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# Catalytic Asymmetric Imine Cross-Coupling Reaction

Xiang-Lei Han, Bin Hu, Chao Fei, Zhe Li, Yang Yu, Cheng Cheng, Bruce Foxman, Jisheng Luo,* and Li Deng*

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**ABSTRACT:** Catalytic asymmetric cross-coupling of imines constitutes a particularly desirable method for the synthesis of chiral vicinal diamines directly from readily available achiral precursors. The potential of this method lies in the possibility of utilizing a variety of imines as reacting partners. However, the realization of highly stereoselective cross-coupling of two different imines proved to be a formidable challenge. Herein we report an unprecedented catalytic asymmetric cross-coupling reaction that tolerates a variety of ketimines and aldimines as nucleophiles and electrophiles, respectively. The realization of this reaction resulted from the development of a new chiral ammonium catalyst, which was guided by insights from studies of catalyst−substrate interactions. With a 0.5 mol % loading of an organocatalyst, this reaction proceeded in a highly diastereo- and enantioselective manner to afford a diverse range of chiral vicinal diamines as nearly single stereoisomers. This catalytic reaction establishes a new approach for the asymmetric synthesis of chiral vicinal diamines.

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Chiral vicinal diamines exist widely in biologically active molecules.[1] They are also used as auxiliaries, reagents, ligands, and organocatalysts in asymmetric synthesis.[1a] Therefore, the development of catalytic asymmetric reactions for the synthesis of chiral diamines has attracted intensive efforts.[2−4] Significant progress has been made in the diamination of olefins,[5] the Mannich reaction of $\alpha$-amino enols/enolates from $\alpha$-amino esters,[6] and the aza-Henry reaction.[7] Recently, Zhu and co-workers reported a chiral phosphoric acid-catalyzed Mannich reaction of aromatic benzaldehyde hydrazone, which established the coupling reaction of hydrazones and imines.[8] Malcolmson and co-workers developed a Cu-catalyzed asymmetric reductive Mannich reaction of azadienes, which realized the coupling reaction of enamines and imines.[9] A particularly appealing strategy for accessing chiral diamines is the imine−imine coupling reaction because imines constitute a class of readily available organic compounds (Scheme 1a). Kobayashi and co-workers reported a single example of the Mannich reaction of glyoxylate imine by activation of the glyoxylate imine as an enol, affording an $\alpha,\beta$-diamino ester (Scheme 1b).[6d] Tang and co-workers realized homocoupling of *N*-methylbenzaldimine through a chiral diboron-mediated [3,3]-sigmatropic rearrangement, delivering the corresponding $C_2$-symmetric 1,2-diphenyldiamine with high ee (Scheme 1c).[10] To fully realize the potential of imine coupling reactions for chiral diamine synthesis, one must be able to accomplish catalytic asymmetric cross-coupling between two different imines while tolerating variations of both imines. To our knowledge, such a catalytic asymmetric imine coupling reaction has not yet been reported. We wish to report a catalytic asymmetric cross-coupling of imines (Scheme 1d). A significant challenge for the development of cross-coupling reactions of different imines is to suppress the homocoupling of imines. An imine umpolung Mannich reaction appeared to be an effective strategy to eliminate the homocoupling of imines. In this reaction, one imine is activated as a nucleophile, while the other remains an electrophile.

The cross-coupling of ketimine **1A** and aldimine **2A**[11] was examined as the model reaction. The reaction with 0.5 mol % CD-**1**,[12] a highly efficient catalyst for asymmetric imine umpolung 1,4-additions, afforded the desired adduct **3A** as a minor product and the undesirable regioisomer **4A** as the major product (**3A**/**4A** = 32/68; Table 1, entry 1). Although **3A** was formed with greater than 20:1 dr and 97% ee, the reaction stopped at 76% conversion. After extensive screening of phenols as additives, we found that reaction with 10 mol % phenol (see Table S1 for details) was completed in 24 h without compromising the stereoselectivities (Table 1, entry 2). We attempted to improve the regioselectivity by reducing the reaction temperature to −50 °C. Although we observed a slight improvement, **4A** was still generated as the major product (**3A**/**4A** = 44/56; Table 1, entry 3). We next turned to catalyst screening. The reaction with CD-**2**, which was derived by replacing the terphenyl group with an anthracenyl group, generated **4A** as the only product (Table 1, entry 4), while replacing the terphenyl group with a phenyl group led to an inactive catalyst (Table 1, entry 5). Well-known chiral ammonium salts such as the Corey catalyst[13] and Maruoka catalyst[14] were found to be inactive (Table 1, entry 5). These results indicated that both the terphenyl and 6-chloro-2,5-diphenyl-4-pyrimidinyl (PYR) groups played essential roles in the activity of CD-**1**.

