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Preparation of Axially Chiral 2,2′-Biimidazole Ligands through Remote Chirality Delivery and Their Application in Asymmetric Carbene Insertion into N–H of Carbazoles

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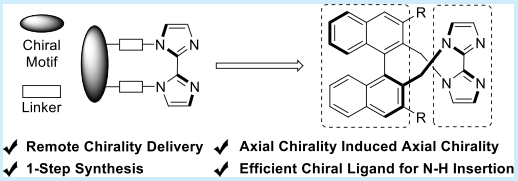
Supporting Information

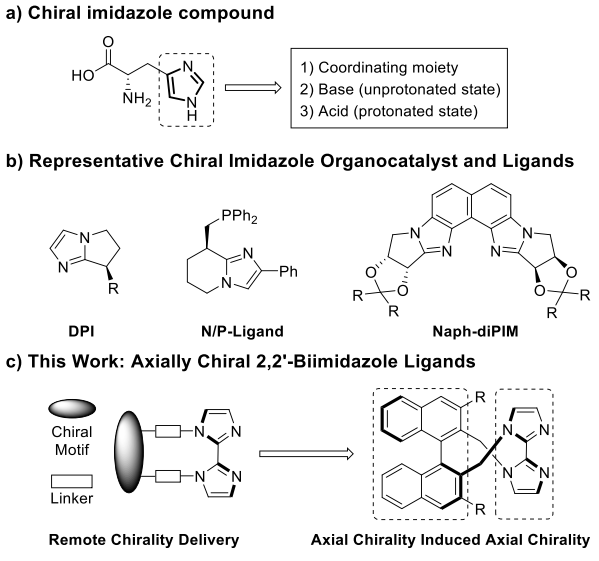
ABSTRACT: Axially chiral biimidazole ligands have been rarely synthesized and studied, in contrast to the significant achievements in the synthesis and application of central chiral imidazole ligands. Herein, a series of novel axially chiral 2,2′-biimidazole ligands were synthesized from the reaction of 2,2′-bis(bromomethyl)-1,1′-binaphthalene and 2,2′-biimidazole in one step through the strategy of remote chirality delivery. These ligands have been proven to be efficient for Cu- or Fe-catalyzed asymmetric insertion of α-aryl-α-diazoacetates into the N–H bond of carbazoles with up to 96% ee.



Imidazoles are ubiquitous and prevalent structural motifs in biologically active molecules and bioprocesses.[1] It is well-known that imidazole served as the side chain of histidine can coordinate with metal ions in metalloproteins. Moreover, the imidazole side group of histidine has a *p*Ka of ∼6, which exhibits amphoteric properties playing an active role in proton processes in biological systems (Scheme 1a).[1d] Inspired by its diverse biological properties, imidazoles have been designed as chiral organocatalysts (NMI, DPI, etc.)[2] and ligands by organic chemists for asymmetric catalysis in organic transformations. Especially, considering the excellent coordination ability of imidazoles with metal ions, the imidazole-based ligands have attracted considerable attention.[3] Many chiral ligands bearing imidazole moieties have been developed and applied in asymmetric hydrogenation, dehydrative allylation, aldol reaction, cycloaddition and Henry reaction, etc.[4] As the representative examples in this area, a series of imidazole-based N/P-ligand have been prepared and utilized in Ir-catalyzed asymmetric hydrogenation by Andersson's group in 2008.[5] Subsequently, Aponick's group successfully synthesized an imidazole-based biaryl N/P-ligand named StackPhos which atropisomer interconversion was inhibited by $\pi-\pi$ stacking. This ligand performed well in the asymmetric Cu-catalyzed A3-coupling reaction.[6] In addtion, the chiral biimidazole also exhibited great potentials in asymmetric transformations. Kitamura and co-workers disclosed the dihydropyrroloimidazole-type bidentate chiral ligands (Naph-diPIM) from 2,7-dibromo-1,8-dinitronaphthalene and appropriate acetonides of optically active 3,4-dihydroxy-pyrrolidine-2-one which was found utility in asymmetric Ru-catalyzed dehydrative allylation and Cu-catalyzed Friedel–Crafts reaction of indoles with trifluoropyruvates with high enantioselectivity (Scheme 1b).[7]

Despite these significant achievements in chiral imidazole ligands, the reported chiral imidazole ligands are mainly concentrated on the central chiral ligands and their application is limited. Therefore, the design and synthesis of efficient and practical chiral imidazole ligands is highly desirable. Among the various types of imidazoles, 2,2′-biimidazoles served as the

