CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200701439

A Library of Chiral Imidazoline–Aminophenol Ligands: Discovery of an Efficient Reaction Sphere

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Abstract: A library of imidazoline–aminophenol ligands was synthesized on solid supports. After immobilization of chiral chloromethylimidazolines **1** and **2** onto the polystyrylsulfonyl chloride, nucleophilic substitution with (*R*)- or (*S*)-phenylethylamine (**3** and **4**) provided four combinations of polymer-supported imidazoline–amine ligands. Further reductive alkylation using salicylaldehydes **7**–**10** provided a series of imidazoline–aminophenol ligands (**L9**–**L24**). Analysis by solid-phase catalysis/circular dichroism high-throughput screening of a copper-catalyzed Henry reaction revealed that ligand **L25**, comprising a (*S*,*S*)-diphenylethylenediamine-derived imidazoline, (*S*)-phenylethylamine, and dibromophenol, was highly efficient, thus providing the adduct of nitromethane and benzaldehyde in 95% *ee*. The combination of stereogenic centers was crucial in promoting the highly stereoselective reactions. The unique reaction sphere of **L25** was also examined in a Friedel–Crafts alkylation of indole and nitroalkene to give the adduct in up to 83% *ee*.

Keywords: asymmetric catalysis · circular dichroism · combinatorial chemistry · high-throughput screening · solid-phase synthesis

Introduction

The creation of a well-organized reaction sphere using highly functionalized chiral ligands is a fascinating goal for stereo-controlled catalysis. The important research topic of asymmetric catalysis has stimulated chemists worldwide to develop numerous chiral ligands for various types of metal-catalyzed reactions.[1] Though modern chemistry has made the design of catalysts possible from a detailed understanding of the reaction mechanism, the development of novel ligands by traditional methods still requires considerable time and hard work. Combinatorial chemistry, which provides easy access to molecular complexity, allows us to rationally and rapidly explore artificial catalysts and to resolve the intrinsic problems of the conventional method.[2,3] Herein, we demonstrate the combinatorial development of a novel catalyst constructed from a newly designed chiral imidazoline–aminophenol ligand.

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An imidazoline-containing chiral ligand was selected for several reasons. A representative example of chiral-ligand chemistry can be seen in the famous bis(oxazoline) ligands, in which the nitrogen atom of a N,O-containing five-membered ring of the oxazoline coordinates to the metal cation to form a complex.[4] The bis(oxazoline)–metal complexes have been utilized in numerous asymmetric reactions. However, despite the beautiful success of bis(oxazoline) ligands in asymmetric catalysis, regulating the electron density of the oxazoline ring has remained an unsolved problem. One way to overcome the limitation of electronic variation on the oxazoline ring is the rational design of a chemical analogue (e.g., imidazoline) of oxazoline.[5]

Imidazoline, the N,N analogue of the N,O-oxazoline, would be a reasonable candidate to meet the demand for electronic tunability (Figure 1 i). Since the oxygen atom of the oxazoline is replaced by an NR group in the imidazoline, the basicity of the ligating nitrogen atom could be accurately adjusted by selection of either an electron-withdrawing or -donating substituent (R). Moreover, in planning a library synthesis of imidazoline-containing ligands on a solid support, the substituent (R) at the nitrogen atom in the imidazoline would offer an interesting site to introduce the linker for immobilization (Figure 1 ii).

With the aim of investigating novel asymmetric catalysts using a library of chiral ligands, we have succeeded in developing a new high-throughput screening (HTS) method by

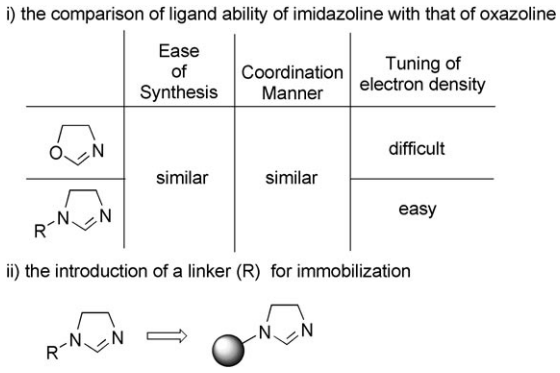
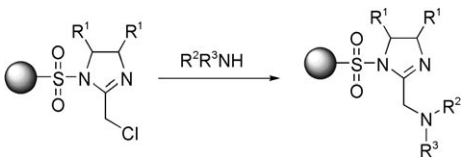


Figure 1. Imidazoline as a ligand.

coupling circular dichroism (CD) detection with a reaction on solid-phase catalysts.[6,7] In the "solid-phase catalysis/CD HTS" method, the origin of chirality is restricted by the solid support. When the catalytic asymmetric reaction is examined by using an achiral substrate in solution, no asymmetric induction occurs; therefore, when the solution is analyzed by using CD, no significant signal should be detected. Because any two enantiomers have exactly opposite CD values at each wavelength, detection of a positive or negative signal by the CD detector would, accordingly, indicate an excess of one of the enantiomers (Figure 2).

