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New bis(1-ferrocenylethyl)amine-derived monodentate phosphoramidite ligands for highly enantioselective copper-catalyzed 1,4-conjugate addition

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ABSTRACT

A new family of chiral bis(1-ferrocenylethyl)amine-derived monodentate phosphoramidite ligands has been prepared and successfully applied in the Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to a variety of α,β-unsaturated compounds, in which up to 99% ee was obtained for nitroalkenes at −78 °C and >98% ee for cyclohexenone at −30 °C, comparable to or higher than those obtained with the most efficient monophosphoramidite ligands reported so far.

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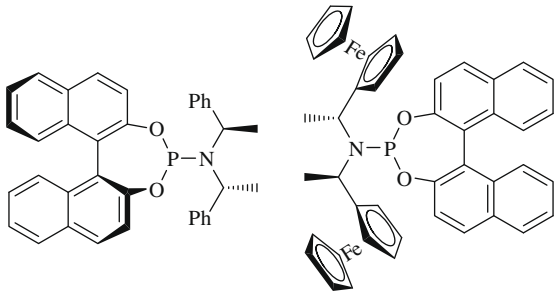
1. Introduction

Enantioselective conjugate addition of organometallic reagents to α,β-unsaturated compounds provides a powerful method for the construction of carbon–carbon bonds bearing a new stereogenic center.[1] One of the most important developments in this area over past several years has been focused on the use of the copper salt combined with chiral monodentate phosphoramidite ligands. Following the pioneering studies from the groups of Alexakis[2] and Feringa,[3] many phosphoramidite ligands have been synthesized and successfully applied in the Cu-catalyzed 1,4-conjugate addition of organozinc reagents to a variety of α,β-unsaturated acceptors.[4] The common structural feature of these phosphoramidite ligands is the existence of a sterically demanding secondary amine moiety, as well as a C_2-symmetrical diol-based framework. It has been disclosed that bulky chiral substituents on the amine moiety of the ligand are necessary to reach high ee, and the most extensively used chiral-hindered secondary amine is commercially available chiral bis(1-phenylethyl)amine. One of the most representative ligands is developed by Feringa et al., as shown in Figure 1.[4a] Although good enantioselectivity could be achieved in the Cu-catalyzed enantioselective conjugate addition of Et_2Zn to cycloalkenones and aliphatic nitroalkenes, the enantioselectivity for addition to aromatic nitroolefins using this ligand is less satisfactory, in which only about 60% ee was obtained at low temperature (−45 °C).[5] Therefore, searching for new monophosphoramidite ligands with properties superior to their predecessors remains an important subject for chemists. Recently, Ojima et al. have reported that modification of Feringa's ligand by replacing the binaphthyl moiety with a biphenyl structure could dramatically improve the enantioselectivity of the addition product of Et_2Zn to aromatic nitroolefins.[6] Using a *tropos* benzophenone-like phosphoramidite ligand, Mikami et al. found that excellent enantioselectivity and catalytic activity could be attained in the Cu-catalyzed asymmetric 1,4-addition of diethylzinc to various nitroalkenes.[7] However, there are few successful reports on scouting for new chiral-hindered secondary amines for the construction of highly enantioselective monophosphoramidites for Cu-catalyzed 1,4-conjugate addition of organozinc reagents to aromatic nitroolefins, partly due to the difficult accessibility of chiral-hindered secondary amines. As a part of our continuous efforts in exploring new chiral ferrocene-based ligands for asymmetric catalysis,[8] we have recently developed an efficient method to manufacture chiral bis(1-ferrocenylethyl)amine. Due to the unique electronic and steric properties of the ferrocence backbone, the introduction of a ferrocene-based hindered amino moiety into the monophosphoramidite framework should greatly change the chiral environ-



Feringa's ligand **1**

(R_c,R_c,R_a)-**2a**
(R_c,R_c,S_a)-**2b**

Figure 1. Feringa's ligand **1** and our developed monophosphoramidite ligands **2a**–**b**.

