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Palladium-Catalyzed Asymmetric Allylic Alkylations of Polynitrogen-Containing Aromatic Heterocycles

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Supporting Information

ABSTRACT: We report the palladium-catalyzed asymmetric allylic alkylation (AAA) reaction of a variety of nitrogen-containing aromatic heterocycles, including pyrazine, pyrimidine, pyridazine, quinoxaline, and benzoimidazole derivatives. The mesityl ester, whose steric bulk prevents competitive deacylation of the electrophile from "hard" nucleophiles, is introduced as a new leaving group in allylic alkylation chemistry. In contrast to our previous studies of AAA reactions with pyridine-based substrates, no precomplexation with a Lewis acid is required before deprotonation with LiHMDS, underscoring the relative acidity of these electron-deficient nucleophiles.

Polynitrogen-containing aromatic heterocycles are ubiquitous structural elements important to a wide range of fine and bulk chemical fields, including natural products synthesis, medicinal chemistry, polymer research, and materials science.[1] Among the many protocols that permit the union of preformed nitrogen-containing aromatic heterocycles with other organic molecules, transition metal-catalyzed cross-coupling reactions have emerged as the principal methods that have greatly increased the facility with which these building blocks can be installed.[2] New transformations that also stereoselectively generate chiral centers provide access to families of compounds with uniquely defined two- and three-dimensional structure, a feature with particular relevance to the needs of pharmaceutical science as well as for other applications.[3] Despite progress in transition metal-catalyzed asymmetric cross-coupling technology,[4] relatively few examples exist of such reactions in which either the nucleophilic or electrophilic coupling partner in an enantioselective C−C bond-forming event is a nitrogen-containing aromatic heterocycle.[5]

We felt that our recent reports on the palladium-catalyzed asymmetric allylic alkylation (AAA) reactions of BF_3-complexed 2-substituted pyridines (Scheme 1)[6,7] would provide a foundation upon which we might explore the reactivity of other nitrogen-containing aromatic heterocycles, with the ultimate objective of developing a general procedure for their use in AAA reactions. Our aim was to simply deprotonate substituted heterocycles and react them stereoselectively with palladium π-allyl electrophiles.[8] Such an achievement would be particularly significant in streamlining the synthetic incorporation of heterocycles with regards to both atom[9] and step economy[10] because the metalation event would not require substrate prefunctionalization, a characteristic feature of cross-coupling chemistry.

Disappointingly, initial attempts to extend our work beyond pyridine-based nucleophiles were unsuccessful. Under the previously optimized conditions, no analogous reactivity was observed for any other BF_3-complexed five- or six-membered nitrogen-containing aromatic heterocycle, including a variety of seemingly analogous pyridazine, pyrazine, and pyrimidine nucleophiles. Metalation with many strong bases was never problematic, as deuterium quenching studies consistently showed. Instead, it was clear that lithiated BF_3-complexed pyridine-based nucleophiles possess a unique reactivity toward palladium π-allyl electrophiles that is not shared with other more electron-deficient heterocycles.

The breakthrough came as we were evaluating the competency of *N*-alkylated pyrazinium salts to undergo reaction with palladium π-allyl species. When an excess of 2,5-dimethylpyrazine was treated with *para*-methoxybenzyl chloride, deprotonated with LiHMDS, and then treated with racemic cyclohex-2-enyl pivalate in the presence of a palladium(0) catalyst, the desired product was observed in 19% conversion (Scheme 2).[11] Unexpectedly, when the pyrazinium salt was prepared in a separate step, no reaction was observed (Scheme 2). Contrary to our hypothesis that an alkylated hetereocycle would prove a suitable nucleophile, it was the *unalkylated* species that reacted. Heterocycles such as pyrazine that are either complexed to a Lewis acid or alkylated become too electron-deficient to undergo nucleophilic attack with allylic ligands on palladium. BF_3 complexes of pyridines, however, are not similarly deactivated; in fact, such complexation is necessary for reactivity. When the reaction was performed in the absence of an activating species, the desired product was obtained in 37% conversion, along with significant amounts of cyclohex-2-enol (Scheme 2). This observation suggested that deacylation of the electrophile was in part responsible for the low reaction yield. After examining a variety of allylic leaving groups, it was discovered that this decomposition could be completely prevented by employing a more sterically hindered mesityl ester, a leaving group that, to our knowledge, has never before been used in an allylic alkyation reaction. Remarkably, despite the strongly basic conditions, no elimination of the allylic ester to yield cyclohexadienes was observed.