The design of a metal catalyst with solid-supported chiral imidazoline–amine ligands is shown in Scheme 1. The linker is attached to the solid support through one of the nitrogen atoms of the imidazoline. Because we have succeeded in immobilizing a chloromethylated imidazoline moiety,[8] the library was designed with imidazoline and amine units as the building blocks. It is also possible to introduce an additional stereogenic center and the R^1 substituent on imidazoline by utilizing a chiral amine at R^2 and/or R^3.



Scheme 1. Polymer-supported chiral imidazoline–amine compounds.

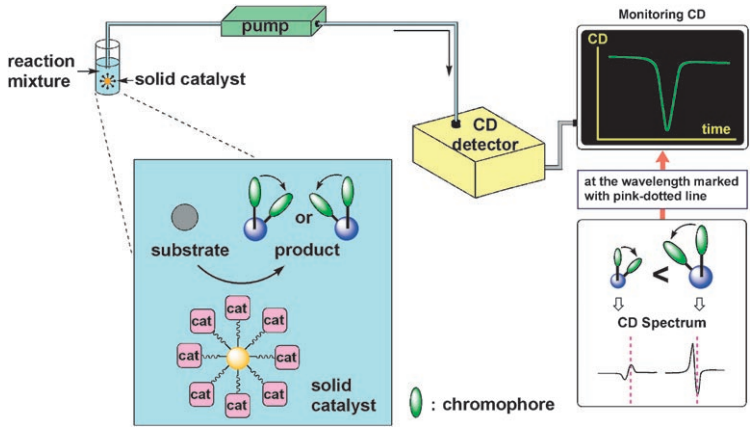


Figure 2. Solid-phase catalysis/CD HTS.

Results and Discussion

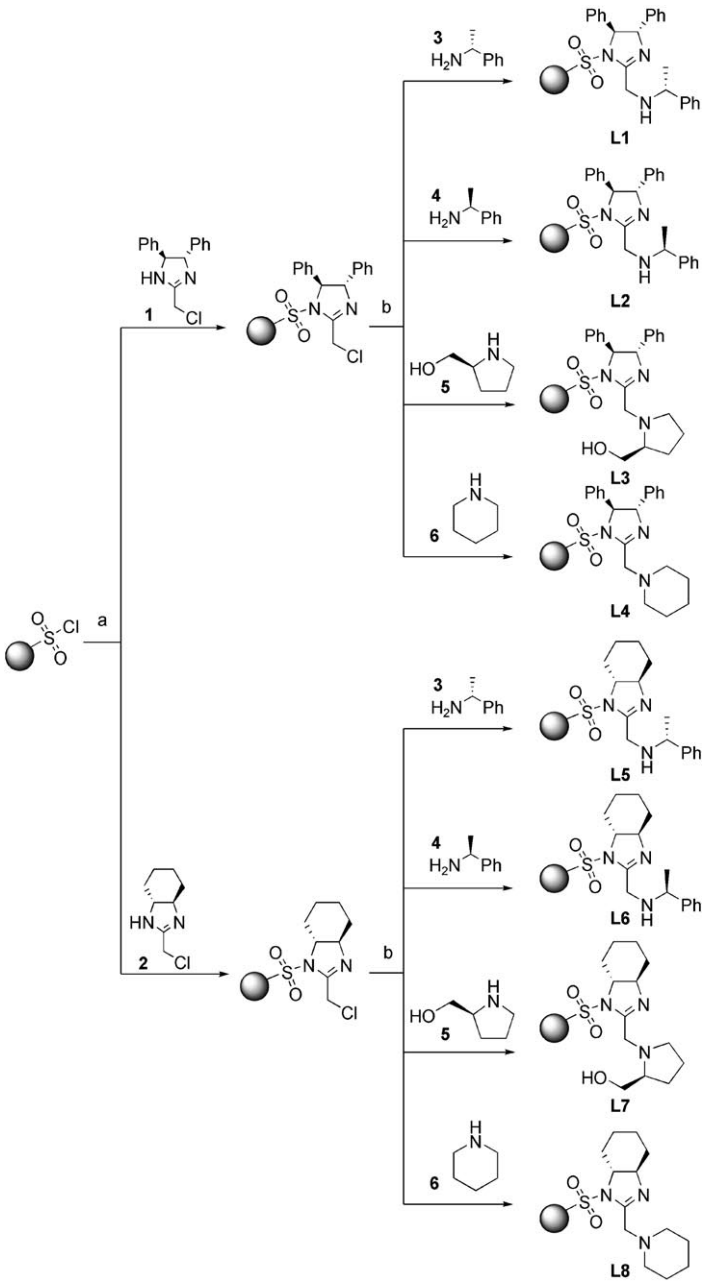
Development of the imidazoline-containing ligands began with the immobilization of imidazoline on the polymer support. Synthesis of the imidazoline–amine library was performed as shown in Scheme 2. After introduction of the chloromethylated imidazolines **1** and **2** onto the polystyrylsulfonyl chloride, nucleophilic substitution with four different amines **3**–**6** provided the first generation of the polymer-supported imidazoline–amine ligands **L1**–**L8**. The construction of the imidazoline–amine compounds was analyzed by IR spectroscopic and elemental analysis.