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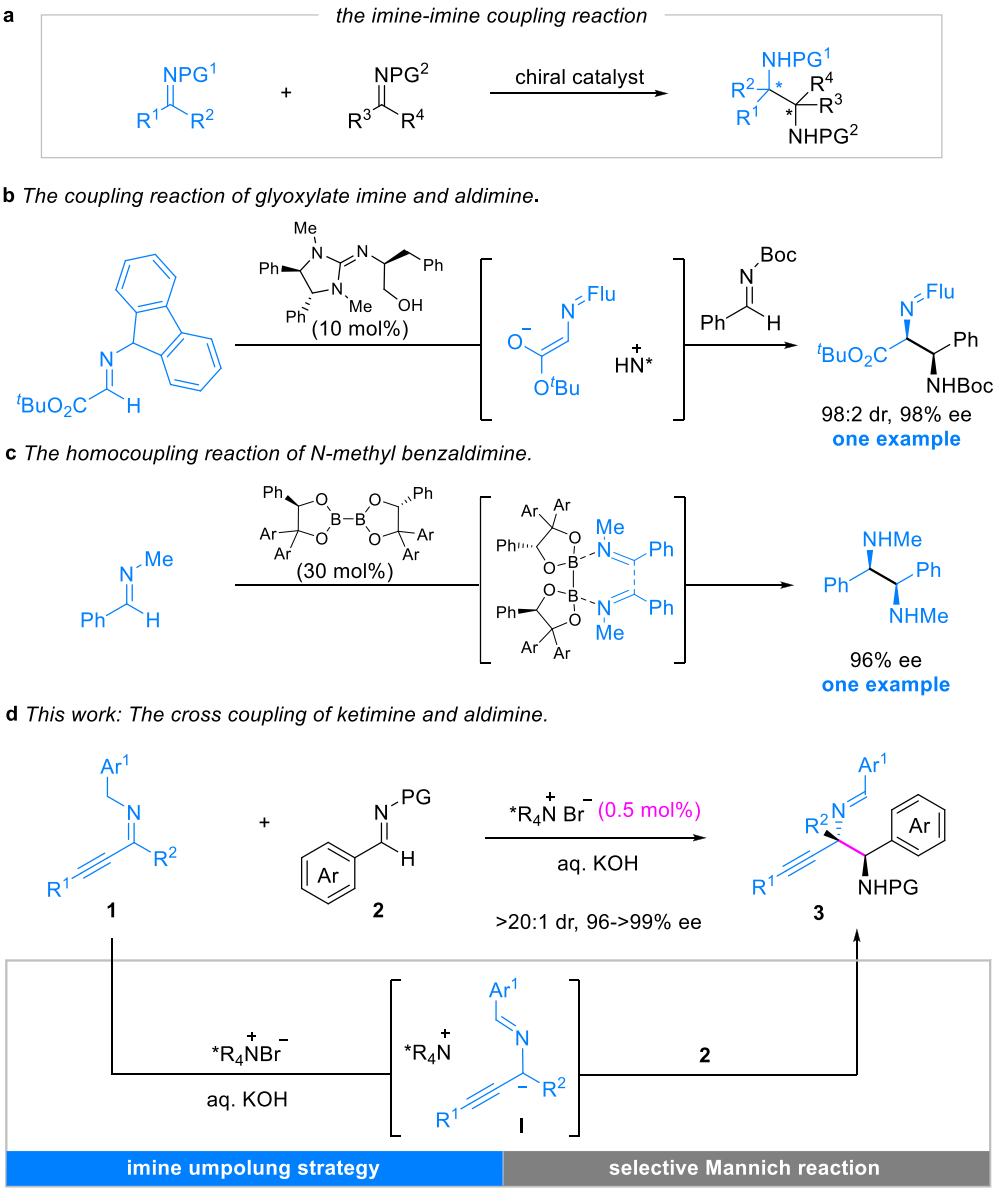
**Scheme 1. Catalytic Asymmetric Imine−Imine Coupling Reactions**




We suspected that the low regioselectivity could result from reactions in different sites where the catalyst interacted with the substrates in a site-dependent fashion. The nitrogen-centered tetrahedron with $C_2$, $C_6$, $C_8$, and $C_{12}$ as vertices presented four quadrants,[13,15] one of which was blocked by the quinuclidine ring, while the other three could be reaction sites (Table 1). We further postulated that by blocking one of the other three quadrants, one might hamper the reaction pathway to generate **4A**. To gain insight into how to accomplish this task through catalyst modifications, we examined the X-ray structure of C-**9**, a pseudoenantiomer of CD-**1** that mediated the reaction of **1A** and **2A** to generate **3A** with greater than 20:1 dr and −86% ee (Figure 1). Assuming that CD-**1** adopted a mirror-image-like conformation with respect to that of C-**9**, we anticipated that a modification of the vinyl group of CD-**1** into a bulky group could provide a steric barrier in quadrant $N{-}C_2{-}C_6{-}C_{12}$. Following these considerations, we prepared CD-**6**, in which the vinyl group of the cinchonidine skeleton was converted into a 2-((triisopropylsilyl)oxy)ethyl group.[15] Gratifyingly, the reaction with CD-**6** gave **3A** as the major regioisomer without compromising the stereoselectivities (**3A**/**4A** = 70/30; Table 1, entry 6). Subsequently, we found that the regioselectivity could be further improved with CD-**7** (**3A**/**4A** = 80/20; Table 1, entry 7).