Scheme 1. Chiral Imidazole Compounds and the Design of Axially Chiral 2,2′-Biimidazole Ligands



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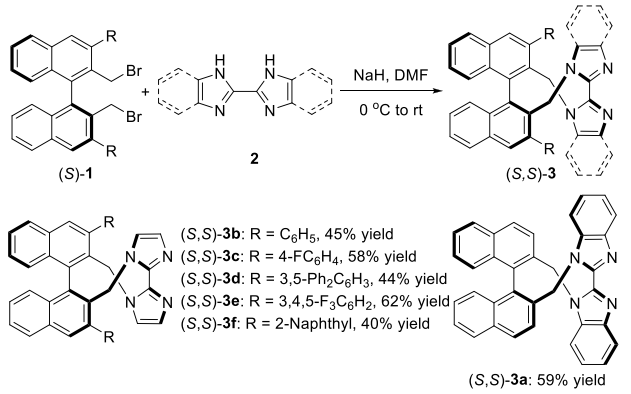
bimeric analogues of imidazole have been used as ligands applying to copper-catalyzed coupling reactions.[8] However, the design of 2,2′-biimidazole compounds as chiral ligands has rarely been reported. These difficulties can be attributed to the lack of efficient method introducing chiral elements into the backbone of 2,2′-biimidazoles. Notably, the strategy of remote chirality delivery plays an important role in the design of axially chiral ligands, demonstrated by the elegant case of C3-TunePhos and their derivatives[9] and axially chiral 2,2′-bipyridine ligands (Cn-ACBP).[10] In these ligands, the chirality can be transferred from central to axial. Inspired by previous work, we envisioned that this remote chirality delivery strategy can be applied to synthesis of chiral 2,2′-biimidazole ligands (Scheme 1c). Herein, a series of binaphthyl-derived axially chiral 2,2′-biimidazole ligands has been designed and synthesized through the strategy of remote chirality delivery (chirality transfer from axial chirality to axial chirality). 2,2′-Biimidazole ligands can be fine-tuned by substitutions on the 3,3′-position of binaphthyl moiety[11] and a flexible backbone. These ligands have been proven to be efficient for Cu- or Fe-catalyzed asymmetric insertion of α-aryl-α-diazoacetates into N−H bond of carbazoles with up to 96% ee.

The synthetic route is shown in Scheme 2, the treatment of (*S*)-3,3′-substituted-2,2′-bis(bromomethyl)-1,1′-binaphthalene

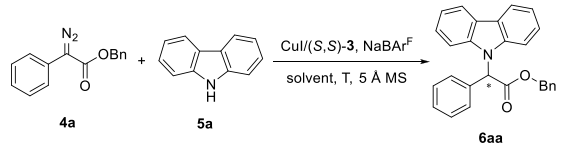
Scheme 2. Syntheses of Axially Chiral 2,2′-Biimidazole Ligands



1[12] with 2,2′-biimidazoles **2** under basic conditions afforded a series of axially chiral 2,2′-biimidazole ligands **3** with moderate yields. This synthetic method features easy operation and provides diverse axially chiral 2,2′-biimidazole ligands in one step, which made it more potential in the application of asymmetric catalysis. The structure and absolute configuration of (*S*,*S*)-**3b** were determined by X-ray diffraction (XRD) analysis.[13] Notably, perfect remote chirality delivery could be realized through chirality transfer of binaphthyl moiety to 2,2′-biimidazole moiety.

With chiral 2,2′-biimidazole ligands in hand, we next started to investigate their performance in transition-metal-catalyzed asymmetric reactions. The chiral *N*-substituted carbazoles are core structure of numerous designed pharmaceutical molecules, which can serve as 5-HT receptor agonists for treatment of central nervous system diseases.[14] In 2017, Van Vranken and co-workers demonstrated Pd-catalyzed N−H insertion reaction between carbazoles and α-diazo-α-phenylacetates by using a PyBOX, providing the products with excellent results.[15] However, high costs and toxicity of Pd reagents may restrict their wide application. As an abundant and inexpensive transition metal, copper has been widely used as a metal precursor for catalytic asymmetric insertion of α-diazoesters into N−H bonds.[16] To our delight, the copper complexes of (*S*,*S*)-**3a** was successfully applied in N−H insertion reaction between carbazoles and α-aryl-α-diazoacetates, giving the desired products in 90% yield and 85% ee (see Table 1, entry 1).