Subsequent optimization experiments revealed that the alkylation could be performed comparably well in a variety of ethereal solvents (Table 1, entries 1−3). Decreasing the amount of base from 3 to 2 equiv led to a small decrease in yield (entry 4). Little to no desired reaction was observed when the lithium counterion was replaced with either potassium or sodium (entries 5 and 6), nor when LiHMDS was substituted with other strong bases

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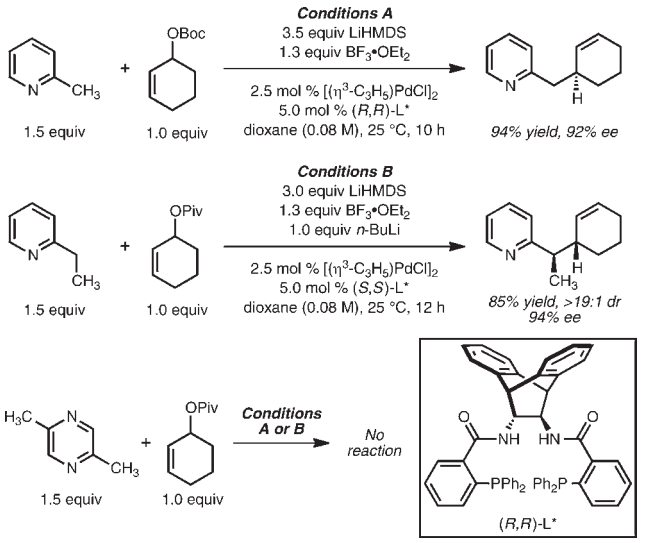
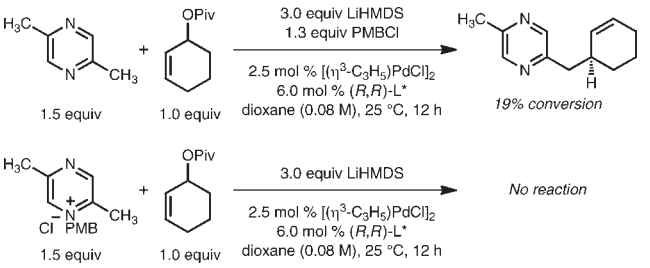
Scheme 1. Attempted Extension of Previous Work with Pyridines



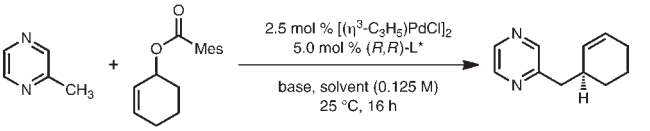
Scheme 2. Alkylation of 2,5-Dimethylpyrazine Prevents the Desired AAA Reaction



(entries 7 and 8), highlighting the critical importance of the lithium aggregate structure on the course of the desired reaction. Using 1.5 equiv of the heterocycle proved optimal; when either more or less was employed, the isolated yield of the desired product decreased, although its enantiomeric excess remained largely unchanged (entires 9−11).

With optimized conditions in hand, the substrate scope of reaction was explored (Figure 1). In addition to 2-methylpyrazine, which could be alkylated with cyclohex-2-en-1-yl 2,4,6-trimethylbenzoate to give **1** in 71% yield and 97% ee, 2,5-dimethylpyrazine could be similarly alkylated to give **2** in 66% yield and 99% ee. Notably, despite the reasonable potential for bis-alkylation, no such product was observed. An important extension of the current work is that particularly electron-deficient nitrogen-containing aromatic heterocycles do not require complexation with an electron-withdrawing Lewis acid such as BF_3 to react with palladium π-allyl complexes. This not only renders the procedure operationally simpler and circumvents potential side reactions caused by the addition of a reactive Lewis acid, but also obviates the requirement that the proximal nitrogen atom be sterically accessible to form a dative bond. In our previous reports, a substrate such as 2,6-lutidine proved unreactive for this reason. In this series, where complexation is not required, a substrate such as 2,6-dimethylpyrazine reacts to give **3** in 83% yield and >99% ee.

Table 1. Selected Optimization Experiments[a]



entry	solvent	base (equiv)	Nu:El[b]	yield[c]	ee[d]
1	dioxane	LiHMDS (3.0)	1.0:1.0	49%	95%
2	DME	LiHMDS (3.0)	1.0:1.0	59%	96%
3	THF	LiHMDS (3.0)	1.0:1.0	51%	95%
4	THF	LiHMDS (2.0)	1.0:1.0	48%	98%
5	THF	NaHMDS (2.0)	1.0:1.0	30%	93%
6	THF	KHMDS (2.0)	1.0:1.0	NR	–
7	THF	NaH (2.0)	1.0:1.0	NR	–
8	THF	KO*t*-Bu (2.0)	1.0:1.0	NR	–
9	THF	LiHMDS (2.0)	1.3:1.0	53%	95%
10	THF	LiHMDS (3.0)	1.5:1.0	71%	97%
11	THF	LiHMDS (4.0)	2.0:1.0	67%	95%

[a] Reactions run on a 0.109 mmol scale. [b] Nu = 2-methylpyrazine, El = cyclohex-2-en-1-yl 2,4,6-trimethylbenzoate. [c] Isolated yield. [d] Determined by chiral HPLC.

