DOI: 10.1002/adsc.201101007

Switchable Stereoselectivity: The Effects of Substituents on the D_2-Symmetric Biphenyl Backbone of Phosphoramidites in Copper-Catalyzed Asymmetric Conjugate Addition Reactions with Triethylaluminium

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Received: December 23, 2011; Revised: March 30, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201101007.

Abstract: A highly enantioselective copper-catalyzed conjugate addition with triethylaluminium was developed using phosphoramidite ligands bearing a D_2-symmetric biphenyl backbone. For these ligands we demonstrated that the 3,3′,5,5′-substituents on the biphenyl backbone can completely reverse the absolute configuration of the products.

Keywords: chirality; conjugate addition; copper; phosphoramidite ligands; stereoselectivity reversal

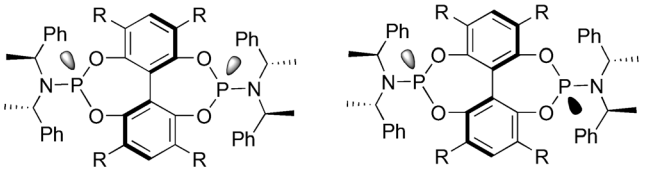
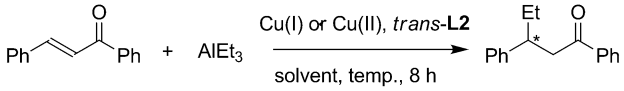


Figure 1. Phosphoramidite ligands with D_2-symmetric biphenyl backbone.

Carbon-carbon bond formation *via* the asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl substrates catalyzed by a chiral catalyst, is one of the most useful synthetic methodologies in organic synthesis.[1,2] Copper-catalyzed enantioselective addition reactions of diethylzinc to α,β-unsaturated carbonyl enones have attracted much attention in the past decade and a number of efficient copper catalysts with chiral ligands has been reported.[2–6] Among the successful chiral ligands, BINOL-,[3] TADDOL-,[4] and BIPOL-derived phosphoramidites[5] have shown remarkable enantioselectivities in the reactions of diethylzinc with enones. New types of biphenyl phosphoramidite ligands **L1–L4** containing a D_2-symmetric backbone were developed by our group (Figure 1). They provided excellent asymmetric catalytic results for the 1,4-conjugate addition of diethylzinc to α,β-unsaturated ketones and nitroalkenes. Their excellent chiral environment and their ability to be easily modified at the 3,3′,5,5′-positions of the biphenyl backbone, make phosphoramidites excellent ligands.[7]

Trialkylaluminium reagents have also been shown to be good candidates as replacements for dialkylzinc in related asymmetric copper-catalyzed conjugate additions.[8,9] A number of organoaluminium reagents is either commercially available or prepared by simple hydro- and carboalumination reactions, providing readily available nucleophilic regents. For example, triethylaluminium is produced in industry in large quantities for the Ziegler–Natta polymerization. However, in contrast to the many examples of trialkylaluminium addition to cyclic enones,[9] there are currently few reports about the conjugate addition of trialkylaluminium to acyclic α,β-unsaturated enones.[10] In particular, additions to acyclic aromatic α,β-unsaturated enones[11] such as chalcone, are not widely exploited. It was envisaged that such a synthetic route would provide valuable compounds for use as intermediates or building blocks in organic chemistry because of their easy derivatization.[12] In order to explore the behavior of phosphoramidite ligands with a D_2-symmetric biphenyl backbone, we utilized them in asymmetric conjugate additions of triethylaluminium to α,β-unsaturated acyclic aromatic enones. Excellent catalytic results were obtained.