Having established the optimized conditions, we next investigated the substrate scope (Scheme 2). With 0.5 mol % CD-**7**, $\alpha$-alkynyl ketimines **1** bearing various aliphatic substituents underwent smooth imine cross-coupling reactions with aldimines **2** with excellent diastereo- and enantioselectivity (>20:1 dr, 96 to >99% ee). Although regioisomer **4** was generated as a minor side product in most cases, diamines **3A**−**3P** and **3a**−**3l** were obtained in 45−85% yield. This reaction readily tolerates various functional groups in the ketimine part, including alkene (**3B**), ether (**3C**), imide (**3D**), alkyne (**3E**), arenes (**3F**−**3J**), chloride (**3K**), and ester (**3L**). The scope of the $\beta$-substituent of the alkynyl group was also examined. It was found that the reaction of alkynyl ketimines with $\beta$-TMS (**3M**) and $\beta$-TES (**3N**) proceeded smoothly with simlar selectivities, while the reaction of 3-phenylethynyl ketimine (**3O**) and ethynyl ketimine (**3P**) provided excellent diastereo-


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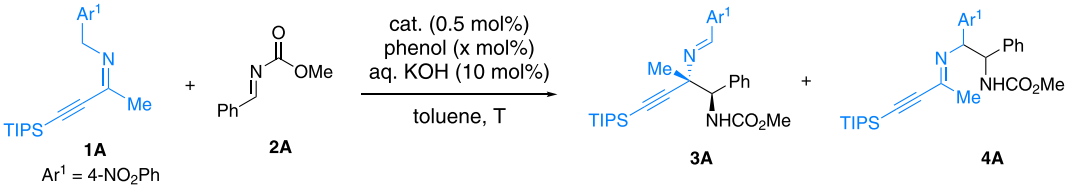
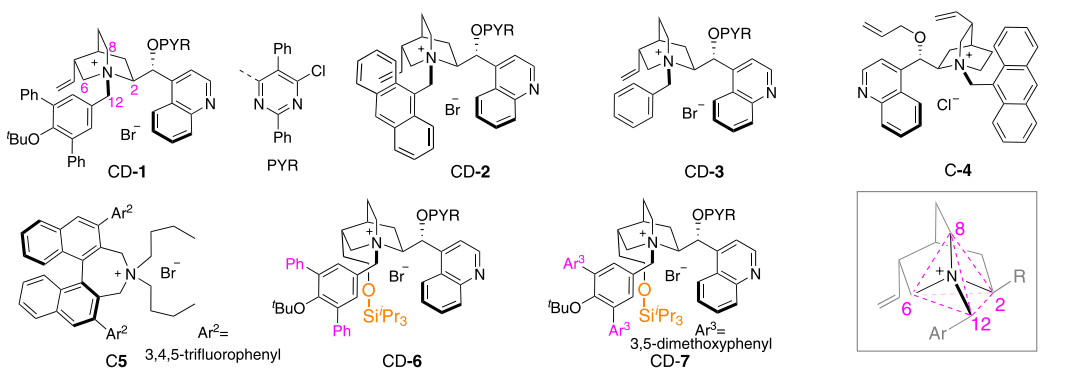
**Table 1. Catalyst Investigation**[a]




| entry | catalyst | mol % phenol ($x$) | $T$ (°C) | time (h) | conversion (%)[b] | regioselectivity [**3A**]/[**4A**][b] | dr of **3A**[b] | ee of **3A** (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | CD-**1** | 0 | −20 | 24 | 76 | 32/68 | >20:1 | 97 |
| 2 | CD-**1** | 10 | −20 | 24 | >99 | 33/67 | >20:1 | 97 |
| 3 | CD-**1** | 10 | −50 | 10 | >99 | 44/56 | >20:1 | 98 |
| 4 | CD-**2** | 10 | −50 | 24 | 62 | 0/100 | – | – |
| 5 | CD-**3**, C-**4**, C**5** | 10 | −50 | 24 | <5 | – | – | – |
| 6 | CD-**6** | 10 | −50 | 10 | >99 | 70/30 | >20:1 | >99 |
| 7 | CD-7 | 10 | −50 | 6 | >99 | 80/20 | >20:1 | >99 |

[a]Reactions were performed with **1A** (0.050 mmol), **2A** (0.10 mmol), catalyst (0.5 mol %), phenol ($x$ mol %), and aqueous KOH (50 wt %, 0.55 μL, 10 mol %) in toluene (0.5 mL). TIPS: triisopropylsilyl. [b]Conversion, regioselectivity, and diastereoselectivity were determined by $^1$H NMR analysis. [c]Determined by HPLC on a chiral column.