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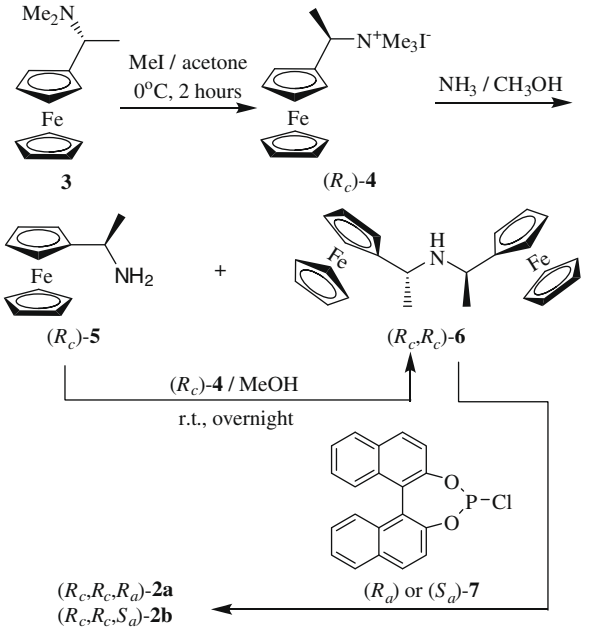
ment of the Cu-complex, which may result in greatly improved enantioselectivity. As a result, herein, we describe our studies on the development of this new class of monodentate phosphoramidite ligands **2** derived from chiral bis(1-ferrocenylethyl)amine and BINOL, for highly enantioselective Cu-catalyzed 1,4-conjugate addition of diethylzinc to various nitroalkenes, cycloalkenones, and acyclic enones. Interestingly, our research found that the central chirality in these ligands determined the absolute configuration of the addition product of Et_2Zn to nitroalkenes, while the axial chirality determined the absolute configuration of the addition product of Et_2Zn to cycloalkenones.

2. Results and discussion

2.1. Synthesis of ligands 2a–b

The monodentate phosphoramidite ligands **2** can be easily prepared from Ugi's amine **3** through a four-step transformation, which is outlined in Scheme 1. The initial step involved the synthesis of the key intermediate, bis(1-ferrocenylethyl)amine (R_c,R_c)-**6**, which was prepared from Ugi's amine **3** through the intermediacy of primary amine **5** using a modified procedure reported by Schmalz et al.[9] Thus, Ugi's amine **3** was treated with MeI in acetone at 0 °C to quantitatively form ammonium salt **4**.[10] Subsequent treatment of ammonium salt **4** with a solution of aqueous NH_3 in MeOH generated primary amine **5** as the major product and the target bis(1-ferrocenylethyl)amine (R_c,R_c)-**6** as minor product. Further treatment of the resulting primary amine **5** with ammonium salt **4** provided the corresponding bis(1-ferrocenylethyl)amine (R_c,R_c)-**6** in good yields. By the reaction of (R_c,R_c)-**6** with chlorophosphite (R_a)- or (S_a)-**7**[11] in toluene at 0 °C in the presence of 3 equiv of Et_3N as a scavenger for the HCl eliminated, diastereomeric ligands (R_c,R_c,R_a)-**2a** and (R_c,R_c,S_a)-**2b** were prepared in reasonable yields. By the use of *n*-BuLi to eliminate the proton in bis(1-ferrocenylethyl)amine (R_c,R_c)-**6,** followed by the treatment with chlorophosphite **7**, the target ligands (R_c,R_c,R_a)-**2a** and (R_c,R_c,S_a)-**2b** can be obtained in an improved yield.

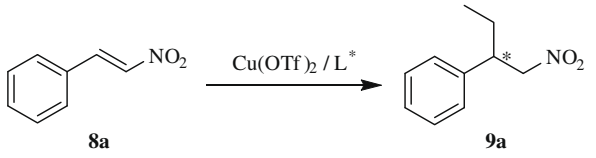


Scheme 1. Preparation of chiral bis(1-ferrocenylethyl)amine-derived monophosphoramidite ligands **2**.