By using the eight polymer-supported chiral imidazoline–amine compounds **L1**–**L8**, we examined the $Cu(OAc)_2$-catalyzed Henry reaction to evaluate the efficiency of the reaction sphere.[9] In all cases, the polystyrene beads turned green after treatment with $Cu(OAc)_2$, which suggested the formation of copper complexes. After carrying out the asymmetric Henry reaction of nitromethane with *ortho*-nitrobenzaldehyde for 48 h, each reaction mixture was analyzed by continuous injection into the solid-phase catalysis/CD HTS system (Figure 2). The resulting profiles are shown in Figure 3. It should be noted that analysis by solid-phase catalysis/CD HTS of a reaction with a good yield but low enantiomeric excess should result in a CD signal of low intensity. Similarly, when catalytic activity is low, thus resulting in a low yield, the intensity of the CD signal is low, even with a high enantiomeric excess. The CD signal is of maximum intensity only when both the chemical yield and enantiomeric excess are ideal. To quantify the results of solid-phase catalysis/CD HTS, we defined a new parameter named the asymmetric conversion yield (ACY), which is given as the square root of the chemical yield multiplied by the enantiomeric excess [Eq. (1)].[6]

$$\mathrm{ACY}\ (\%) = \sqrt{\mathrm{yield}\ (\%) \times ee\ (\%)} \qquad (1)$$

Conventional analysis of the Henry reaction by using chiral stationary-phase HPLC is presented in Table 1.

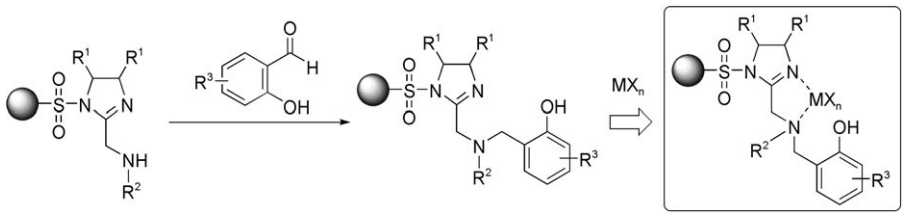
Although the first generation polymer-supported imidazoline–amine/$Cu(OAc)_2$ catalysts successfully promoted the Henry reaction, the observed asymmetric inductions remained low. Only **L1**, **L2**, and **L5**, which have a combination of imidazoline and phenylethyl-



Scheme 2. Library of imidazoline–amine ligands: a) chloromethylated imidazoline, triethylamine, CH_2Cl_2; b) corresponding amine, KI, MeCN.

amine moieties, provided adducts at around 10% *ee*. These results prompted us to redesign the polymer-supported imidazoline-containing ligands.

The second generation of imidazoline-containing ligands is shown in Scheme 3. Starting from the imidazoline–amine compounds prepared from a primary amine (R^2NH_2), a further transformation by using reductive amination would enlarge the diversity of the library.



Scheme 3. Polymer-supported imidazoline–aminophenol compounds.

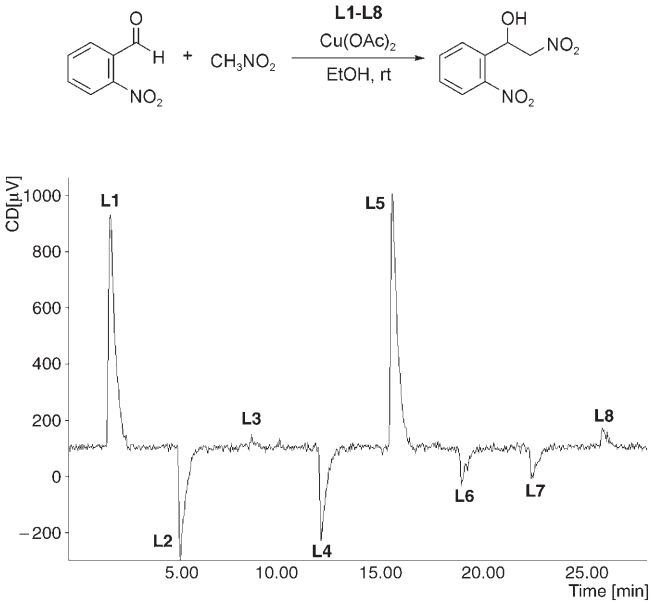


Figure 3. Solid-phase catalysis/CD HTS of the Henry reaction promoted by imidazoline–amine/$Cu(OAc)_2$ catalysts.

Table 1. Asymmetric Henry reaction catalyzed by imidazoline–amine/$Cu(OAc)_2$.