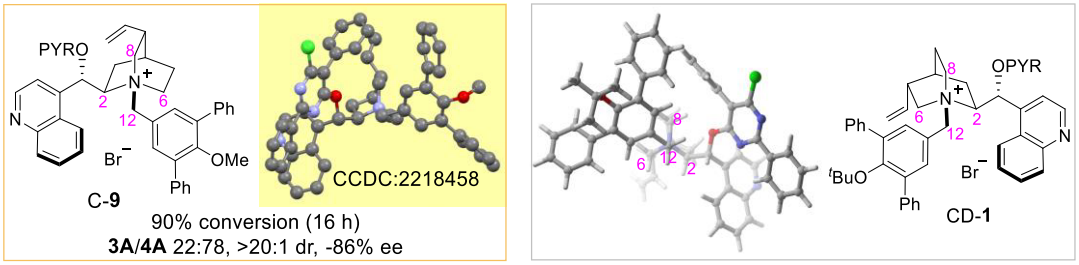



**Figure 1.** X-ray structure of C-**9** and a mirror-image-like conformation with respect to that of C-**9**.

and enantioselectivity and slightly decreased regioselectivity. We carried out the reaction of a ketimine bearing a 1-butynyl group. The reaction proceeded to completion under the standard reaction conditions, affording **3Q** with >99% ee and >20:1 dr in 17% yield. The **3Q**/**4Q** ratio was determined to be 22/78. We next examined the scope of electrophile benzaldimines **2** bearing different substituents. The reactions proceeded efficiently, affording diamines **3a**−**3l** with excellent diastereoselectivity (>20:1 dr) and enantioselectivity (97 to >99% ee) in 52−78% yield. As shown in Scheme 2, alkyl (**3a**, **3b**), thia (**3c**), alkoxy (**3d**, **3e**), and halogen groups at the *ortho*, *meta*, and *para* positions (**3g**−**3l**) were well-tolerated in this reaction.

As shown in Scheme 3, the chiral diamine products could be readily transformed to various diamine derivatives. For example, the imine group of **3A** was hydrolyzed with aqueous HCl (3 *N*) at room temperature to furnish amine **5** as the hydrogen chloride salt in good yield. Upon treatment of **5** with aqueous HBr, diamine **6** could be obtained in 86% yield. The alkynyl group in adduct **3P** could be converted to various structures via classic Sonogashira coupling and click reactions (Scheme 3b). Because the catalyst could tolerate variation of the alkyl substituents in ketimines **1**, we could prepare chiral diamines containing *N*-substituted quaternary stereocenters bearing similar aliphatic groups (Scheme 3c).

To understand the origin of the improved regioselectivity by CD-7, we carried out $^1$H NMR titration studies[16] to gain insight into the impact of the bulky silyl ether group on how the catalyst interacted with electrophile imine **2A**. Ammonium salts CD-7′ and CD-**10**′ with tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ([BArF]$^-$) as the counteranion were prepared from the corresponding ammonium bromides CD-7 and CD-**10** (Scheme 4).[17−19] CD-7′ and CD-**10**′ were examined as catalysts for the imine cross-coupling reaction. As shown in Scheme 4, catalyst CD-7′ provided the desired adduct **3A** with the same high dr and ee as in the CD-7-catalyzed reaction.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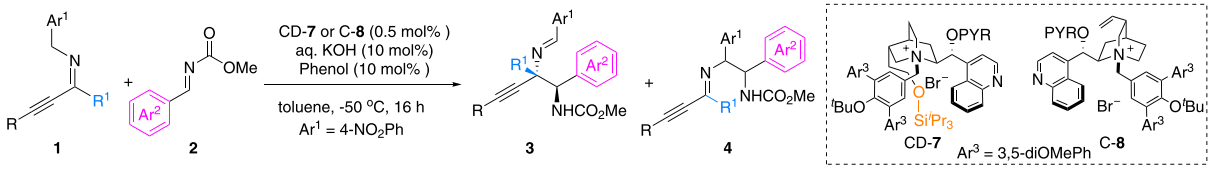
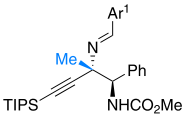
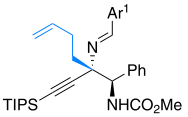
**Scheme 2. Substrate Scope**[a,b]



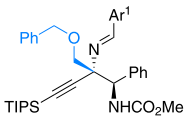
**3A**

CD-**7**: >99% ee, >20/1 dr
**3A**/**4A** 81/19, 75% yield
C-**8**: -99% ee, >20/1 dr
**3A**/**4A** 65/35, 61% yield



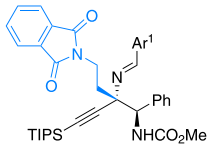
**3B**

CD-**7**: >99% ee, >20/1 dr
**3B**/**4B** 77/23, 76% yield
C-**8**: >-99% ee, >20/1 dr
**3B**/**4B** 63/27, 60% yield