Table 1. Screening of reaction conditions.[a]



1a 2a

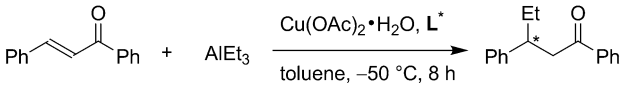
Entry	Cu salt	Solvent	Temp. [°C]	Yield [%][b]	*ee* [%][c]
1	$Cu(I)(MeCN)_4PF_6$	toluene	−30	73	48 (*R*)
2	$Cu(II)(OTf)_2$	toluene	−30	55	36 (*R*)
3	$Cu(II)(acac)_2$	toluene	−30	88	85 (*R*)
4	Cu(I)TC	toluene	−30	78	28 (*R*)
5	$Cu(I)(C_6H_6)OTf$	toluene	−30	63	60 (*R*)
6	$Cu(II)(OAc)_2{\cdot}H_2O$	toluene	−30	83	87 (*R*)
7[d]	$Cu(II)(OAc)_2{\cdot}H_2O$	toluene	−30	82	83 (*R*)
8	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−30	82	92 (*R*)
9	$Cu(II)(OAc)_2{\cdot}H_2O$	THF	−30	69	38 (*R*)
10	$Cu(II)(OAc)_2{\cdot}H_2O$	DCM	−30	81	83 (*R*)
11	$Cu(II)(OAc)_2{\cdot}H_2O$	DMF	−30	58	10 (*R*)
12	$Cu(II)(OAc)_2{\cdot}H_2O$	DIPE	−30	78	90 (*R*)
13	$Cu(II)(OAc)_2{\cdot}H_2O$	MTBE	−30	80	92 (*R*)
14[e]	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−20	84	92 (*R*)
15	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−40	80	92 (*R*)
16	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−50	79	93 (*R*)
17[f]	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−78	56	86 (*R*)
18[g]	$Cu(II)(OAc)_2{\cdot}H_2O$	Et_2O	−50	78	80 (*R*)

[a] 1 mol% Cu salt, 2 mol% ligand, 1.2 equiv. $AlEt_3$.
[b] Yield of the isolated product.
[c] Determined by HPLC, Chiralcel OJ-H column. The absolute configuration was determined by comparison with literature data.[12]
[d] 1 mol% Cu salt, 1 mol% ligand, 1.2 equiv. $AlEt_3$.
[e] The reaction mixture was stirred for 6 h.
[f] The reaction mixture was stirred for 16 h.
[g] 1 mol% Cu salt, 2 mol% ligand, 1.2 equiv. $AlMe_3$.

trans-**L2** provided excellent enantioselectivities for the asymmetric conjugate addition of diethylzinc to α,β-unsaturated carbonyl substrates and nitroalkenes.[7] The conjugate addition of triethylaluminium to chalcone **1a** was performed in the presence of 2 mol% of *trans*-**L2** and 1 mol% of copper salt in toluene, at a temperature of −30 °C (Table 1). $Cu(OAc)_2{\cdot}H_2O$ was found to be the most suitable catalyst precursor because of its high reactivity and enantioselectivity (entries 1–6). The reaction was originally performed using a 1:1 ratio of copper:ligand. The enantioselectivity of the reaction was found to be lower compared to that when the amount of ligand was increased (Cu:ligand = 1:2) (entries 6 and 7). This phenomenon was also observed in our previous reports using similar ligands.[7a,b] With *trans*-**L2** as the ligand and $Cu(OAc)_2{\cdot}H_2O$ as the copper source, we investigated the effect that the solvent had on the reaction. Ether solvents such as Et_2O, DIPE and MTBE all provided excellent results (entries 6, 8–13).

Using the aforementioned conditions and Et_2O as a solvent, the reaction was performed at varying temperatures (Table 1, entries 8, 14–16). Similarly good yields were obtained from −20 °C to −50 °C with the best enantioselectivity being observed at −50 °C. Reducing the temperature of the reaction to −78 °C re-

Table 2. Screening of ligands.[a]



1a 2a

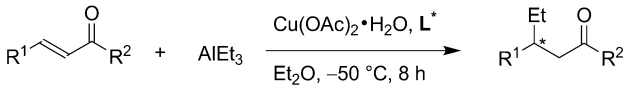
Entry	**L**	Yield [%][b]	*ee* [%][c]
1	*cis*-**L1**	78	81 (*S*)
2	*trans*-**L1**	76	68 (*S*)
3	*cis*-**L2**	80	82 (*R*)
4	*trans*-**L2**	82	93 (*R*)
5	*trans*-**L3**	81	62 (*R*)
6	*trans*-**L4**	75	56 (*R*)

[a] 1 mol% Cu salt, 2 mol% ligand, 1.2 equiv. $AlEt_3$.
[b] Yield of the isolated product.
[c] Determined by HPLC, Chiralcel OJ-H column. The absolute configuration was determined by comparison with literature data.[12]

sulted in an obvious drop in yield and a slight decrease in enantioselectivity. This was probably due to the poor solubility of the substrate in Et_2O at this temperature (entry 17). We replaced triethylaluminium with trimethylaluminium using the optimal conditions and discovered that the enantioselectivity, while still good (80% *ee*), was lower than that obtained when using triethylaluminium (entries 16 and 18).