Entry	Ligand	Yield [%][a]	*ee* [%]	ACY [%]
1	**L1**	74	12	30
2	**L2**	64	13	26
3	**L3**	39	<1	6
4	**L4**	79	5	20
5	**L5**	81	11	30
6	**L6**	79	2	13
7	**L7**	54	2	10
8	**L8**	82	1	9

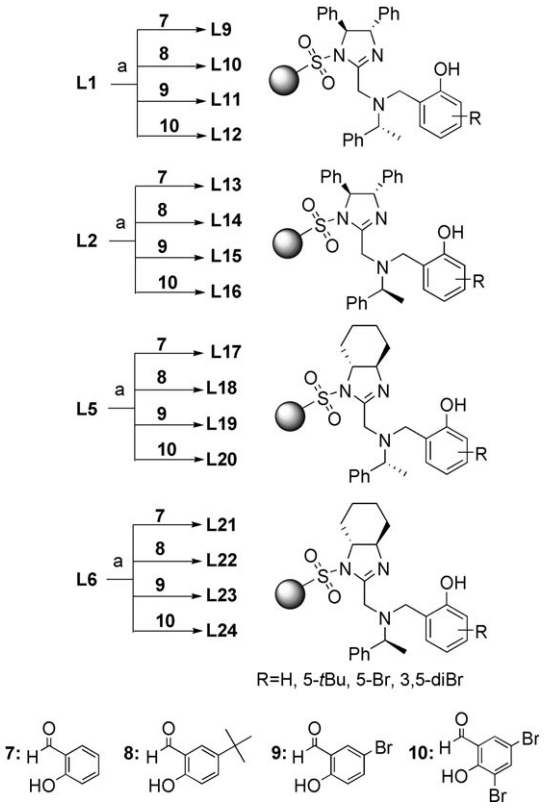
[a] Yield was determined by ^{1}H NMR spectroscopic analysis.

Because various salicylaldehydes are commercially available, a series of imidazoline–aminophenol compounds was newly designed. In forming the catalyst from the imidazoline–aminophenol ligands, the phenolic hydroxy group would interact with the metal center and possibly also mediate the approach of the substrate to the catalytic site by cooperative effects. The acidity of the hydroxy functionality and/or the size of the reaction sphere would be regulated by the R^3 group on the aromatic ring.

The second-generation imidazoline-containing ligands were prepared from the polymer-supported imidazoline–

amine compounds (Scheme 4). Thus, further reductive alkylation of **L1**, **L2**, **L5**, and **L6** with salicylaldehydes **7**–**10** provided a series of imidazoline–aminophenol ligands **L9**–**L24**. After classification of the library based on the type of chiral imidazoline species, the metal catalysts were prepared by reaction with CuCl[6] or $Cu(OAc)_2$ (Table 2).

With a total of 32 polymer-supported chiral catalysts **C1**–**C32** in hand, the copper-catalyzed Henry reaction was examined again. After carrying out the asymmetric Henry reaction of nitromethane and *ortho*-nitrobenzaldehyde for 48 h, each reaction mixture was analyzed by continuous injection into a solid-phase catalysis/CD HTS system, thus giving the profile shown in Figure 4.



Scheme 4. Library of imidazoline–aminophenol ligands: a) corresponding salicylaldehyde; then $NaBH_3CN$, MeOH.

Table 2. Matrix of catalyst preparation.

Catalyst Preparation

L9-L16: CuCl → C1-C8; $Cu(OAc)_2$ → C9-C16

L17-L24: CuCl → C17-C24; $Cu(OAc)_2$ → C25-C32

Building blocks			7	8	9	10
1	3	CuCl	C1(L9)	C3(L10)	C5(L11)	C7(L12)
	4		C2(L13)	C4(L14)	C6(L15)	C8(L16)
	3	$Cu(OAc)_2$	C9(L9)	C11(L10)	C13(L11)	C15(L12)
	4		C10(L13)	C12(L14)	C14(L15)	C16(L16)
2	3	CuCl	C17(L17)	C19(L18)	C21(L19)	C23(L20)
	4		C18(L21)	C20(L22)	C22(L23)	C24(L24)
	3	$Cu(OAc)_2$	C25(L17)	C27(L18)	C29(L19)	C31(L20)
	4		C26(L21)	C28(L22)	C30(L23)	C32(L24)

Obviously, catalysts **C14** (i.e., **L15**/$Cu(OAc)_2$) and **C16** (i.e., **L16**/$Cu(OAc)_2$) showed similar CD intensities after the reaction. Some representative reaction mixtures were analyzed by the conventional method using chiral stationary-phase HPLC (Table 3). The ability to identify the best catalysts without analyzing all the reaction mixtures is an important feature of our approach.

Conventional analysis using chiral stationary-phase HPLC revealed that **C16** provided the *S*-enriched Henry adduct in 63% yield with 40% *ee*, and the reaction using **C14** provided the *S* adduct in 88% yield with 28% *ee*. Thus, the ACYs were similar for the two catalysts, namely, approximately 50%. The inversion of enantioselectivity using **C31** was confirmed by isolation of the *R*-enriched product. In terms of the structure–activity relationship, the stereogenic center of the R^2 group strongly affected the catalyst efficiency. For example, **C15** (i.e., **L12**/$Cu(OAc)_2$), the epimer of **C16**, had a dramatically decreased CD intensity, and the *R*-enriched product was obtained in 61% yield with 6% *ee*. Furthermore, the presence of a 3,5-dibromo substituent on the salicylaldehyde unit is crucial for high enantioselectivity.