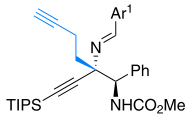
**3C**

>99% ee, >20/1 dr
**3C**/**4C** 95/5, 80% yield



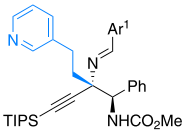
**3D**

>99% ee, >20/1 dr
**3D**/**4D** 90/10, 81% yield



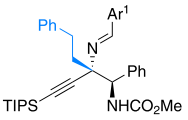
**3E**

>99% ee, >20/1 dr
**3E**/**4E** 87/13, 85% yield



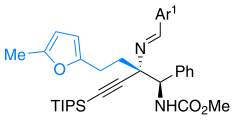
**3F**

>99% ee, >20/1 dr
**3F**/**4F** 87/13, 70% yield



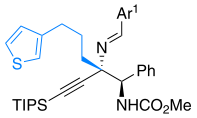
**3G**

>99% ee, >20/1 dr
**3G**/**4G** 80/20, 71% yield



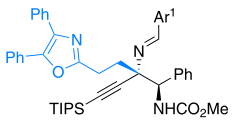
**3H**

>99% ee, >20/1 dr
**3H**/**4H** 77/23, 68% yield



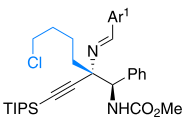
**3I**

>99% ee, >20/1 dr
**3I**/**4I** 77/23, 75% yield



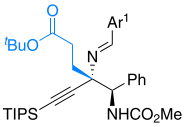
**3J**

>99% ee, >20/1 dr
**3J**/**4J** 71/29, 69% yield



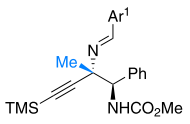
**3K**

>99% ee, >20/1 dr
**3K**/**4K** 78/22, 56% yield



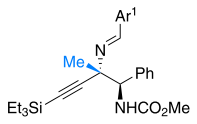
**3L**

>99% ee, >20/1 dr
**3L**/**4L** 77/23, 60% yield



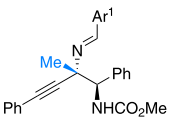
**3M**

>99% ee, >20/1 dr
**3M**/**4M** 71/29, 70% yield



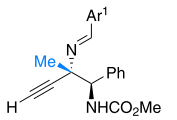
**3N**

96% ee, >20/1 dr
**3N**/**4N** 75/25, 71% yield



**3O**

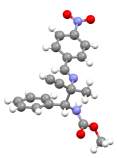
>99% ee, >20/1 dr
**3O**/**4O** 47/53, 45% yield



**3P**

>99% ee, >20/1 dr
**3P**/**4P** 60/40, 59% yield

≡



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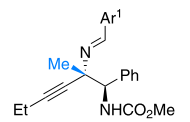
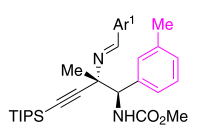


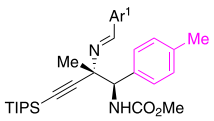
**3Q**

>99% ee, >20/1 dr
**3Q**/**4Q** 22/78, 17% yield



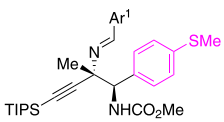
**3a**

97% ee, >20/1 dr
**3a**/**4a** 85/15, 71% yield



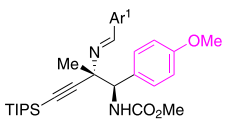
**3b**

>99% ee, >20:1 dr
**3b**/**4b** 78/22, 76% yield



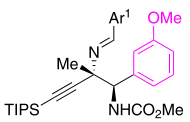
**3c**

98% ee, >20/1 dr
**3c**/**4c** 74/26, 71% yield



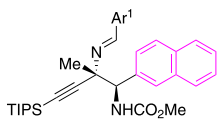
**3d**

CD-**7**: >99% ee, >20/1 dr
**3d**/**4d** 80/20, 77% yield
C-**8**: -98% ee, >20:1 dr
**3d**/**4d** 66/34, 61% yield



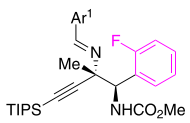
**3e**

>99% ee, >20/1 dr
**3e**/**4e** 80/20, 78% yield



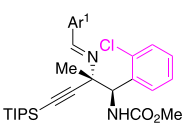
**3f**

97% ee, >20/1 dr
**3f**/**4f** 71/29, 62% yield



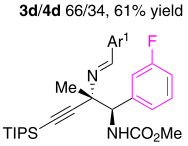
**3g**

>99% ee, >20/1 dr
**3g**/**4g** 57/43, 54% yield



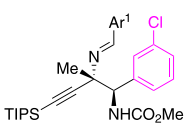
**3h**

>99% ee, >20/1 dr
**3h**/**4h** 54/46, 52% yield



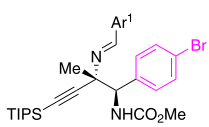
**3i**

>99% ee, >20/1 dr
**3i**/**4i** 61/39, 59% yield



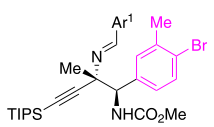
**3j**

>99% ee, >20/1 dr
**3j**/**4j** 65/35, 62% yield



**3k**

CD-**7**: >99% ee, >20/1 dr
**3k**/**4k** 72/28, 69% yield
C-**8**: -97% ee, >20/1 dr
**3k**/**4k** 60/40, 56% yield



**3l**

>99% ee, >20/1 dr
**3l**/**4l** 71/29, 69% yield

[a]Reactions were performed with **1** (0.20 mmol), **2** (0.40 mmol), CD-7 or C-**8** (0.5 mol %), phenol (10 mol %), and aqueous KOH (50 wt %, 0.22 μL, 10 mol %) in toluene (2.0 mL) at −50 °C for 16 h. The dr values were determined by $^1$H NMR analysis, and the ee values were determined by HPLC on a chiral column. [b]Yields of isolated **3** are reported.

