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Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to N-Boc Imines and Nitroalkenes

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Supporting Information Placeholder

ABSTRACT: A chiral Pd(II)–bis(oxazoline) complex was found to be highly effective in promoting the first direct diastereo- and enantioselective addition of alkylazaarenes to N-Boc aldines and nitroalkenes under mild conditions. Deprotection of Boc-protected products proceeded readily to provide amines in high yields.

Azaarenes and α-stereogenic amines are ubiquitous structures in biologically active pharmaceuticals, agrochemicals, and natural products. Therefore, the development of new catalytic enantioselective methods to construct molecules containing both of these chemotypes should be of significant utility. In this regard, the catalytic enantioselective Friedel–Crafts addition of electron-rich azaarenes (such as indoles and pyrroles) to imines or enamides has been studied extensively. A complementary but currently undeveloped strategy is the direct catalytic enantioselective union of alkylazaarenes with imines or their derivatives (Figure 1). In this reaction, complexation of a chiral metal complex to the nitrogen atom of a C=N moiety within the azaarene can potentially facilitate an α-deprotonation of a 2-alkyl substituent under basic conditions to generate a chiralazaallylmetal species that can then undergo stereoselective addition to an imine (Figure 1A). This approach would allow enantioselective access to 2-β-aminoalkylazaarenes, substructures that appear in various biologically active drug candidates such as DPP-4 inhibitors and GlyT-1 inhibitors for the treatment of type 2 diabetes and schizophrenia, respectively (Figure 1B).

Although this strategy has not yet, to our knowledge, been realized, who have reported racemic additions of alkylazaarenes to N-sulfonylimines catalyzed by Pd(II), Sc(III), or Cu(II) complexes (Figure 1C). Also of relevance are racemic Sc(III)-catalyzed Michael additions of alkylazaarenes to enones and an α,β-unsaturated pyrrole, and Yb(II)-catalyzed Michael additions of alkylazaarenes to alkylidene malonitriles. While these reports demonstrate important proof of concept, the low acidity of alkylazaarenes means that high temperatures are often required, which may hinder the development of enantioselective variants. Furthermore, the substrates employed were mostly methyla[a]renes; when higher alkylazaarenes were employed, poor diastereoselectivities were often obtained. Finally, in the additions to imines, the substrates employed were mainly N-tosylimines, and removal of the tosyl group from the products would require strongly reducing conditions that are generally incompatible with sensitive functionality. Herein, we describe the first catalytic diastereo- and enantioselective additions of 2-alkylazaarenes to N-Boc imines. The reactions are promoted by a chiral Pd(II)-bis(oxazoline) complex under experimentally convenient conditions, proceeding at ambient temperature or at 50–60 °C in undried solvent under an air atmosphere. Importantly, deprotection of the amine in the products can be achieved simply by treatment with mild acid. Furthermore, examples of the corresponding additions to nitroalkenes are also provided.

We envisaged that incorporation of an electron-withdrawing group into an azaarene would further acidify the α-protons of a pendant alkyl substituent by stabilization of the conjugate base through conjugation (Scheme 1), allowing deprotonation under conditions that would be much milder than those previously reported and hence more suited to enantioselective catalysis. In addition, acidifying groups such as nitro, cyano, or ester substituents would provide highly useful functional handles for subsequent manipulation of the products.

Figure 1. Catalytic additions of alkylazaarenes to imines (1A and 1C) and relevant biologically active molecules (1B).

Scheme 1. Strategy for lowering the pKₐ of alkylazaarenes.
Our investigations began with evaluation of chiral complexes based around metal acetate salts, where it was hoped that the acetate counterions would exhibit sufficient basicity to effect α-deprotonation of an alkylazaarene. Following extensive investigations, we found that the complex composed of Pd(OAc)$_2$ (5 mol %) and a tetraphenyl bis(oxazoline) ligand L$_1$ (5 mol %) was highly effective in promoting the addition of various alkylazaarenes to imine 2a in CHCl$_3$ with high diastereoselectivities (up to >95:5 dr) and enantiomeric excesses (up to 99% ee) (Table 1). For example, 2-alkyl-6-nitrobenzoxazoles reacted smoothly with 2a at room temperature to give products 3a–3c containing methyl, ethyl, or n-propyl groups at the α-carbon, respectively (entries 1–3). An α-methoxy substituent on the alkylazaarene was also tolerated, although the ee of the minor diastereomer was only 47% (entry 4). Interestingly, 2-methyl-6-nitrobenzoxazole was not a good substrate as the addition product formed initially underwent a second addition to imine 2a. The process is not limited to the use of substrates containing nitro groups on the azarene; substrates containing ester or cyano groups underwent reaction to give products 3e–3g, respectively, in high yields (entries 5–7). While the lower reactivities of these substrates required an increase in reaction temperature to 50 °C to obtain high conversions, high stereoselectivities were maintained. Other azarenes that are tolerated include 6-nitrobenzothiazole (entry 8) and 3-nitropyridine (entries 9 and 10).

Next, the scope of the process with respect to the imine was studied (Chart 1). Pleasingly, a range of aromatic N-Boc aldimes containing various substituents (such methyl, bromo, chloro, nitro, cyano, or methoxy) at the para or meta positions of the phenyl ring successfully reacted with a number of alkylazaarenes to provide products with high diastereo- and enantiomeric excesses. An ortho-substituted phenyl group on the imine was also tolerated (product 4e), although the diastereoselectivity was somewhat diminished in this case.