With the optimal conditions in hand, several phosphoramidites containing a D_2-symmetric biphenyl backbone were investigated to identify the most efficient ligand. Ligand screening revealed that all the phosphoramidite ligands in Figure 1 were effective for this transformation (75–82% yield, 56–93% *ee*) (Table 2). The substituents at the 3,3′,5,5′-positions of the biphenyl backbone of the ligands showed a significant influence on the catalysis. To our surprise, both enantiomers could be obtained with high enantioselectivities (*S*-**2a**: up to 81% *ee*; *R*-**2a**: up to 93% *ee*) (entries 1 and 4) by using ligands with different substituents at the 3,3′,5,5′-positions of the D_2-symmetric biphenyl backbone. Both *cis*- and *trans*-**L1** lacking substituents at the 3,3′,5,5′-positions, gave *S* configuration products. *cis*-**L1** gave a higher enantioselectivity than *trans*-**L1** (entries 1 and 2). Ligands *cis*-**L2** and *trans*-**L2**–**L4**, containing substituents on the biphenyl backbone, all provided *R* configuration products. Up

Table 3. Scope of substrates.[a]



1a–1p **2a–2p**

Entry	Substrate	R^1	R^2	**L**	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	Ph	*cis*-**L1**	78	81 (*S*)
				trans-**L2**	82	93 (*R*)
2	**1b**	*o*-MeC_6H_4	Ph	*cis*-**L1**	79	78 (*S*)
				trans-**L2**	76	80 (*R*)
3	**1c**	*m*-MeC_6H_4	Ph	*cis*-**L1**	85	90 (*S*)
				trans-**L2**	82	94 (*R*)
4	**1d**	*p*-MeC_6H_4	Ph	*cis*-**L1**	79	90 (*S*)
				trans-**L2**	84	94 (*R*)
5	**1e**	*p*-$MeOC_6H_4$	Ph	*cis*-**L1**	81	95 (*S*)
				trans-**L2**	81	96 (*R*)
6	**1f**	*p*-BrC_6H_4	Ph	*cis*-**L1**	86	73 (*S*)
				trans-**L2**	87	92 (*R*)
7	**1g**	2-naphthyl	Ph	*cis*-**L1**	80	88 (*S*)
				trans-**L2**	83	91 (*R*)
8	**1h**	Ph	*o*-MeC_6H_4	*cis*-**L1**	78	76 (*S*)
				trans-**L2**	77	79 (*R*)
9	**1i**	Ph	*m*-MeC_6H_4	*cis*-**L1**	83	90 (*S*)
				trans-**L2**	80	94 (*R*)
10	**1j**	Ph	*p*-MeC_6H_4	*cis*-**L1**	82	92 (*S*)
				trans-**L2**	85	96 (*R*)
11	**1k**	Ph	*p*-$MeOC_6H_4$	*cis*-**L1**	87	91 (*S*)
				trans-**L2**	82	97 (*R*)
12	**1l**	Ph	*p*-ClC_6H_4	*cis*-**L1**	87	71 (*S*)
				trans-**L2**	87	87 (*R*)
13	**1m**	Ph	*p*-$CF_3C_6H_4$	*cis*-**L1**	82	73 (*S*)
				trans-**L2**	83	80 (*R*)
14	**1n**	Ph	2-naphthyl	*cis*-**L1**	79	86 (*S*)
				trans-**L2**	84	91 (*R*)
15	**1o**	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	*cis*-**L1**	89	>99.9 (*S*)
				trans-**L2**	90	>99.9 (*R*)
16	**1p**	Ph	Me	*cis*-**L1**	80	85 (*S*)
				trans-**L2**	82	92 (*R*)

[a] 1 mol% Cu salt, 2 mol% ligand, 1.2 equiv. $AlEt_3$.
[b] Yield of the isolated product.
[c] Determined by HPLC, Chiralcel OJ-H column. The absolute configuration was determined by comparison with literature data.[12]

to 93% *ee* was obtained with methyl-substituted *trans*-**L2** (entries 3–6).