Importantly, the CD-7′-promoted cross-coupling reaction provided **3A** as the major product, albeit with lower regioselectivity. On the other hand, imine coupling reactions with both CD-**10**′ and CD-**10** afforded **3A** as a minor product.



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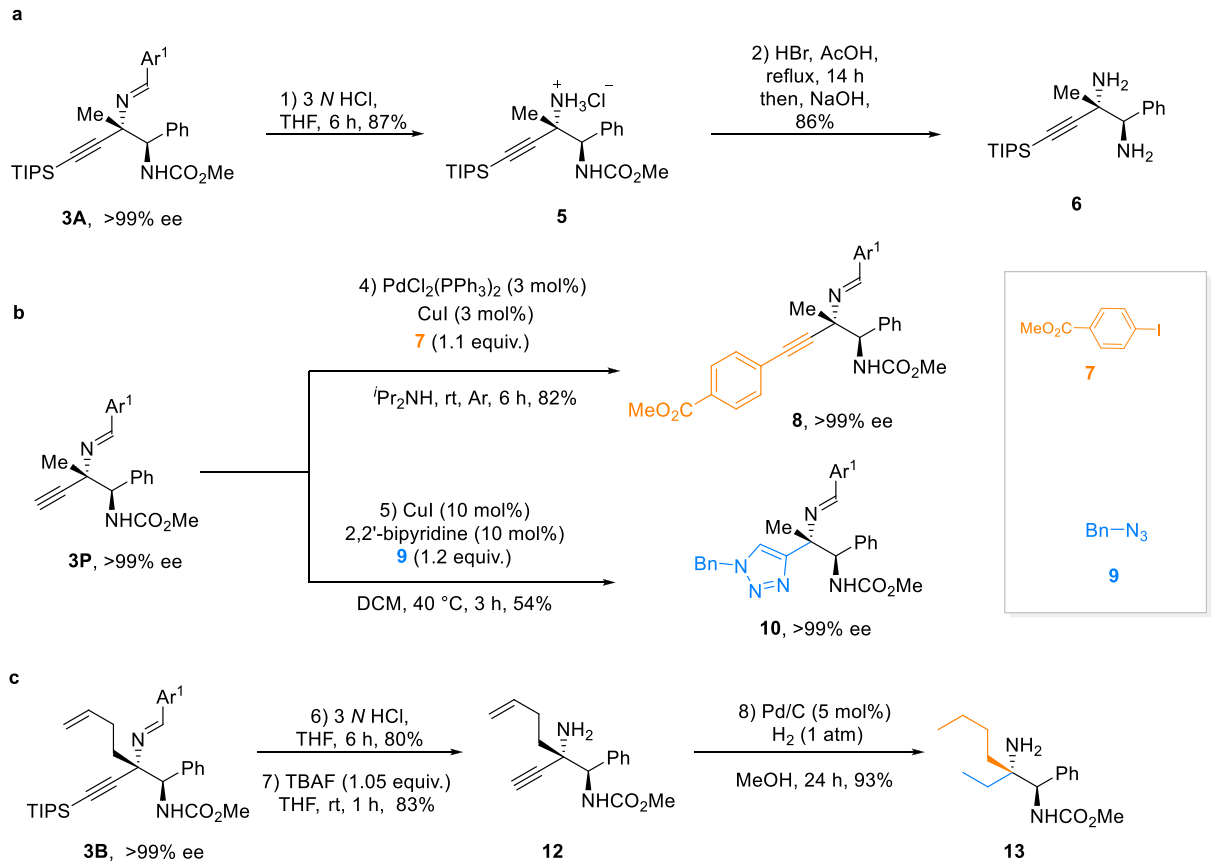
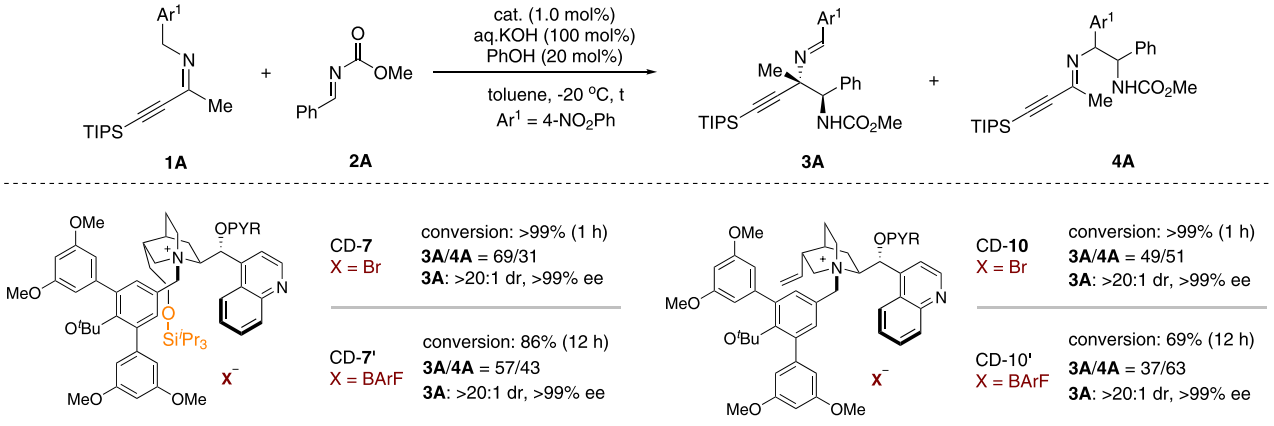
**Scheme 3. Derivatizations of the Products**




