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Copper-Catalyzed Asymmetric Arylation of *N*-Heteroaryl Aldimines via an Elementary Step of 1,4-Insertion

Chunlin Wu,[†a] Xurong Qin,[†a] Adhitya Mangala Putra Moeljadi,[b] Hajime Hirao[b] and Jianrong Steve Zhou[a]*

Abstract: Copper complexes of monodentate phosphoramidites efficiently promote asymmetric arylation of *N*-azaaryl aldimines with arylboroxines. DFT calculations and kinetic isotopic experiments support an elementary step of 1,4-insertion in the reaction pathway, in which an aryl-copper species adds directly across four atoms C=N-C=N in *N*-azaaryl aldimines.

Chiral alkylamines are important motifs in modern medicines and they are present in about 15% of blockbuster drugs. Therefore, efficient stereoselective synthesis of these compounds has received much attention amongst synthetic chemists.[1] Of particular interest to us, chiral *N*-azaaryl alkylamines are present in quite a number of medicines and drug candidates (Figure 1). For example, ontazolast is a drug currently used for the treatment of inflammation.[2] Chiral amine-substituted thiazole, pyrazole and imidazopyridazine are also found in many therapeutic agents that target depression, Alzheimer's disease and malaria.[3] Moreover, aminopyrimidines are present in an isocitrate dehydrogenase (IDH) inhibitor[4] and difulmetorim. The latter is a new-generation fungicide to protect wheat and barley.[5]

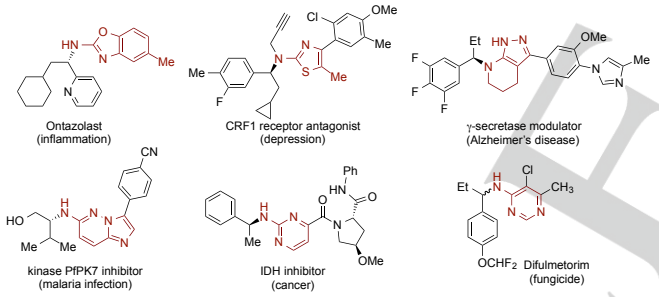
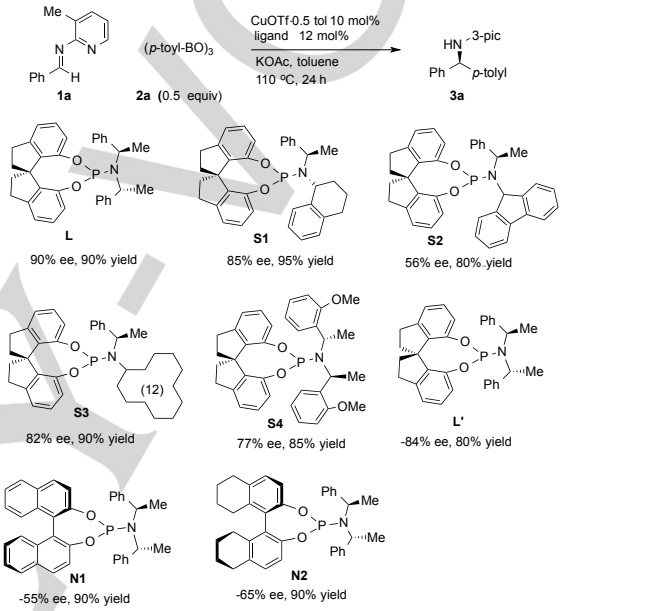


Figure 1. Examples of chiral medicines and agrochemicals containing *N*-azaaryl amines.

Catalytic asymmetric arylation of imines using benchtop-stable arylboron reagents is a simple, convergent method to prepare chiral benzylic and benzhydryl amines from readily available reagents.[6] For this reaction, noble metal catalysts, mostly based on rare and expensive rhodium[7] and palladium,[8] proved to be particularly effective, owing to efforts of Hayashi,[9] Lin and Xu,[10] Zhang,[11] Manolikakes,[12] and others.[13] From a mechanistic standpoint, both rhodium and palladium catalysts use 1,2-insertion of arylmetal species to imines.[14] In most cases, imines activated with *N*-sulfonyl and *N*-sulfamoyl groups were used. Recently, chiral 1,1'-biphenols and thioureas were also used in asymmetric addition of arylborons to reactive α-iminoesters.[15]



Scheme 1. Screening of chiral phosphoramidites for model arylation.