Table 1. Evaluation of Reaction Parameters[a]



entry	solvent	temperature, *T* (°C)	(*S*,*S*)-**3**	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	DCM	30	(*S*,*S*)-**3a**	90	85
2	$CHCl_3$	30	(*S*,*S*)-**3a**	90	87
3	toluene (tol)	30	(*S*,*S*)-**3a**	92	86
4	THF	30	(*S*,*S*)-**3a**	72	7
5	^{t}BuOMe	30	(*S*,*S*)-**3a**	74	92
6	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3a**	92	93
7	^{t}BuOMe/tol (1:1)	40	(*S*,*S*)-**3a**	92	92
8	^{t}BuOMe/tol (1:1)	50	(*S*,*S*)-**3a**	90	91
9	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3b**	82	81
10	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3c**	87	86
11	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3d**	82	90
12	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3e**	84	81
13	^{t}BuOMe/tol (1:1)	30	(*S*,*S*)-**3f**	84	81

[a]Conditions: **4a** (0.10 mmol), **5a** (0.15 mmol), CuI (5.0 mol %), (*S*,*S*)-**3** (5.0 mol %), $NaBAr^F$ (12 mol %), 5 Å MS (200 mg), solvent (2.0 mL), 12 h. [b]Isolated yields. [c]Determined by chiral HPLC.

Original experiments employed α-diazo-α-phenylacetate **4a** and carbazole **5a** at 30 °C in the presence of CuI/(*S*,*S*)-**3** as a catalyst and $NaBAr^F$ as an additive (Table 1). Initially, the reaction proceeded smoothly in DCM, giving the desired product **6aa** in 90% yield and 85% ee. Other different solvents were also evaluated, and it was found that the high yields were also achieved in toluene and chloroform, albeit with the moderate enantioselectivities. When the reaction solvent was THF, the yield was decreased to 72% (Table 1, entry 4). It was noted that *tert*-butyl methyl ether was proved to be beneficial for enantio-control, albeit comparatively low activity was observed (Table 1, entry 5). Fortunately, when a mixture solvent of toluene and ^{t}BuOMe with ratio of 1:1 was used, the optimal result was obtained (Table 1, entry 6). To further improve the efficiency of reaction, the temperature was increased to 40 and 50 °C, and yield was not obviously increased, although enantioselectivity slightly decreased. Therefore, we still selected 30 °C as the optimal temperature. Intrigued by these promising results, a series of axially chiral

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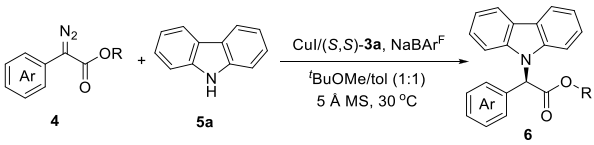
2,2′-biimidazole ligands (*S*,*S*)-**3** were explored (Table 1, entries 9−13). We are pleased to find that all the chiral biimidazole ligands could give good results. The 2,2′-biimidazole ligands (*S*,*S*)-**3a** was proved to be beneficial for the reaction, furnishing the desired product in 93% ee and 92% yield. Thus, the optimized conditions were established as CuI (5.0 mol %)/(*S*,*S*)-**3a** (5.0 mol %)/$NaBAr^F$ (12 mol %)/5 Å MS/^{t}BuOMe:Tol (1:1)/30 °C.

With the optimized reaction conditions established, we next investigated the substrate scope by reacting various α-diazo-α-arylacetates **4** with carbazole **5a** (see Table 2). As expected,

Table 2. Cu-Catalyzed Asymmetric Insertion of α-Aryl-α-diazoacetates into the N−H Bonds of Carbazoles[a]