2.2. Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to nitroalkenes

In the first set of experiments, we used nitrostyrene as a substrate to evaluate the efficacy of our newly developed phosphoramidite ligands **2** in the Cu-catalyzed asymmetric 1,4-conjugate addition, and the results are summarized in Table 1. Nitroalkenes, especially aromatic nitroalkenes, are still a class of challenging substrates for 1,4-conjugate addition, only some recent reports disclosed that some chiral monodentate and bidentate phosphorus-containing ligands exhibited excellent enantioselectivity for this substrate class.[5–7,12]

Table 1
Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to nitrostyrene **8a**[a]



8a **9a**

Entry	Ligand	*T* (°C)	Solvent	ee[b] (%)
1	(R_c,R_c,S_a)-**1**	−45	PhMe	59 (−)[c]
2	(R_c,R_c,R_a)-**2a**	25	PhMe	41 (*R*)
3	(R_c,R_c,S_a)-**2b**	25	PhMe	72 (*R*)
4	(R_c,R_c,S_a)-**2b**	0	PhMe	84 (*R*)
5	(R_c,R_c,S_a)-**2b**	−15	PhMe	85 (*R*)
6	(R_c,R_c,S_a)-**2b**	−30	PhMe	85 (*R*)
7	(R_c,R_c,S_a)-**2b**	−78	PhMe	97 (*R*)
8	(R_c,R_c,S_a)-**2b**	−78	Et_2O	30 (*R*)
9	(R_c,R_c,S_a)-**2b**	−78	THF	24 (*R*)
10	(R_c,R_c,S_a)-**2b**	−78	DCM	80 (*R*)

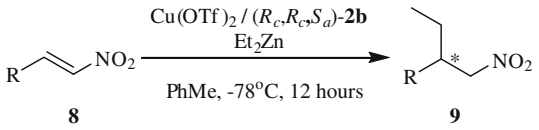
[a] Reactions were performed with 0.25 mmol of substrate in 2 mL of solvent for 12 h. The catalyst loading was 2.4 mol %. Copper salt/L* = 1/2.2, nitrostyrene/Et_2Zn = 1/1.4. Full conversions were achieved in all reactions.
[b] Enantiomeric excesses were determined by GC using a γ-DEX-225 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature.
[c] Reported by Feringa et al.

Feringa's ligand **1**, a highly efficient ligand for the Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to cyclic enones, proved to be ineffective for aromatic nitroalkenes and gave only 59% ee in the reaction of diethylzinc with nitrostyrene at low temperature (−45 °C) (entry 1).[5] Remarkably, bis(1-ferrocenylethyl)amine-derived monophosphoramidite (R_c,R_c,S_a)-**2b** showed an ee-value of 72% for this same transformation even at room temperature, indicating that (R_c,R_c,S_a)-**2b** possesses higher enantioselectivity than the corresponding Feringa's ligand **1** (entries 1 and 3). It is clear that (R_c)-central chirality and (S_a)-axial chirality are a matching configuration in this reaction since (R_c,R_c,S_a)-**2b** exhibited much better enantioselectivity than its (R_c,R_c,R_a)-diastereomer **2a** (entries 2 and 3). It is interesting that (R_c,R_c,R_a)-**2a** and (R_c,R_c,S_a)-**2b** gave the addition product with the same configuration, suggesting that the absolute configuration of the amino moiety of the ligands determined the chirality of the addition product no matter what the configuration of the binathphyl moiety was. We then used ligand (R_c,R_c,S_a)-**2b** to optimize the reaction conditions. Firstly, the effect of reaction temperature was examined. With ligand (R_c,R_c,S_a)-**2b**, a significant improvement in enantioselectivity was observed at lower reaction temperatures without affecting the reaction rate (entries 3–7). For example, the reaction with (R_c,R_c,S_a)-**2b**/$Cu(OTf)_2$ gave the addition product with 84% ee at 0 °C (entry 4). However, further lowering of the reaction temperature to −15 °C and −30 °C did not improve the enantioselectivity (entries 5 and 6). Interestingly, the reaction at −78 °C resulted in significant increased enantioselectivity, giving the addition prod-