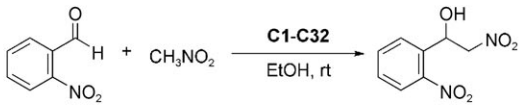
Based on the results of solid-phase catalysis/CD HTS, the well-defined chiral ligand **L25** was synthesized by solution-phase synthesis (Scheme 5) and applied to the asymmetric Henry reaction. As a result, the catalyst **L25**/$Cu(OAc)_2$ provided the Henry adduct in good yield with high enantiomeric excess (Table 4).

High enantiomeric excess was obtained, even at room temperature, for various aromatic aldehydes; not only electron-deficient substrates (Table 4, entries 1–3) were successful. For example, *ortho*-methoxybenzaldehyde was converted into the corresponding adduct in 90% yield with 90% *ee* (Table 4, entry 5). Moreover, aliphatic aldehydes were smoothly converted into nitroaldols in good yields with high enantiomeric excess (Table 4, entries 9–13). When the catalyst activity was not sufficient to promote the reaction, the addition of triethylamine was helpful in obtaining a sufficient yield while maintaining the enantiomeric excess.[9a]

The complex reaction sphere produced by **L25** was also demonstrated in the catalytic asymmetric Friedel–Crafts alkylation of indole using nitroalkene (Table 5).[10] The reaction of indole and nitrostyrene was catalyzed smoothly by **L25**/CuOTf (Tf = triflate), and the adduct was obtained in 97% yield with 75% *ee*. The aliphatic nitroalkene was also converted into the products, and the enantiomeric excess was as high as 83% (Table 5, entry 8). It is noteworthy that the optical purity of the product examined in entry 6 was increased to 98% *ee* by a single recrystallization from ethanol.

Conclusion

A library-based study that employed imidazoline–aminophenol ligands successfully identified a unique reaction sphere



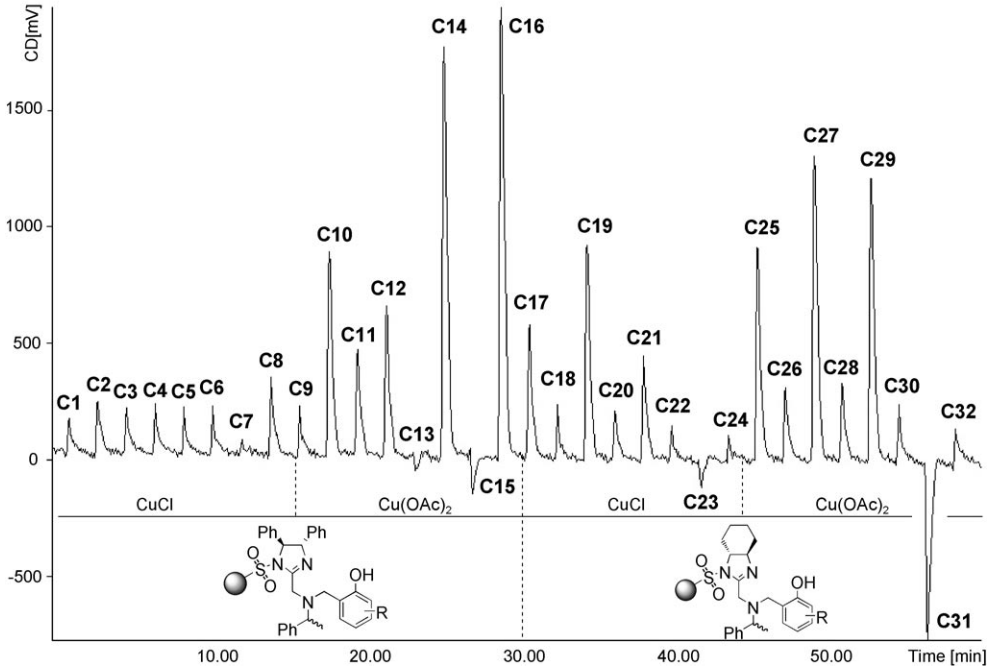
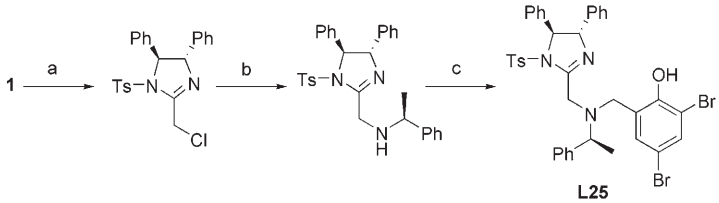


Figure 4. Solid-phase catalysis/CD HTS of the Henry reaction promoted by the second generation imidazoline–aminophenol/Cu catalysts.

Table 3. Asymmetric Henry reaction catalyzed by imidazoline–aminophenol/Cu complexes.