**Scheme 4. Structures of CD-7′ and CD-10′ and Their Catalytic Activities in Cross-Coupling Reactions**[a]




[a]Reactions were performed with **1A** (0.10 mmol), **2A** (0.20 mmol), catalyst (1.0 mol %), phenol (20 mol %), and aqueous KOH (50 wt %, 11.0 μL, 100 mol %) in toluene (1.0 mL) at −20 °C. Conversions, regioselectivities, and diastereoselectivities were determined by $^1$H NMR analysis, and ee values were determined by HPLC on a chiral column.

In the titration of CD-7′ with **2A**, the signals of ammonium α-CH ($H_8$, $H_{12}$, $H_{12'}$) and $H_{5'}$ shifted downfield, while the signals of ammonium α-CH ($H_2$, $H_6$) barely shifted (Scheme 5b; see pp 55−56 in the Supporting Information for details). In the titration of CD-**10**′ with **2A**, the signals of ammonium α-CH ($H_2$, $H_6$, $H_8$, $H_{12}$) and $H_{5'}$ significantly shifted downfield (Scheme 5c). These titration results indicated that both quadrants $N$−$C_2$−$C_6$−$C_{12}$ and $N$−$C_2$−$C_8$−$C_{12}$ of CD-**10** interacted with **2A**, while CD-7, due to the presence of a bulky silyl ether group, interacted with **2A** primarily in quadrant $N$−$C_2$−$C_8$−$C_{12}$. When CD-**10** was employed as a catalyst, the Mannich reaction might occur in both quadrants $N$−$C_2$−$C_6$−$C_{12}$ and $N$−$C_2$−$C_8$−$C_{12}$, resulting in competing side reactions toward **4** (**3A**/**4A** = 67/33, >20:1 dr, >99% ee). With CD-7 as the catalyst, the Mannich reaction took place mostly in quadrant $N$−$C_2$−$C_8$−$C_{12}$, thereby enhancing the desired reaction toward **3** (**3A**/**4A** = 80/20, >20:1 dr, >99% ee). Conventionally, chiral ammonium salts have been postulated to form ion pair complexes with nucleophilic anions in asymmetric phase transfer catalysis.[20] Based on computational studies, Smith and co-workers postulated hydrogen-bonding interactions between ammonium α-CHs and nucleophilic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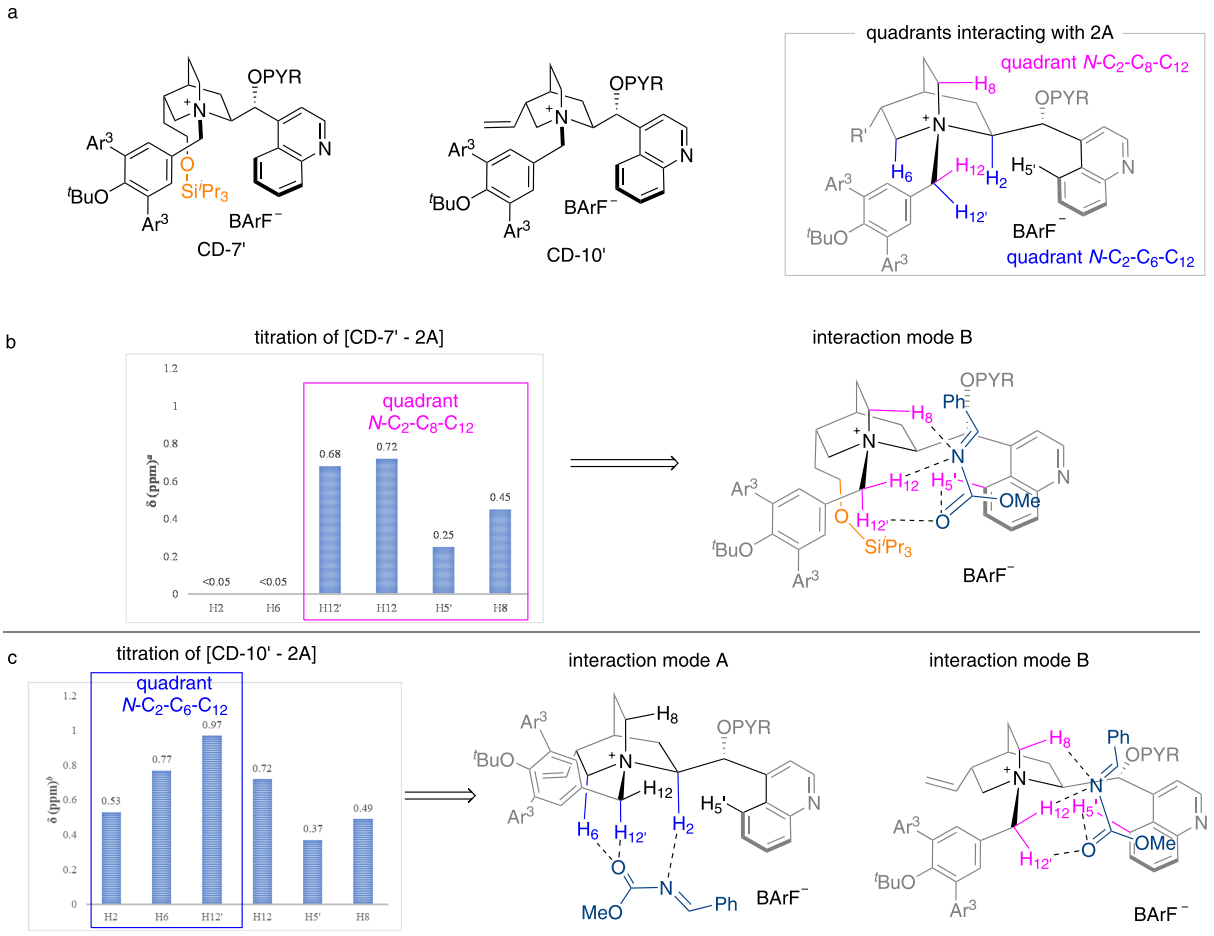
**Scheme 5. Study of the Interaction between the Catalyst and Electrophile Imine 2A**[a,b]