uct in 97% ee with full conversion, comparable to those obtained by the most efficient ligands reported so far (entry 7). The solvent also had a great influence on the enantioselectivity. Thus, the reactions performed in Et_2O and THF afforded the addition product with extremely low enantioselectivity, while an excellent enantioselectivity was obtained using PhMe as solvent (entries 7–10).

Reactions of various aromatic, heteroaromatic, and alkyl nitroalkenes with diethylzinc catalyzed by (R_c,R_c,S_a)-**2b**/Cu(OTf)$_2$ were then evaluated in PhMe at −78 °C for 12 h, and the results are summaried in Table 2. As shown in the Table 2, (R_c,R_c,S_a)-**2b**/Cu(OTf)$_2$ catalytic system was highly efficient for this kind of challenging reaction, giving the best enantioselectivity of up to 99% ee. For aromatic nitroalkene substrates, the substituent on the phenyl ring has a great effect in the enantioselectivity, and the substrates with an electron-withdrawing group tended to give higher catalytic activity and enantioselectivity than those with electron-donating substituent. For example, the reaction of methyl substituted substrate **8b** provided **9b** in only 81% ee with 85% conversion (entry 2), whereas the reaction of the corresponding bromo-substituted substrate **8e** gave the addition product **9e** in 99% ee with full conversion (entry 5). Heteroaromatic nitroalkene **8f** as a substrate resulted in 93% ee with 91% conversion (entry 6). Aliphatic nitroalkene **8g** also showed good enantioselectivity (88% ee) but slightly low conversions (entry 7). Employment of 1-nitroprop-1-ene dimethylacetal **8h** as a substrate afforded the product **9h** with 94% ee and full conversion (entry 8).

Table 2
Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to nitroalkenes **8**[a]



Entry	Substrate	Conv. (%)	ee[b] (%)
1	**8a** (R = Ph)	100 (92)	97
2	**8b** (R = *p*-MeC$_6$H$_4$)	85 (78)	81
3	**8c** (R = *p*-MeOC$_6$H$_4$)	98 (81)	87
4	**8d** (R = *p*-ClC$_6$H$_4$)	100 (96)	94
5	**8e** (R = *p*-BrC$_6$H$_4$)	100 (84)	99
6	**8f** (R = 2-thienyl)	91 (87)	93
7	**8g** (R = *c*-C$_6$H$_{11}$)	62 (58)	88
8	**8h** (R = (MeO)$_2$CH)	100 (89)	94

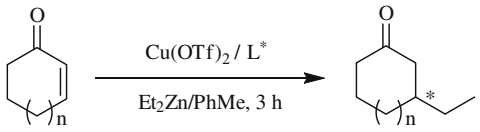
[a] Reactions were performed with 0.25 mmol of substrate in 2 mL of PhMe at −78 °C for 12 h. The catalyst loading was 2.4 mol %. Copper salt/L* = 1/2.2, nitroalkene/Et_2Zn = 1/1.4. The conversions were determined by GC and the isolated yields were provided in parentheses.