Initially, we attempted copper-catalyzed arylation of aldimines with arylboroxines and searched for chiral ancillary ligands (Scheme 1).[16] Among a dozen of aldimines carrying different groups on the nitrogen atom that we have tested (see Schemes 5 and 6c), aldimine **1a** bearing an *N*-3-picolyl ring afforded the desired product in both good yield and excellent stereoselectivity. Thus, 10 mol% copper catalyst ligated by spiro-1,1'-diindanyl phosphoramidite **L**[17] promoted arylation of *p*-tolylboroxine **2a** to deliver benzhydryl amine **3a** in 90% ee and 90% yield. Modification of the amine fragment of **L** failed to improve the stereoselectivity further unfortunately (**S1-4**). Later, we prepared ligand **L'** with inverted spiro chirality, which led to the opposite enantiomer of **3a** as the major isomer (-84% ee). Therefore, the spiro-backbone is the dominant stereo-determining element in the catalyst. Furthermore, two Feringa ligands **N1**-**2** only provided **3a** in moderate ee values. 0.5 equiv of *p*-tolylboroxines also gave **3a** in 85% yield after 2 days. Other arylboron regents were also tested such as $PhB(OH)_2$, $PhBF_3K$, PhBpin and PhB(cat), which provided no desired product. As a note of caution, the reaction was sensitive to trace amounts of added water, so dry solvents must be used.

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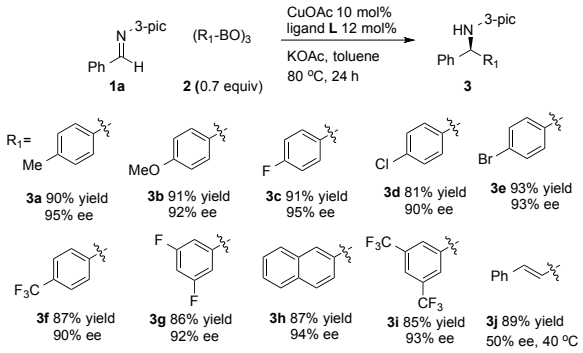
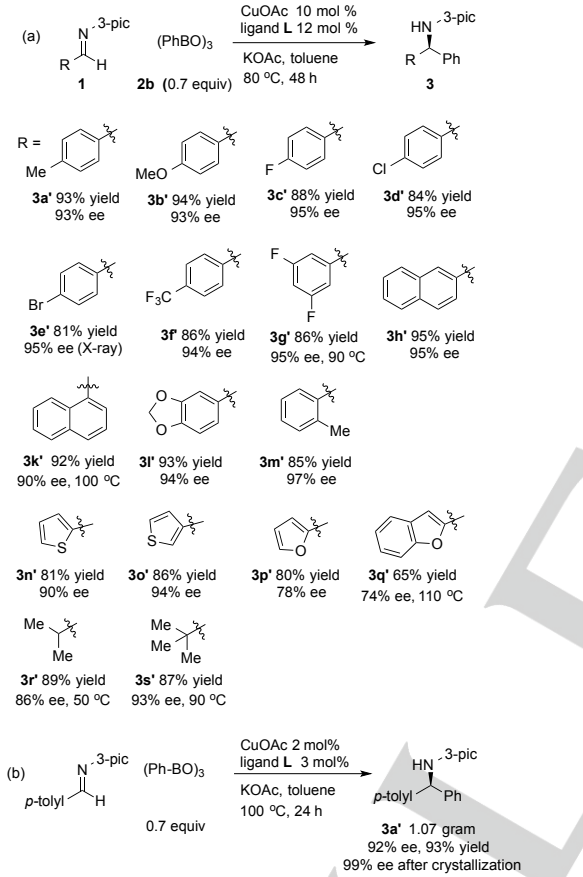