With *cis*-**L1** (R = H) and *trans*-**L2** (R = Me) used as a reversal ligand pair, we expected to induce the formation of both absolute configurations in the products. A wide range of aromatic enones was examined to investigate the scope of the substrates and the reversal in stereoselectivity (Table 3). To our delight, a complete switch in stereoselectivity was observed for all of the substrates. The introduction of a methyl group at the *ortho*-position on the phenyl ring (R^1 or R^2) of substrate **1**, led to a drop in enantioselectivity for both of the ligands. This may be attributed to the effect of steric hindrance (entries 1, 2 and 8). However, the introduction of a methyl group at the *meta*- and *para*-positions of the phenyl ring R^1 or R^2 led to an increase in enantioselectivity (entries 1, 3, 4, 9 and 10). When a methoxy group was introduced at the *para*-position of the phenyl ring R^1 or R^2, a much higher increase in enantioselectivity was observed (entries 1, 5 and 11). Conversely, electron-withdrawing substituents such as a *para*-bromo group on the phenyl ring R^1 or *para*-chloro or trifluoromethyl groups on the phenyl ring R^2, were detrimental to the enantioselectivity (entries 1, 6, 12 and 13). Furthermore, replacing the phenyl ring, R^1 or R^2, with 2-naphthyl-substituted substrates, increased the enantioselectivity of the reaction when using *cis*-**L1** as the ligand. The related *trans*-**L2** ligand gave slightly lower enantioselectivity (entries 7 and 14). The above results suggested that the electron-donating properties of the *para*-position substituent on the phenyl ring R^1 or R^2 gave a proportional greater improvement in terms of enantioselectivity. Therefore we chose **1o** containing *para*-methoxy groups on both phenyl rings of R^1 and R^2 as the substrate to carry out the reaction (entry 15). As expected, both enantiomers were obtained in >99.9% *ee* (entry 15), in which the switch in stereoselectivity was achieved by only changing the substituent and not the chirality of the ligand. We also performed the reaction using a typical acyclic enone, benzalacetone (**1p**). Using *cis*-**L1** and *trans*-**L2** as a ligand pair, products were obtained with high enantioselectivities and reversed absolute configurations (entry 16).

We tried to use the single crystal X-ray structure of *cis*-**L1** (Figure 2) for an explanation for the above phenomenon by comparison with the previously reported X-ray crystal structures of *trans*-**L1**–**L3**.[13] The dihedral angles of these ligands are summarized in Table 4. The dihedral angles of *cis*-**L1** and *trans*-**L1** lacking substituents at the 3,3′,5,5′-positions were unaffected. When methyl groups were introduced to the 3,3′,5,5′-positions of the biphenyl backbone, the dihedral angles of the ligand increased compared to those of *cis*-**L1** and *trans*-**L1**. When the substituent was changed to an ethyl group (*trans*-**L3**), the dihedral angle decreased to a value similar to those of *cis*-**L1** and *trans*-**L1**. However, *trans*-**L3** gave the opposite absolute configuration of the conjugate addition products when compared to *cis*-**L1** and *trans*-**L1**. These results indicate that it is the substituents at the 3,3′,5,5′-positions of the biphenyl backbone that affect the absolute configuration of the conjugate addition products, rather than the dihedral angle of the ligands.

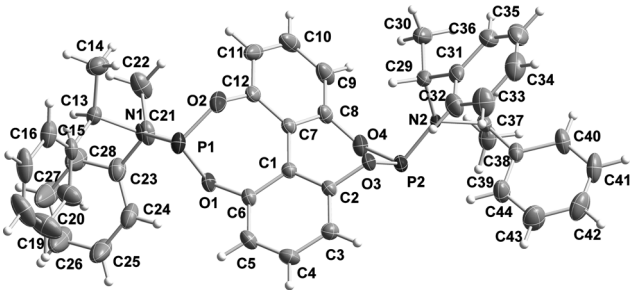


Figure 2. X-ray crystal structure of *cis*-**L1**.