[b] Ee were determined by GC using a γ-DEX-225 capillary (0.25 mm × 30 m) column or HPLC using a Chiralcel OD column

2.3. Cu-catalyzed conjugate addition of Et_2Zn to cyclic and acyclic enones

To further demonstrate the catalytic efficiency of the newly developed monophosphoramidites **2**/Cu(OTf)$_2$ system, we next investigated their application in the catalyzed asymmetric 1,4-conjugate addition of diethylzinc to cyclohexenone. As shown in Table 3, both diastereomers were highly effective ligands for this transformation, and showed high enantioselectivity even at room temperature (97% ee and 95% ee, respectively) (entries 1 and 2). Interestingly, (R_c,R_c,R_a)-**2a** displayed higher enantioselectivity than its (R_c,R_c,S_a)-diastereomer **2b** and the configuration of the product was determined by the chirality of the binaphthyl backbone of the ligand, which is opposite to the results obtained in the reaction of nitroalkenes. The reaction was not temperature-dependent. Lowering the reaction temperature from room temperature to −30 °C slightly increased the enantioselectivity to over 98% ee by use of ligand (R_c,R_c,R_a)-**2a** (entry 7). As has been shown that monophosphoramidite/Cu-catalyzed conjugate addition to 2-cyclopentenone suffers from substantially lower enantioselectivity than that for 2-cyclohexenone using the same ligand,[4c,k] (R_c,R_c,R_a)-**2a** and (R_c,R_c,S_a)-**2b** are also ineffective for the reaction of cyclopentenone **10b**, and only gave **11b** in 37% ee and 32% ee, respectively (entries 9 and 10). For 2-cycloheptenone **10c**, (R_c,R_c,S_a)-**2b** exhibited higher enantioselectivity and gave the addition product in 98% ee (entry 12).

Table 3
Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to cyclic enones **10**[a]



Entry	Ligand	Substrate (n)	T (°C)	Conv. (%)	ee[b] (%)
1	(R_c,R_c,R_a)-**2a**	**10a**: n = 1	25	100	97 (*R*)
2	(R_c,R_c,S_a)-**2b**	**10a**: n = 1	25	100	95 (*S*)
3	(R_c,R_c,R_a)-**2a**	**10a**: n = 1	0	100	96 (*R*)
4	(R_c,R_c,S_a)-**2b**	**10a**: n = 1	0	100	96 (*S*)
5	(R_c,R_c,R_a)-**2a**	**10a**: n = 1	−15	100	98 (*R*)
6	(R_c,R_c,S_a)-**2b**	**10a**: n = 1	−15	100	96 (*S*)
7	(R_c,R_c,R_a)-**2a**	**10a**: n = 1	−30	100 (97)	>98 (*R*)
8	(R_c,R_c,S_a)-**2b**	**10a**: n = 1	−30	100 (90)	97 (*S*)
9	(R_c,R_c,R_a)-**2a**	**10b**: n = 0	−30	100 (91)	37 (*R*)
10	(R_c,R_c,S_a)-**2b**	**10b**: n = 0	−30	100 (88)	32 (*S*)
11	(R_c,R_c,R_a)-**2a**	**10c**: n = 2	−30	100 (98)	94 (*R*)
12	(R_c,R_c,S_a)-**2b**	**10c**: n = 2	−30	100 (96)	98 (*S*)

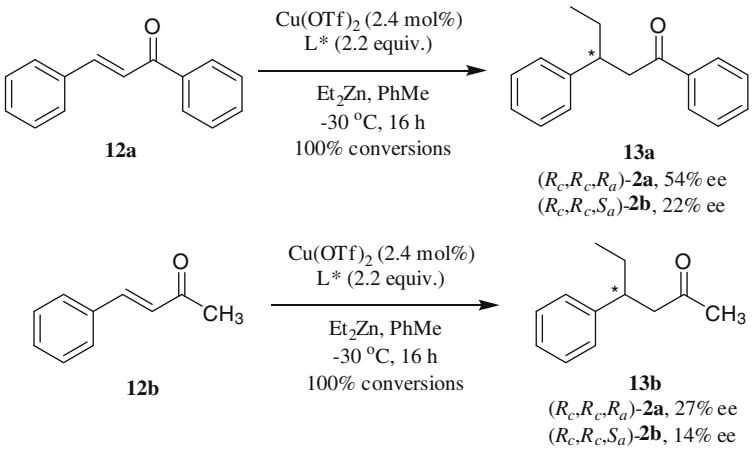
[a] Reactions were performed with 0.25 mmol of substrate in 2 mL of PhMe for 3 h. The catalyst loading was 2.4 mol %. Copper salt/L* = 1/2.2, cyclic enone/Et_2Zn = 1/1.5. Full conversions were achieved in all reactions, and the isolated yields are provided in parentheses.