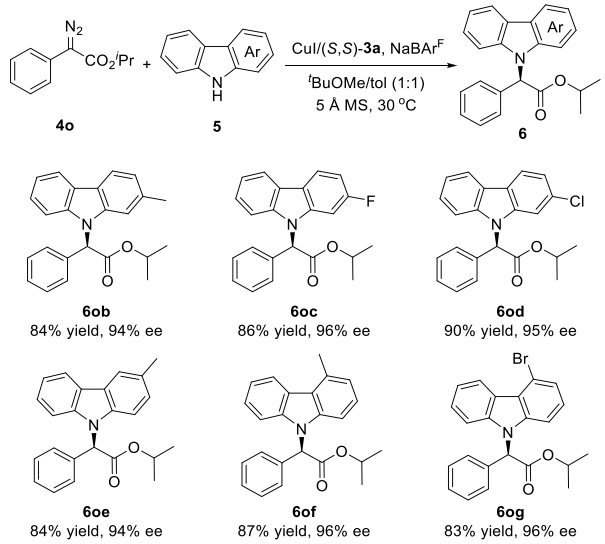
entry	Ar	R	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	Ph	Bn	92 (**6aa**)	93
2	4-MeC_6H_4	Bn	94 (**6ba**)	91
3	3-MeC_6H_4	Bn	91 (**6ca**)	93
4	4-MeOC_6H_4	Bn	88 (**6da**)	87
5	3-MeOC_6H_4	Bn	85 (**6ea**)	91
6	4-PhC_6H_4	Bn	94 (**6fa**)	90
7	4-FC_6H_4	Bn	93 (**6ga**)	92
8	4-ClC_6H_4	Bn	87 (**6ha**)	90
9	4-BrC_6H_4	Bn	89 (**6ia**)	89
10	3-BrC_6H_4	Bn	87 (**6ja**)	84
11	2-naphthyl	Bn	86 (**6ka**)	94
12	3-thienyl	Bn	81 (**6la**)	81
13	Ph	Me	86 (**6ma**)	88
14	Ph	Et	91 (**6na**)	90
15	Ph	^{i}Pr	90 (**6oa**)	95

[a]Conditions: **4** (0.10 mmol), **5a** (0.15 mmol), CuI (5.0 mol %), (*S*,*S*)-**3a** (5.0 mol %), $NaBAr^F$ (12 mol %), 5 Å MS (200 mg), ^{t}BuOMe/tol (2.0 mL, 1:1), 12−24 h. [b]Isolated yields. [c]Determined by chiral HPLC.

various diazo substrates **4** performed very well under the optimized conditions. The influence of the steric and electronic properties of substituent on the phenyl ring of **4** was exploited. The reaction gave the desired products with high yields and enantioselectivities, when electron-donating groups were introduced into the phenyl ring of **4**. Notably, the steric effects of the aryl substituent of **4** rarely influenced the reaction (**6aa**−**6ea**). Substrates **4** with electron-withdrawing groups on the phenyl ring had little effect on enantioselectivity. Although electron-withdrawing groups obviously slowed the reaction down, satisfactory yields were still achieved by prolonging the reaction time (**6ga**−**6ja**). In the case of 2-naphthyl-substituted diazoacetates, the reaction gave the corresponding product with 94% ee and 86% yield (**6ka**). Furthermore, heteroaromatic thienyl-substituted diazoacetates also were suitable, affording the desired product with 81% ee and 81% yield (**6la**). Finally, the reaction of diazoacetates bearing different ester groups was examined, and a slightly higher enantioselectivity was observed upon increasing the steric hindrance (**6ma**−**6oa**). The isopropyl group afforded a higher ee value (95% ee).

To further demonstrate the versatility of our method. The second stage of exploration of the reaction scope focused on various substituted carbazoles (Scheme 3). Pleasingly, good

Scheme 3. Cu-Catalyzed Asymmetric Insertion of α-Aryl-α-diazoacetates into the N−H Bonds of Carbazoles[a]



[a]Conditions: **4o** (0.10 mmol), **5** (0.15 mmol), CuI (5.0 mol %), (*S*,*S*)-**3a** (5.0 mol %), $NaBAr^F$ (12 mol %), 5 Å MS (200 mg), ^{t}BuOMe/tol (2.0 mL,1:1), 24 h.

yields and excellent enantioselectivities were also achieved under the standard conditions. The results indicated that this protocol was compatible with electron-donating group as well as electron-withdrawing groups at the 2-position of carbazoles (**6ob**−**6od**). For the 3-methyl-9*H*-carbazole (**5e**), the reaction proceeded smoothly, delivering the product **6oe** with 84% yield and 94% ee. In addition, the carbazoles with a methyl group or a bromo group at the 4-position were also converted to the target products with excellent enantioselectivities (**6of**−**6og**).