Scheme 2. Organoboroxines in asymmetric addition to **1a.**

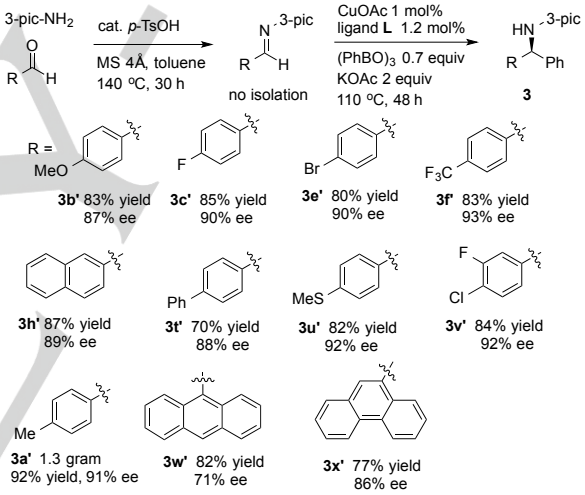


Scheme 3. (a) Examples of arylation of aldimines. (b) A gram-scale arylation of an aldimine.

The optimized copper catalyst of ligand **L** was applicable to asymmetric arylation of aldimine **1a** using both electron-rich and poor aryl boroxines (**3a**-**i**) (Scheme 2). In particular, aryl fluorides, chlorides and bromides were well tolerated (**3c**-**e** and **3g**), but aryl iodides inhibited the desired transformation. In the reaction of *o*-tolyl boroxine, the corresponding product was obtained in good yield, albeit in moderate 66% ee. 4-Pyridyl boroxine did not react at all whiles 3-pyridyl analogues led to about 10% yield. Methyl boroxine did not react at all. Unfortunately, the addition of *trans*-styryl boroxine (**3j**) resulted in only moderate 50% ee.

Many aromatic aldimines of different electronic and steric properties on aryl rings also reacted smoothly with phenyl boroxine (Scheme 3). Moreover, heterocycles such as thiophene, furan and benzofuran (**3n'**-**q'**) were tolerated. We found that *sec*- and *tert*-alkyl aldimines (**3r'**-**s'**) also reacted well, but linear aliphatic aldehydes led to a complex mixture during aldimine formation. A brominated product **3e'** was suitable for single-crystal X-ray diffraction and its configuration was determined to be 1*S*.[18] In a scale-up reaction, 2 mol% of the copper catalyst was sufficient to produce one gram of **3a** when the reaction temperature was raised from 80 to 100 °C (Scheme 3b). A simple crystallization readily improved optical purity of **3a'** to 99%. *N*-picolylamine **3a'** can be easily converted to the *N*-Boc amine via a reported procedure.[19]

To streamline the synthesis of benzhydryl amines, we condensed 3-picolyl-2-amine and aryl aldehydes in the presence of a catalytic amount of tosylic acid together with molecular sieve (Scheme 4). The resulting aldimines were used directly, without purification, in the next step of catalytic arylation.[20] At 110 °C, we found that 1 mol% copper catalyst was sufficient to achieve full conversion in all cases, which was accompanied by a slight drop of ee values.



Scheme 4. Streamlined arylation of aromatic aldimines.

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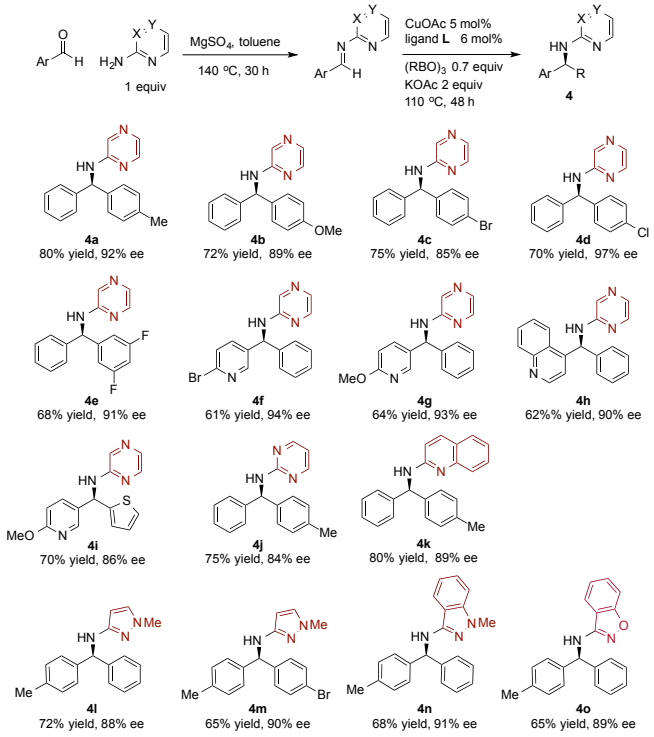