[b] Enantiomeric excesses were determined by GC using a γ-DEX-225 capillary (0.25 mm × 30 m) column or a Chiral select 1000 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature.

Under optimum conditions, that is, use of 2.4 mol % of catalyst prepared in situ from Cu(OTf)$_2$ and 2.2 equiv of ligand, we examined the 1,4-addition of diethylzinc to acyclic enones (Scheme 2). However, the results suggested that these newly developed phosphoramidite compounds are inferior ligands for this reaction in term of the enantioselectivity, although full conversions were achieved in all cases. For the addition to both substrates, (R_c,R_c,R_a)-**2a** displayed higher enantioselectivity than its (R_c,R_c,S_a)-diastereomer **2b**.

3. Conclusion

In conclusion, we have developed a new family of chiral bis(1-ferrocenylethyl)amine-derived monophosphoramidite ligands for Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to a variety of substrates including aromatic nitroalkenes, aliphatic nitroalkenes, cyclic enones and acyclic enones. In the reaction of nitroalkenes, (R_c,R_c,S_a)-**2b** exhibited higher enantioselectivity than its diastereomer (R_c,R_c,R_a)-**2a**, and gave the best result in up to 99% ee with full conversion, comparable to the most efficient ligands reported so far. In the reaction of cyclic enones, both (R_c,R_c,R_a)-**2a** and (R_c,R_c,S_a)-**2b** displayed high performance, giving enantioselectivities of up to 97% ee even at room temperature, and representing one of the most efficient catalytic systems for this transformation. Interestingly, the central chirality in these monophosphoramidite ligands determined the absolute configuration of the addition product of Et_2Zn to nitroalkenes; while the axial



Scheme 2. Cu-catalyzed conjugate addition of Et_2Zn to acyclic enones **12** with monophosphoramidite ligands **2**.

chirality determined the absolute configuration of the addition product of Et_2Zn to cyclic enones. However, these ligands proved to be inefficient for the addition to acyclic enones, providing only low enantioselectivities. Further investigations of other catalytic asymmetric reactions with these monophosphoramidite ligands are underway and progress will be disclosed in due course.

4. Experimental

4.1. General

All synthetic reactions and manipulations were performed in a nitrogen or argon atmosphere using standard Schlenk techniques. Hydrogenations were carried out in a stainless steel autoclave. Solvents were reagent grade, dried, and distilled before use following the standard procedures. Nitroalkenes **8a**–**h**[13] are known compounds, which were prepared according to literature methods. All other chemicals were obtained commercially.

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on BRUKER DEX-400 spectrometer. Chemical shift values (δ) are denoted in ppm down field from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra (MS) were measured on a Agilent 6890-5973N instrument. Optical rotations were recorded using a JASCO P-1020 high sensitive polarimeter. Enantiomeric excesses were determined by chiral capillary GC and chiral HPLC analysis.

4.2. Synthesis of chiral bis(1-ferrocenylethyl)amine (R_c,R_c)-6

A solution of (*R*)-*N*,*N*,*N*-trimethyl-1-ferrocenylethyl-ammonium iodide **4** (4.0 g, 0.01 mol) and (*R*)-1-ferrocenyl-ethylamine **5** (2.3 g, 0.01 mol) in 50 mL of acetonitrile was stirred for 20 h at ambient temperature. The solvent was then removed in vacuo, and the residue was treated with 8.5% of aqueous H_3PO_4 and washed with ether. The aqueous phase was then neutralized with 20% of aqueous NaOH, and extracted with CH_2Cl_2. The combined organic phases were dried over K_2CO_3. After removal of the solvent, the residue was purified by flash chromatography and recrystallized from *n*-hexane to give 3.0 g of (R_c,R_c)-**6** as an orange solid (68% yield). Mp: 96–97 °C; $[\alpha]_D^{20} = -69.4$ (*c* 0.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.09–4.19 (m, 18H), 3.52 (q, *J* = 6.4 Hz, 2H), 1.35 (d, *J* = 6.4 Hz, 6H).