Further experiments were conducted to shed light upon the importance of the position of the electron-withdrawing group on the azarene. First, the reactivity of 2-ethyl-5-nitrobenzoxazole (5) was evaluated, since mesomeric stabilization (−M effect) of the conjugate base of 5 by the 5-nitro substituent is not possible. Surprisingly, 5 underwent efficient coupling with 2a at room temperature to give 6 as a 94:6 inseparable mixture of diastereomers in 74% yield, with enantiomeric excesses of 90% ee and 78% ee for the major and minor diastereomers, respectively (eq 1). This result demonstrates that in this case, the inductive electron-withdrawing...
nature of the nitro group (−I effect) is sufficient for good reactivity, and suggests the scope of this process may be significantly broader than presented herein.

In contrast, while 2-ethyl-4-nitrobenzoxazole (7) might have been expected to exhibit high reactivity in this process, this substrate provided the product 8 in low yield with poor diastereo- and enantioselectivity (eq 2). Presumably, coordination of the nitro group to the palladium center of the catalyst is responsible for the poor performance of this alkylazaarene.

Deprotection of the Boc group from the products was readily accomplished by treatment with HCl in MeOH (generated by dissolving TMSCl in MeOH), as shown by the formation of the amines 9 and 10 from 3c and 3j in 93% and 90% yield, respectively (eq 3 and 4). In the case of 10, very slight erosion in the diastereomeric purity was observed (eq 4).

We have found that nitroalkenes are also suitable coupling partners for 2-alkylazaarenes using the same catalyst system. For example, substrates 1c and 1j underwent conjugate addition to nitroalkenes 11a or 11b to provide 12a–12c as single diastereomers with high enantioselectivities (Chart 2).

To investigate the role of the acetate counterions in this process, the reaction of Table 1, entry 1 was repeated using Pd(TFA)$_2$ in place of Pd(OAc)$_2$. No reaction occurred, indicating that the basicity of the counterion is crucial for reactivity. An analogous experiment using Pd(OBz)$_2$ gave 3a in 90% yield, 74:26 dr, and 87/90% ee (major/minor). Furthermore, a similar experiment using Pd(OPiv)$_2$ gave 3a in 38% yield, 56:44 dr, and 80/90% ee (major/minor). The dependence of both the diastereo- and enantioselectivity on the counterion suggests that the carboxylate is involved in the stereoselectivity-determining step. Presumably, one carboxylate remains bound to palladium throughout the reaction.

On this basis, Figure 2 presents a tentative stereochemical model for these reactions. Deprotonation of the alkylazaarene by an acetate ligand of complex 13 leads to species 14, in which the azaallyl ligand possesses E-stereochemistry to minimize steric interactions between the R-substituent and the other ligands. Approach of the imine toward the azaallyl ligand is likely to occur via trajectories approximately perpendicular to the ligand plane, to allow binding/activation of the imine at an axial coordination site. In species 14, approach of the imine from the top face is relatively unhindered. In species 15, however, in which the azaallyl ligand adopts an alternative conformation, approach of the imine from the top face is hindered by the acetate ligand, whereas approach from the bottom face is unhindered.
face is hindered by the phenyl groups of the chiral ligand.

Four distinct transition state models resulting from 
conformation 14 can be envisaged. TS 3 and TS 4, in which the 
imine possesses an s-cis geometry, appear to be unfavorable 
on the basis of their eclipsing interactions. Of the more favorable 
staggered conformations TS 1 and TS 2, in which an 
imine s-trans geometry is adopted, TS 2 is likely to be disfavored 
owing to the steric clash of the tert-butyl group of the imine with 
one of the methyl groups of the chiral ligand. Therefore, reaction 
through TS 1 is favored. Similar arguments can be in 
oked to explain the stereochemical outcome of the nitroalkane 
aditions, through TS 5.

Finally, to demonstrate the synthetic utility of the products, 
3j was converted into biaryl 18 by a sequence involving nitro 
group reduction, conversion of the resulting amine 16 into 
bromide 17, and Suzuki–Miyaura coupling (Scheme 2).

![Scheme](https://example.com/scheme.png)

In conclusion, we have described the first catalytic enantio 
oselective additions of alkylazarenes to N-Boc imines and 
itronealkanes. Under the action of a chiral Pd(II)–bis(oxazoline) 
plex, the reactions proceed with high levels of diastere 
and enantioselectivity. By exploiting the acidifying effect of 
trio, cyano, or ester groups on the azarene, the reactions occur under mild, experimentally convenient reaction conditions 
(dried solvent, air atmosphere, and often ambient tem 
perature). In the case of the imine addition products, deproto 
ction of the Boc group is readily accomplished to reveal the 
comparing amines. This work lays the foundation for the development of further catalytic enantioselective addition re 
ctions of alkylazarenes for the production of novel chiral 
azaarene-containing building blocks. Studies in this area are 
ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for all new comp 
ounds, and crystallographic data in cif format. This material is 
available free of charge via the Internet at http://pubs.acs.org.

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(18) See Supporting Information for the structures of 1a–1j.

(19) The relative and absolute configurations of the products ob 
tained herein were assigned by analogy with those of 3j, 9, and 12b 
which were determined by X-ray crystallography using a copper rad 
ation source. See Supporting Information for details.

(20) For reviews of nitroalkanes as conjugate acceptors, see: (a) 

(21) Repeating the reaction of Table 1, entry 4 using Pd(TFA)2 in 
place of Pd(OAc)2, in the presence of Et3N (10 mol %) gave 3a in 
32% conversion, 95:5 dr, and 88/4% ee (major/minor)