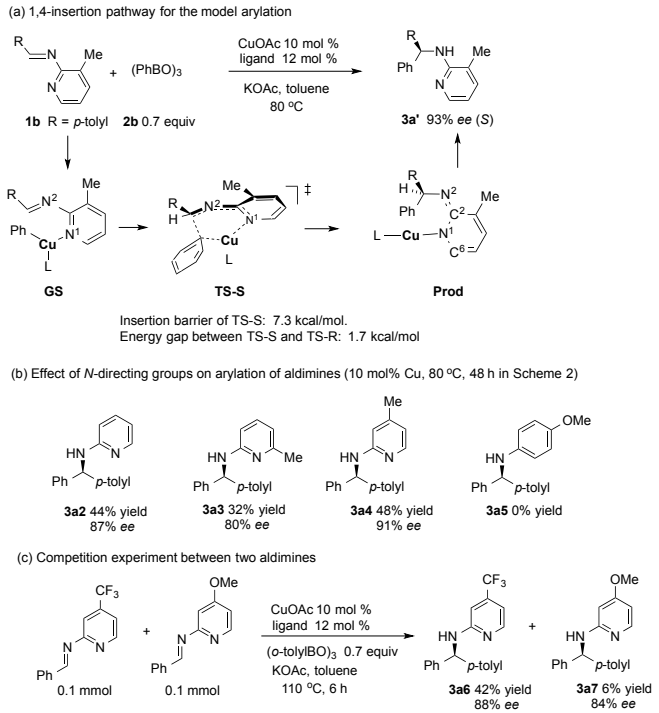
Scheme 5. Streamlined arylation of other *N*-azaaryl aldimines.

Furthermore, a streamlined procedure was established for asymmetric synthesis of biarylmethylamines from other heteroaryl amines derived from pyrazine (**4a-i**), pyrimidine (**4j**), quinoline (**4k**), pyrazole (**4l-m**), 2-indazole (**4n**) and 2-benzoisoxazole (Scheme 5). Herein, magnesium sulfate was used instead of molecular sieve, to improve the reproducibility of aldimine condensation. We found that the reactions in Scheme 5 were generally slower than those of *N*-2-picolyl aldimines; therefore, 5 mol% copper catalyst was needed to achieve good conversion at 110 °C, owing to relatively weak binding of these azacycles to the copper catalyst. Unfortunately, derivatives of azolyl amines of 1,3-oxazole, imidazole and 1,3-benzothiazole led to desired amines in good yields, but in 0-10% ee, probably because of competitive binding of these azoles to generate achiral copper catalysts.

We studied the insertion of phenylcopper(I) complex[21] with a single phosphoramidite **L** into bound aldimine **1b,** using DFT calculations (B3LYP-D3(BJ)(SCRF)//B3LYP-D3(BJ)/B1 level) (Scheme 6a). In ground state **GS**, the coordination geometry around the copper center was trigonal planar. The three-coordinate organocopper(I) centers have been reported by others previously as key intermediates or as key fragments in copper-catalyzed reactions.[22] Instead of classical 1,2-insertion,[12] we identified that 1,4-insertion of the copper-carbon bond into the core fragment of $C{=}N^2{-}C{=}N^1$ of **1b** was the more energetically favored pathway (Scheme 6a).[23] The activation barrier leading to the major (*S*)-isomer was 7 kcalmol^{-1}. Moreover, the energy gap between two transition states **TS-S** and **TS-R** was 1.7 kcalmol^{-1}, in good agreement with the observed 93% ee. We also calculated 1,2-insertion pathways, which had much higher insertion barriers (21 and 23 kcalmol^{-1} leading to (*R*)- and (*S*)-isomer), but it predicted the (*R*)-enantiomer as the major, in contradiction with experimental results.

The 1,4-insertion step led to immediate product **Prod** with a partially *dearomatized* pyridine, which helped to disperse the negative charge on the iminyl nitrogen. Wiberg bond index analysis revealed that from **GS** to **Prod**, the bond order of $N^1{-}C^2$ decreased from 1.29 to 1.15, while that of $N^2{-}C^2$ increased significantly from 1.16 to 1.52.