Table 4. Dihedral angles of ligands.

Entry	Ligand	Dihedral angle
1	*cis*-**L1**	42.46°
2	*trans*-**L1**	42.16°
3	*trans*-**L2**	46.67°
4	*trans*-**L3**	43.86°

In order to explain the reversal phenomenon, a stereochemical pathway has been proposed according to our experimental results (Figure 3). As a copper ion coordinates to one phosphorus on the ligand,[14] the other phosphorus remains relatively far away from the reaction center. Both the *cis* and *trans* configurations of the ligands therefore have little effect on the absolute configuration of the products. The steric repulsion between the substituents at the 3,3′- or 5,5′-positions of the biphenyl backbone and the aryl groups of the substrate, may determine the result of the reversed stereochemical phenomenon in the 1,4-addition. For the transition states involving **L1** (the ligand bearing no substituents at the 3,3′,5,5′-positions of the biphenyl backbone) and coordination with the copper ion, steric repulsion between the phenyl group of ligand **L1** and the aryl group of the substrate in **L1**-TS2 was larger than that in **L1**-TS1. This leads to the 1,4-adduct with an *S* isomer configuration. However, when substituents at the 3,3′,5,5′-positions of the biphenyl backbone were introduced, the steric repulsion between the phenyl group of ligand **L2** and the aryl group of the substrate in transition state **L2**-TS2, was smaller than that between the substituent at the 3,3′,5,5′-positions of the biphenyl backbone and aryl group of the substrate in **L2**-TS1. This leads to the 1,4-adduct with the *R* isomer configuration.

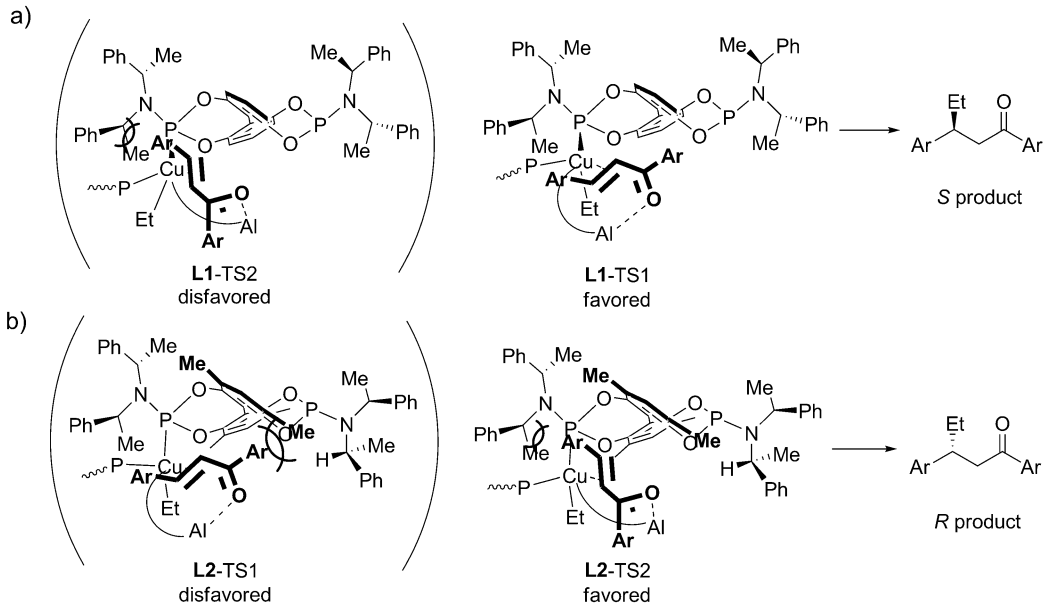
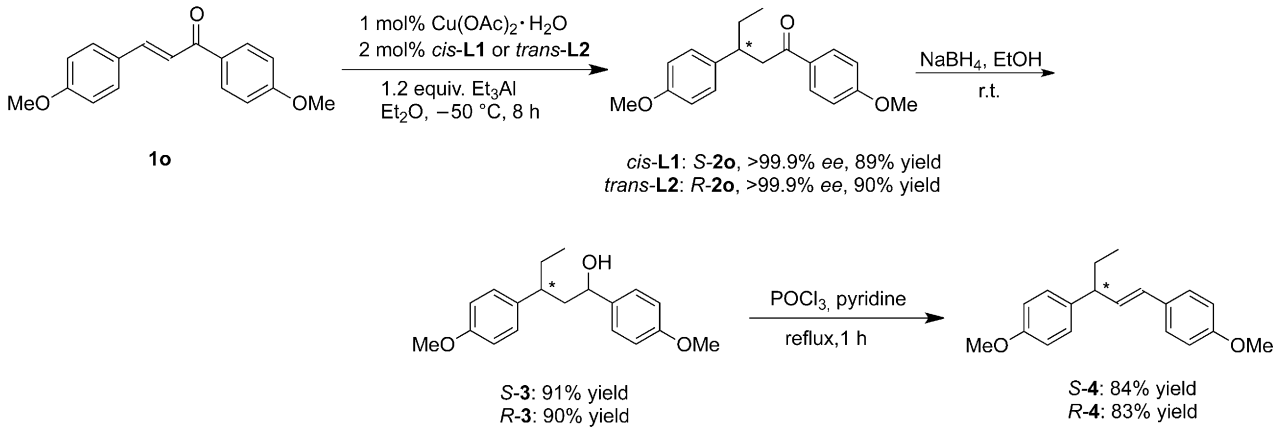


