid. M.p. 87 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 6.97 (s, 1 H), 4.74 (dd, *J* = 8.0, 5.2 Hz, 1 H), 3.53–3.50 (m, 1 H), 3.46–3.40 (m, 1 H), 3.21 (t, *J* = 6.0 Hz, 2 H), 2.53–2.47 (m, 1 H), 2.11–1.98 (m, 2 H), 1.86–1.80 (m, 1 H), 1.46–1.43 (m, 1 H), 1.32–1.24 (m, 8 H), 0.89–0.85 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.3, 135.2, 131.8, 128.9, 124.9, 60.1, 50.6, 42.5, 39.4, 31.2, 29.0, 27.1, 25.6, 24.5, 23.1, 14.2, 11.1 ppm. $[\alpha]_D^{23}$ = −123.8 (*c* = 0.72, $CHCl_3$). HRMS (ESI$^+$): calcd. for $C_{20}H_{29}BrN_2NaO_2$ [M + Na]$^+$ 431.1310; found 431.1305.

Representative Procedure for the Cu-Catalysed Enantioselective Conjugate Addition to Cyclic Enones with R_2Zn Reagents: An oven-dried round-bottomed flask (10 mL) equipped with a magnetic stirrer bar was sealed with a septum and evacuated using a Schlenk line. The reaction vessel was filled with inert N_2 gas using an N_2 balloon. Ligand **6a** (3.1 mg, 6 μmol), copper(I) thiophene-2-carboxylate (CuTc; 0.77 mg, 4 μmol), and toluene (1.4 mL) were added to the flask. The mixture was stirred for 1 h at 22 °C, then it was cooled to −35 °C in a dry ice/acetone bath. Et_2Zn (1.0 M in hexanes; 0.6 mL, 0.6 mmol) was added slowly by syringe. 2-Cyclohexen-1-one (**11a**; 19.3 μL, 0.2 mmol) was added by microsyringe, and the solution was stirred at −35 °C for 4 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (4 mL). The solution was diluted with Et_2O, and the organic layer was separated by using a pipette with a bulb. The aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (Et_2O/petroleum ether, 1:20) to give 3-ethylcyclohexanone (**12a**; 18.9 mg, 0.15 mmol, 77 %) as a colourless oil.

3-Ethylcyclohexanone (12a): Colourless oil (77 % yield); 95 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 85 °C, FID; t_{major} = 13.738 min, t_{minor} = 15.394 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature;[22] $[\alpha]_D^{23}$ = +17.4 (*c* = 0.92, $CHCl_3$); lit.[23] value for the (*S*) enantiomer $[\alpha]_D^{23}$ = −15.6 (*c* = 1.00, $CHCl_3$).

3-Ethylcycloheptanone (12b): Colourless oil (51 % yield); 94 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 85 °C, FID; t_{minor} = 24.872 min, t_{major} = 25.267 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[22] $[\alpha]_D^{23}$ = +55.9 (*c* = 0.42, $CHCl_3$).

3-(1-Methylethyl)cyclopentanone (12c): Colourless oil (71 % yield); 83 % *ee* determined by GC [Lipodex E column

(30 m × 0.25 mm), 70 °C, FID; t_{minor} = 24.466 min, t_{major} = 24.911 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[22] $[\alpha]_D^{23}$ = +152 (*c* = 0.25, $CHCl_3$).

3-(1-Methylethyl)cyclohexanone (12d): Colourless oil (84 % yield); 94 % *ee* determined by GC [Lipodex E column (30 m × 0.25 mm), 85 °C, FID; t_{major} = 21.116 min, t_{minor} = 25.165 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[22] $[\alpha]_D^{23}$ = +17.3 (*c* = 0.42, $CHCl_3$).

3-Butylcyclohexanone (12e): Colourless oil (67 % yield); 87 % *ee* determined by GC [γ-dex column (30 m × 0.25 mm), 100 °C, FID; t_{minor} = 54.160 min, t_{major} = 55.178 min]. ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[22] $[\alpha]_D^{23}$ = +26.4 (*c* = 0.32, $CHCl_3$).

Acknowledgments

This research was supported by the Undergraduate Research Program (UGRP) funded by DGIST.

Keywords: Asymmetric catalysis · Michael addition · Nucleophilic addition · N,P ligands · Ligand design · Zinc

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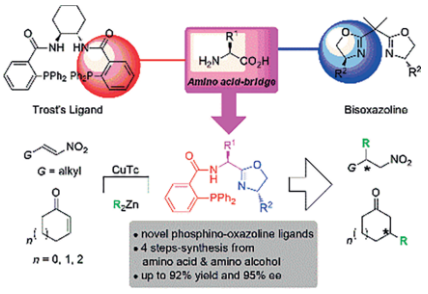
Received: March 24, 2018

Asymmetric Catalysis



New phosphino-oxazoline ligands have been developed, and the ligands have been used for Cu-catalysed enantioselective conjugate additions to (*E*)-nitroalkenes.

DOI: 10.1002/ejoc.201800476