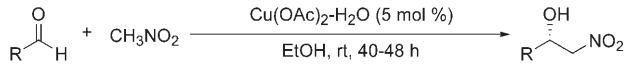
Entry	Catalyst	Yield [%][a]	*ee* [%]	ACY [%]
1	**C10**	57	8 (*S*)	21
2	**C14**	88	28 (*S*)	50
3	**C15**	61	6 (*R*)	19
4	**C16**	63	40 (*S*)	50
5	**C19**	33	34 (*S*)	33
6	**C25**	83	18 (*S*)	39
7	**C27**	74	21 (*S*)	39
8	**C29**	68	21 (*S*)	38
9	**C31**	35	35 (*R*)	19

[a] Yield was determined by ^{1}H NMR spectroscopic analysis.



Scheme 5. Synthesis of well-defined chiral ligand **L25**. a) TsCl, *i*Pr$_2$NEt, MeCN; b) (*S*)-phenylethylamine, KI, DMF; c) **10**; then NaBH$_3$CN, MeOH. DMF = *N*,*N*-dimethyl formamide, TsCl = tosyl chloride.

Table 4. Henry reaction catalyzed by **L25**/Cu(OAc)$_2$.

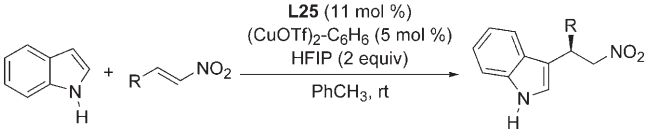


Entry	R-	Yield [%]	*ee* [%]
1	*o*-NO$_2$-C$_6$H$_4$-	98	94
2	*p*-NO$_2$-C$_6$H$_4$-	99	90
3	*m*-NO$_2$-C$_6$H$_4$-	96	92
4	C$_6$H$_5$-	76	95
5	*o*-MeO-C$_6$H$_4$-	90	90
6	*p*-F-C$_6$H$_4$-	84	87
7	*p*-Cl-C$_6$H$_4$-	94	83
8	1-naphthyl	98	75
9[a,b]	PhCH$_2$CH$_2$-	82	80
10[a,c]	cyclohexyl	81	91
11[a,b]	pentyl	96	90
12[a,b]	butyl	78	90
13[a,b]	isobutyl	99	90

[a] The reaction was performed in *n*PrOH. [b] Amount of Et$_3$N added = 5 mol%. [c] Amount of Et$_3$N added = 1 mol%.

that was efficient in a stereoselective copper-catalyzed Henry reaction and a Friedel–Crafts alkylation of indole and nitroalkene. Predicting the actual catalytic activity of **L25** simply from its molecular structure remains a challenge even in modern chemistry, and the creation of such a ligand would be difficult without the use of combinatorial technol-

Table 5. Friedel–Crafts alkylation of indole with nitroalkenes.



Entry	R-	*T* [h]	Yield [%]	*ee* [%]
1	C_6H_5-	47	97	75
2	*p*-NO_2-C_6H_4-	20	> 99	80
3	*p*-MeO-C_6H_4-	18	97	55
4	*p*-Br-C_6H_4-	9	99	75
5	*p*-Cl-C_6H_4-	10	99	74
6	3,4-OCH_2O-C_6H_3-	23	86	67
7	*n*-pentyl-	23	97	78
8	$PhCH_2CH_2$-	28	97	83

ogy. Research into other new and powerful asymmetric catalysts is in progress using the solid-phase catalysis/CD HTS system.

Experimental Section

(4*S*,5*S*)-2-(Chloromethyl)-4,5-dihydro-4,5-diphenyl-1*H*-imidazole (1): Chloroorthoacetic acid triethyl ester (1.17 mL, 6.12 mmol) was added to a solution of (1*S*,2*S*)-1,2-diphenylethylene-1,2-diamine (1 g, 4.71 mmol) in AcOH (23.5 mL), and the reaction mixture was stirred for 15 h at room temperature. After dilution in $CHCl_3$ (100 mL), the reaction mixture was neutralized with 2 M NaOH (aq.), and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give the chloromethylated imidazoline **1** (1.01 g, 80% yield) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.38$ (s, 2H), 4.82 (s, 2H), 5.35 (br s, 1H, NH), 7.24–7.38 ppm (m, 10H, aromatic).

Preparation of polymer-supported imidazoline–aminophenol ligands: Polymer-supported chloromethylated imidazoline (step (a) in Scheme 2): The sulfonyl chloride polystyrene beads (loading: 4.50 mmol g^{-1}; purchased from Nova BioChem; 200 mg, 0.9 mmol) were weighed into a dried two-necked round-bottomed flask and swollen in anhydrous CH_2Cl_2 (1.5 mL) under an argon atmosphere for 30 min at room temperature. Chloromethylated imidazoline **1** (1.3 equiv, 1.2 mmol) in dry CH_2Cl_2 (1.5 mL) and triethylamine (280 μL, 2 mmol) was added to the swollen beads. The reaction mixture was stirred at room temperature for 24 h. The filtrated beads were exposed to air and subjected to the following wash protocol: distilled water (2×3 mL), followed by three repetitions of alternate washes with dry methanol (3 mL) and dry CH_2Cl_2 (3 mL). After drying under vacuum, the resulting beads were kept for further experiments in a refrigerator.