The new 1,4-insertion mechanism also received some experimental support (Scheme 6). (a) The 3-methyl group on *N*-picolyl aldimines reinforced the *s-cisoid* reactive conformation of aldimines by exerting $A^{1,3}$-type strain and thus accelerated the insertion process. Its omission or replacement at other positions on the *N*-pyridine resulted in much slower conversions (**3a2-4**). (b) The *N*-3-picolyl ketimine of acetophenone failed to react, because the iminyl methyl group disfavors the *s-cisoid* conformation. (c) All of other aldimines carrying *N*-anisyl (**3a5**), *N*-1-naphthyl, *N*-benzyl, *N*-Boc and *N*-Cbz groups lacked the ability to bind to the copper center, so did not react. (d) In a competition experiment leading to the formation of **3a6** and **3a7** carrying 4-CF_3 and 4-OMe groups on the *N*-pyridine ring, the former was formed much faster than the latter (42% yield versus 6% yield after 6 h), consistent with the important role played by the *N*-pyridine in stabilizating the developing negative charge during insertion. (e) All aldimines carrying other types of *N*-azacycles in Scheme 5 can easily undergo partial dearomatization to accommodate the negative charge. (f) A stoichiometric reaction between mesitylcopper(I), aldimine **1a** and ligand **L** (1 equiv) was performed in toluene (20 h at 110 °C). It resulted in 74% conversion and an adduct in <2% ee. In a background reaction, only 22% conversion was detected indicating ligand acceleration effect. (g) A Hammett plot was constructed for phenylation of several analogues of aromatic aldimine **1b** with different para-substituents on the aryl rings (OMe, Me, F, Cl and CF_3). A relatively large ρ value of +1.04 revealed a strong correlation between electron-deficient nature of aldimines and insertion rates.



Scheme 6. (a) 1,4-addition transition state **TS-S** leading to the major (*S*)-isomer. (b) Effect of different *N*-directing groups in aldimines on arylation and (c) substituents on *N*-pyridine group.

The DFT-optimized transition states indicated that the copper catalyst ligated with a single bulky phosphoramidite **L**[24] was sufficient for excellent enantiofacial induction during arylation. Ligand **L** adopted a specific baseball glove-like conformation, by minimizing steric interaction between its two large 1-phenylethyl groups (Figure 2). Consequently, one of them shielded the bottom-right quadrant (front view), whereas an aromatic ring of the spiro-diindanyl backbone pointed into the top-left space. Thus, the bottom-left quadrant was left widely open to house the reacting partners.

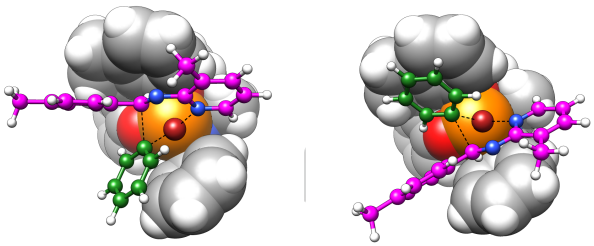


Figure 2. Transition state **TS-S** (left) and disfavored **TS-R** (right) for phenylation of (**L**)(phenyl)Cu(I) complex and bound aldimine **1b**. **L** is shown in space-filling representation and copper and other reacting ligands in ball-and-stick. Copper in magenta, carbon of Cu-bound phenyl ligand in green, nitrogen and carbon of aldimine **1b** in blue and pink.

In summary, we report the first example of catalytic enantioselective arylation of *N*-azaaryl aldimines using benchtop-stable arylboroxines, which affords pharmaceutically relevant chiral benzylic and benzhydryl amines in excellent ee values.

Acknowledgement

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Keywords: copper catalysis • imine addition • chiral alkylamines • asymmetric arylation • heteroaromatic amines

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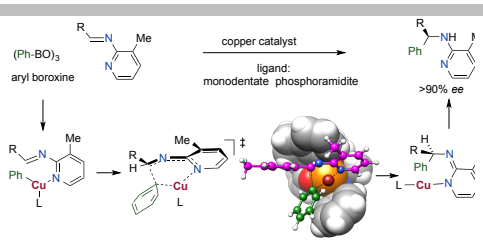
N-heterocyclic nitrogen of aldimines is directly involved in 1,4-insertion of aryl-copper species



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