[a]$^1$H NMR chemical shifts ($\delta$) of CD-7′ [5.0 mM] in toluene-$d_8$ with 50.0 equiv of **2A**. [b]$^1$H NMR chemical shifts ($\delta$) of CD-**10**′ [5.0 mM] in toluene-$d_8$ with 75.0 equiv of **2A**.

enolate and carbonyls in the asymmetric intramolecular C−C bond-forming reaction.[21,22] Recently, Vetticatt, Waser, Adamo, and co-workers detected hydrogen-bonding interactions between a chiral ammonium catalyst and the electrophiles in a highly enantioselective reaction.[23−26] The current studies, to our knowledge, provide the first example of tuning such hydrogen-bonding interactions by catalyst modifications to realize an efficient asymmetric reaction.

In summary, we developed an unprecedented catalytic asymmetric cross-coupling reaction of imines. With only 0.5 mol % catalyst, this reaction allowed the employment of various ketimines as nucleophiles and aldimines as electrophiles to afford a diverse range of chiral 1,2-diamines in a highly stereoselective manner. The realization of this reaction resulted from the development of a new chiral ammonium catalyst, which was guided by insights into catalyst−electrophile interactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c00051.

Experimental procedures and analysis data for all new compounds (PDF)

### Accession Codes

CCDC 2141554 and 2218458 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, U.K.; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Jisheng Luo** − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science and Research Center for Industries of the Future, Westlake University, Hangzhou 310030, China;* orcid.org/0000-0001-8571-5619; Email: luojisheng@westlake.edu.cn

**Li Deng** − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science and Research Center for Industries of the Future, Westlake University, Hangzhou 310030, China;* orcid.org/0000-0003-2233-0222; Email: dengli@westlake.edu.cn

### Authors

**Xiang-Lei Han** − *Department of Chemistry, Zhejiang University, Hangzhou 310027, China; Key Laboratory of*

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*Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science and Research Center for Industries of the Future, Westlake University, Hangzhou 310030, China*

**Bin Hu** − *Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States;* orcid.org/0000-0002-9212-0776

**Chao Fei** − *Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States*

**Zhe Li** − *Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States*

**Yang Yu** − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science and Research Center for Industries of the Future, Westlake University, Hangzhou 310030, China;* orcid.org/0000-0001-9622-5340

**Cheng Cheng** − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science and Research Center for Industries of the Future, Westlake University, Hangzhou 310030, China*

**Bruce Foxman** − *Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States;* orcid.org/0000-0001-5707-8341

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c00051

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### Notes

The authors declare no competing financial interest.

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