Nucleophilic amination (step (b) in Scheme 2): The beads prepared in step (a) were weighed (96 mg, 0.2 mmol) into a dried two-necked round-bottomed flask and swollen in anhydrous MeCN (2 mL) under an argon atmosphere for 30 min at room temperature. KI (103 mg, 0.6 mmol) and the corresponding amine (1.0 mmol) were added to the swollen beads. The reaction mixture was then stirred at 40 °C for 24 h. The filtered beads were exposed to air, and subjected to the following wash protocol: distilled water (2×3 mL), followed by three repetitions of alternate washes with dry methanol (3 mL) and dry CH_2Cl_2 (3 mL). After drying under vacuum, the resulting beads were kept for further experiments in a refrigerator.

Reductive alkylation (Scheme 4): The beads prepared in step (b) were weighed (103 mg, 0.068 mmol) into a dried two-necked round-bottomed flask and swollen in anhydrous MeOH (2 mL) under an argon atmosphere for 30 min at room temperature. The corresponding salicylaldehyde (5 equiv, 0.34 mmol) was added to the swollen beads. After stirring at 40 °C for 1 h, $NaBH_3CN$ (1 M in THF; 136 μL, 0.136 mmol) was added, and the reaction mixture was kept stirring at the same temperature for 24 h. The filtered beads were exposed to air, and subjected to the following wash protocol: distilled water (2×3 mL), followed by three repetitions of alternate washes with dry methanol (3 mL) and dry CH_2Cl_2 (3 mL). After drying under vacuum, the resulting beads were kept for further experiments in a refrigerator.

Preparation of the solid-phase catalysts (Table 2): The beads prepared in Scheme 4 were weighed into a dried test tube. A copper salt (CuCl (1.0 mg, 0.01 mmol) or $Cu(OAc)_2$ (2.0 mg, 0.01 mmol)) was added to the beads in anhydrous $CHCl_3$/MeOH (1:1, v/v), and the reaction mixture was stirred at 40 °C for 24 h. The resulting beads were washed with dry CH_2Cl_2 (5×3 mL) and dried in vacuo.

Asymmetric Henry reaction using solid catalysts (Figures 3 and 4): Nitromethane (432 μL, 8.0 mmol) and *ortho*-nitrobenzaldehyde (30.2 mg, 0.2 mmol) were added to the polymer-supported catalyst in anhydrous ethanol (0.4 mL). The asymmetric reaction was allowed to proceed for 48 h.

Direct injection (Figures 3 and 4): The solid-phase catalyst/CD HTS system comprised an autosampler (JASCO AS-2057), a pump (JASCO PU-2080), and a CD detector (JASCO CD-2095). The autosampler and the CD detector were connected by a Teflon tube. The sample was prepared by diluting the reaction mixture (10 μL) with ethanol (990 μL). At intervals of 1.5 min, 5 μL of the sample was injected. The CD was operated at 254 nm and the flow rate of the system was 1.0 mL min^{-1}. The CD data was analyzed using JASCO-BORWIN software. The enantiomeric excess of the representative reaction mixtures were analyzed by chiral stationary-phase HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH = 9:1, flow rate = 0.8 mL min^{-1}).

2-{[(1*S*)-*N*-{[(4*S*,5*S*)-4,5-Dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazol-2-yl]-methyl}-1-phenylethanamino]methyl}-4,6-dibromophenol (L25): Tosylation (step (a) in Scheme 5): TsCl (248 mg, 1.3 mmol) was added to a solution of **1** (271 mg, 0.94 mmol) and *i*Pr_2NEt (257 μL, 1.5 mmol) in dry MeCN (4.7 mL) at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched by addition of saturated $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to yield (4*S*,5*S*)-(2-chloromethyl)-4,5-dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazole (401 mg 94% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H, Ts-CH_3), 4.69 (d, $J = 12.5$ Hz, 1H, CH_2Cl), 4.92–4.99 (m, 3H), 6.88–7.50 ppm (m, 14H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 38.6, 71.9, 77.7, 126.0, 126.3, 127.5, 127.7, 128.1, 128.6, 128.8, 129.4, 134.9, 140.5, 140.5, 144.6, 155.7 ppm; MS: *m*/*z*: 425 $[M+H]^+$.

Nucleophilic amination (step (b) in Scheme 5): (*S*)-1-Phenylethylamine (0.82 mL, 6.4 mmol) was added to a solution of (4*S*,5*S*)-2-(chloromethyl)-4,5-dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazole (543 mg, 1.28 mmol) and KI (575 mg, 3.8 mmol) in dry DMF (6.4 mL). After stirring at room temperature for 14 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ and the aqueous layer was extracted with diethyl ether. After washing the combined organic extracts three times with water, the organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give (1*S*)-*N*-{[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazol-2-yl]methyl}-1-phenylethanamine (677 mg 97% yield) as a white amorphous solid. ^{1}H NMR(400 MHz, $CDCl_3$): $\delta =$ 1.42 (d, $J = 6.5$ Hz, 3H), 2.40 (s, 3H, Ts-CH_3), 3.79–3.92 (m, 2H), 4.00 (q, $J = 6.5$ Hz, 1H), 4.84 (d, $J = 5.3$ Hz, 1H), 4.92 (d, $J = 5.3$ Hz, 1H), 6.81–7.40 ppm (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 24.4, 46.4, 57.8, 72.1, 77.7, 126.1, 126.4, 126.9, 127.1, 127.3, 127.6, 128.1, 128.5, 128.6, 128.9, 129.7, 135.2, 141.2, 141.3, 144.4, 144.7, 158.9 ppm, HRMS (FAB$^+$) calcd for $C_{31}H_{32}N_3O_2S$ $[M+H]$ 510.2215; found: 510.2212.