Figure 3. Proposed stereochemical pathway showing the facial coordination of the copper atom with the enone substrate.



Scheme 1. Asymmetric synthesis of the alkene **4**.

Finally, we utilized the ligand pair *cis*-**L1** and *trans*-**L2** to synthesize enantiopure alkene **4** *via* an asymmetric conjugate addition reaction (Scheme 1). Alkene **4** exhibits a diverse range of biological properties such as antimalarial and antiplasmodial activities (Scheme 1).[15] Thus utilizing ligands *cis*-**L1** and *trans*-**L2**, the *S* and *R* enantiomers of **2o** were obtained *via* the asymmetric 1,4-addition of triethylaluminium to 1,3-bis(4-methoxyphenyl)pentan-1-one (**1o**). $NaBH_4$ reduction of the ketones (*S*- and *R*-**2o**) followed by alcohol elimination (*S*- and *R*-**3**) gave the desired compounds with high overall yields and complete enantioselectivity (both >99.9% *ee*). To the best of our knowledge, this is the first example of the asymmetric synthesis of **4**.

In conclusion, we have developed a highly enantioselective copper-catalyzed conjugate addition of triethylaluminium to acyclic aromatic enones (up to >99.9% *ee*), with phosphoramidite ligands bearing a D_2-symmetric biphenyl backbone. These types of ligands demonstrated that the 3,3′,5,5′-substituents on the biphenyl backbone can completely reverse the absolute configuration of the products, thus simplifying the process of accessing either enantiomer. The synthesis of chiral alkene **4** was also completed, with both enantiomers being obtained in high overall yields and excellent enantioselectivities.

Experimental Section

Typical Procedure for the Conjugate Addition to Chalcone 1a

A flame-dried Schlenk tube was charged with $Cu(OAc)_2{\cdot}H_2O$ (1.0 mg, 0.005 mmol) and ligand (7.8 mg,

0.01 mmol) under an N_2 atmosphere, and the mixture was dissolved in dry Et_2O (1.5 mL). The solution was stirred at 25 °C for 30 min and then cooled to −50 °C. Triethylaluminium (1.2 mmol, 1.2 mL of 1 M hexane solution) was added dropwise to the above solution. The colour of the solution gradually turned to light yellow after 5 min at −50 °C. The substrate **1a** (104.3 mg, 0.5 mmol dissolved in 1.0 mL dry toluene) was then added dropwise. The mixture was stirred at −50 °C for 8 h before quenching with aqueous saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the addition product. The enantiomeric excess of the product was determined by chiral HPLC.

Acknowledgements

This work was partially supported by the National Natural Science Foundation of China (Nos. 20972095 and 21172143), Science and Technology Commission of Shanghai Municipality (No. 10dz1910105), Nippon Chemical Industrial Co., Ltd., and Shanghai Jiao Tong University.

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