The initial success of our chiral 2,2′-biimidazole ligands prompted us to further evaluate their practical utility. Iron, as an abundant and environmentally benign metal, is an ideal alternative to the precious metals. Iron catalysts could be used in the asymmetric transformations of diazo compounds in view of the facile change of oxidation state and the distinct Lewis acid character.[17] To best of our knowledge, the enantioselective catalytic N−H insertion reaction by using iron complexes as catalyst remains a great challenge to organic chemists.[18] We decided to further evaluate the above 2,2′-biimidazole ligands in iron-catalyzed enantioselective insertion of the N−H bonds of carbazoles.

Initially, the optimized reaction condition was established by a series of screening experiments. Using $Fe(OTf)_2$/(*S*,*S*)-**3a** as a catalyst in *p*-xylene at 30 °C and $NaBAr^F$ as an additive, the reaction was conducted smoothly to give the target product in 72% yield and 93% ee (see Table S1 in the Supporting Information for details). All the chiral 2,2′-biimidazole ligands were evaluated, it was found that the electron-deficient ligands ((*S*,*S*)-**3c**, (*S*,*S*)-**3e**) gave higher yields and enantioselectivities than electron-rich ligands ((*S*,*S*)-**3b**, (*S*,*S*)-**3d**, (*S*,*S*)-**3f**). When (*S*,*S*)-**3a** was used, the highest ee value (93%) was obtained.

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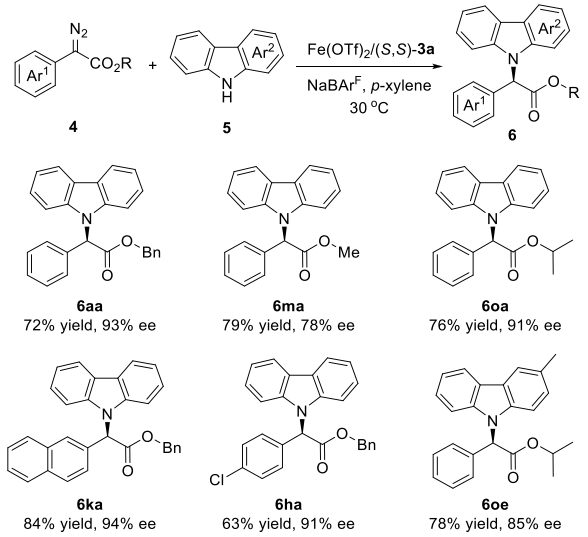
Under the optimized reaction conditions, several substrates were briefly examined for N−H insertion. As shown in Scheme 4, all the reaction could conduct smoothly, giving the products

Scheme 4. Fe-Catalyzed Asymmetric Insertion of α-Aryl-α-diazoacetates into the N−H Bonds of Carbazoles[a]



[a]Conditions: **4** (0.10 mmol), **5** (0.15 mmol), $Fe(OTf)_2$ (5.0 mol %), (*S*,*S*)-**3a** (5.0 mol %), $NaBAr^F$ (12 mol %), *p*-xylene (2.0 mL), 24 h.

in moderate yields and high enantioselectivities. First, the influence of ester size of the diazo compounds on activity and enantioselectivity of the N−H insertion was investigated, the benzyl ester afforded product with higher enantioselectivity (**6aa**−**6oa**). The best enantioselectivity was obtained for 2-diazo-2-(naphthalen-2-yl)acetate (**6ka**). When the electron-withdrawing group (−Cl) was introduced into the phenyl ring of **4**, the yield was decreased to 63% (**6ha**). The methyl on carbazole substrate was tolerated (**6oe**), but lower enantioselectivity was obtained, possibly because of the hindrance of methyl group.

In summary, we have designed and developed a series of novel axially chiral 2,2′-biimidazole ligands from (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene and 2,2′-bimidazoles in one step through the strategy of remote chirality delivery, which have shown excellent enantioselectivities and activities for Cu-catalyzed asymmetric insertion of α-aryl-α-diazoacetates into the N−H bond of carbazoles. Moreover, the highly enantioselective iron-catalyzed insertion of α-diazoacetates into the N−H bond have been realized by using iron complexes of chiral 2,2′-biimidazole ligands as a catalyst, with up to 94% ee. Note that this study paves a new way for further development of chiral imidazole ligands and realizes the application of 2,2′-biimidazole ligands in asymmetric catalysis. Further applications of these chiral 2,2′-biimidazole ligands in other catalytic asymmetric reactions are under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00687.

General procedures and NMR spectra of obtained compounds (PDF)

Accession Codes

CCDC 1887410 and 1887411 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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