Reductive alkylation (step (c) in Scheme 5): 3,5-Dibromosalicylaldehyde (476 mg, 1.7 mmol) was added to a solution of (1*S*)-*N*-{[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazol-2-yl]methyl}-1-phenylethanamine

(173 mg, 0.34 mmol) in dry MeOH (1.7 mL) at room temperature. After stirring for 1 h at room temperature, sodium cyanoborohydride (1 M in THF; 0.68 mL, 0.68 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 24 h and then quenched by the addition of saturated $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give 2-{[(1*S*)-*N*-{[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-1-tosyl-1*H*-imidazol-2-yl]methyl}-1-phenylethanamino]methyl}-4,6-dibromophenol (**L25**; 180 mg, 68% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.50 (d, $J = 6.8$ Hz, 3H), 2.35 (s, 3H), 3.77–3.95 (m, 3H), 4.08–4.11 (m, 2H), 4.67 (d, $J = 3.9$ Hz, 1H), 5.04 (m, 1H), 6.66–7.55 (m, 21H), 11.26 ppm (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 47.8, 53.3, 55.7, 72.3, 76.1, 110.0, 111.6, 125.4, 125.5, 125.8, 126.7, 127.2, 127.3, 128.1, 128.35, 128.4, 128.5, 129.2, 129.9, 131.8, 134.3, 134.7, 141.0, 141.1, 142.3, 144.5, 153.8, 159.8, 164.1 ppm; HRMS (FAB+): calcd for $C_{38}H_{35}Br_2N_3O_3S$ [M+H] 772.0844; found: 772.0831; IR: $\tilde{\nu} = 3028$, 1647, 1365, 1163 cm^{-1}; $[\alpha]_D^{18} = +2.96°$ ($c = 1.0$ M, $CHCl_3$).

Solution-phase asymmetric Henry reaction of aromatic aldehydes (Table 4, entries 1–8): $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) and **L25** (8.5 mg, 0.011 mmol) were placed in a two-necked flask. After the addition of ethanol (0.4 mL), the reaction mixture was stirred for 1 h in argon. Nitromethane (432 μL, 8 mmol) and the corresponding aldehyde (0.2 mmol) were added to the resulting clear-blue solution under an argon atmosphere. After stirring for 40–48 h at room temperature, the reaction mixture was purified by column chromatography on silica gel to afford the adduct. The enantiomeric excess of the product was determined by HPLC analysis on a chiral stationary-phase column.

Solution-phase asymmetric Henry reaction of aliphatic aldehydes (Table 4, entries 9–13): $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) and **L25** (8.5 mg, 0.011 mmol) were placed in a two-necked flask. After addition of 2-propanol (0.3 mL), the reaction mixture was stirred for 1 h in argon. Nitromethane (54 μL, 1 mmol), triethylamine (0.01 mmol) in *n*PrOH (0.1 mL), and the corresponding aldehyde (0.2 mmol) were added to the resulting clear-blue solution under an argon atmosphere. After stirring for 40–48 h at room temperature, the reaction mixture was purified by column chromatography on silica gel to afford the adduct. The enantiomeric excess of the product was determined by HPLC analysis on a chiral stationary-phase column.

Asymmetric Friedel–Crafts alkylation with L25: $[(CuOTf)_2] \cdot C_6H_6$ (4.4 mg, 0.0087 mmol) and **L25** (14.9 mg, 0.019 mmol) were placed in a two-necked flask under an argon atmosphere. After the addition of toluene (0.85 mL), the reaction mixture was stirred for 2 h. Nitroalkene (0.34 mmol), 1,1,1,3,3,3-hexafluoroisopropyl alcohol (35 μL, 0.34 mmol), and indole (20 mg, 0.17 mmol) were added to the resulting clear-green solution under an argon atmosphere. After stirring at room temperature, the reaction mixture was purified by column chromatography on silica gel to afford the adduct. The enantiomeric excess of the products was determined by HPLC on a Daicel Chiralcel OD-H column (hexane/*i*PrOH = 70:30, 0.7 mL min^{-1}, 254 nm).

Acknowledgements

This study was supported by the Industrial Technology Research Grant Program in 2006 from the New Energy and Industrial Technology Development Organization (NEDO) of Japan; a Grant-in Aid for Scientific Research on Priority Areas (No. 19028007, "Chemistry of Concerto Catalysis") from the Ministry of Education, Culture, Sports, Science and Technology, Japan; and a grant from the Uehara Memorial Foundation.

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Received: September 12, 2007
Published online: January 9, 2008