4.3. General procedure for the synthesis of monodentate phosphoramidite ligands 2

Method A: To a stirred solution of the (*R*)- or (*S*)-chlorophosphite **7** (0.35 g, 1 mmol) in toluene (2.5 mL) were added dropwise (*R*,*R*)-bis(1-ferrocenylethyl)amine **6** (0.44 g, 1 mmol) and Et_3N (3 mmol) in the same solvent (2.5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and the precipitate of $Et_3N{\cdot}HCl$ salts formed was removed by filtration. The toluene was evaporated from filtrate to give the crude product, which was further purified by Al_2O_3 column chromatography. Further purification was done through recrystallization using CH_2Cl_2/*n*-hexane.

Method B: A solution of (*R*,*R*)-bis(1-ferrocenylethyl)amine **6** (0.44 g, 1 mmol) in THF (5 mL) at −78 °C under argon was treated dropwise with *n*-butyllithium (2.5 M hexane). The reaction mixture was stirred for 1 h, and then allowed to warm to 0 °C. A solution of the (*R*)- or (*S*)-chlorophosphite **7** (0.35 g, 1 mmol) in toluene (2.5 mL) was added dropwise to the above reaction mixture. The solvent was removed, and the residue was submitted to column chromatography.

(R_c,R_c,R_a)-**2a**: orange solid (426 mg, 56.4%). Mp: 147–148 °C; $[\alpha]_D^{25} = -581$ (*c* 0.598, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.87 (m, 4H), 7.58–7.20 (m, 8H), 4.28–3.85 (m, 20H), 1.53 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 133.5, 131.9, 130.9, 129.9, 128.8, 127.7, 126.6, 125.2, 124.6, 123.7, 122.9, 122.3, 91.4, 70.2, 69.3, 68.8, 68.3, 67.7, 50.4 (d, *J* = 12.5 Hz), 23.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 152.3. HR-MS, calcd for $C_{44}H_{39}NO_2PFe_2$ (M+1): 756.1412, found: 756.1451.

(R_c,R_c,S_a)-**2b**: orange solid (459 mg, 60.8%). Mp: 152–153 °C; $[\alpha]_D^{25} = -42$ (*c* 0.518, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.86 (m, 4H), 7.55–7.21 (m, 8H), 4.16–3.98 (m, 12H), 3.65 (br, 8H), 1.52 (br, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 150.4, 149.7, 132.9, 132.8, 131.4, 130.6, 130.2, 129.2, 128.4, 128.1, 126.9, 126.8, 126.3, 126.1, 124.8, 124.7, 122.8, 122.4, 122.2, 90.7, 70.2, 68.5, 68.2, 67.2, 66.8, 49.2 (d, *J* = 13 Hz), 21.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 150.5. HR-MS, calcd for $C_{44}H_{39}NO_2PFe_2$ (M+1): 756.1412, found: 756.1428.

4.4. General procedure for asymmetric 1,4-conjugate addition

Copper salt (0.006 mmol) and ligand (0.013 mmol) in toluene (2 mL) were stirred at room temperature for 1 h. After cooling to the indicated temperature, substrate (0.25 mmol) was added and stirred for 5 min, then 0.35 mL of Et_2Zn (1 M in toluene or in hexane) was added slowly. After stirring at the indicated temperature for the indicated time (α,β-unsaturated ketones for 3 h, nitroalkenes for 12 h), the reaction was quenched by aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were washed by brine and dried over $MgSO_4$. After removal of the solvent, the residues were purified by a short silica gel column. Conversions and ee-values were determined by GC or HPLC.

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