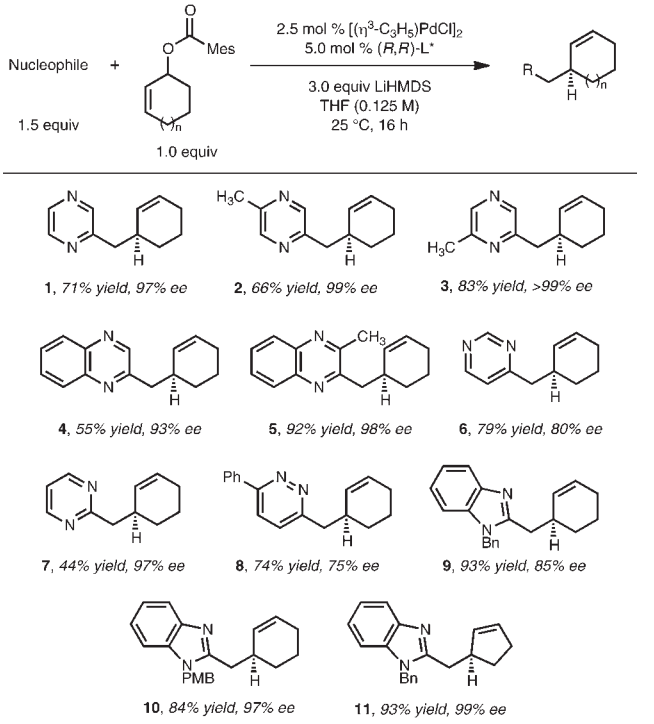


Figure 1. AAA reactions of nitrogen-containing aromatic heterocycles.

Reactions with both 2-methylquinoxaline and 2,3-dimethylquinoxaline provide the desired products (**4** and **5**) in 55% and 92% yield, respectively, and in 93% and 98% ee, respectively. Instead of a 1,4-configuration of nitrogen atoms, as found in both pyrazines and quinoxalines, a 1,3-configuration is also possible, as seen in the example of 4-methylpyrimidine, which gives **6** in 79% yield and 80% ee. The reacting center can also be placed between the two nitrogen atoms of pyrimidine: the reaction of 2-methylpyrimidine provides alkylated product **7** in a reduced yield of 44% but in high

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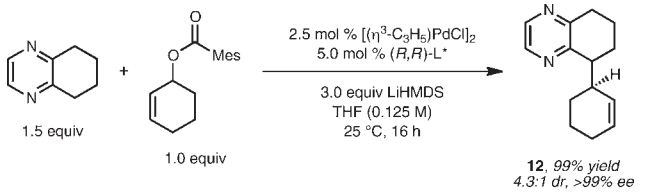
Scheme 3. Diastereo- and Enantioselective Allylic Alkylation of 5,6,7,8-Tetrahydroquinoxaline



enantiomeric excess (97% ee). Reaction of 3-phenyl-6-methylpyridazine, a heterocycle with a 1,2 configuration of nitrogen atoms, gives **8** in 75% yield and 75% ee.

In addition to 6-membered nitrogen-containing heterocycles, 5-membered ring-derived nucleophiles also participate in the palladium-catalyzed process. Both 1-benzyl-2-methyl-1*H*-benzo[*d*]imidazole and 1-(4-methoxybenzyl)-2-methyl-1*H*-benzo[*d*]imidazole react with cyclohex-2-en-1-yl 2,4,6-trimethylbenzoate to provide the desired products (**9** and **10**) in 85% and 93% yield, respectively, and 97% and 99% ee, respectively. Finally, 5-membered ring-derived electrophiles are also tolerated, as can be seen in the example of cyclopent-2-en-1-yl 2,4,6-trimethylbenzoate, which reacts with 1-benzyl-2-methyl-1*H*-benzo[*d*]imidazole to give **11** in 83% yield and >99% ee.

We next asked whether it would be possible to control the concomitant formation of a second stereocenter on a more substituted nitrogen-containing aromatic heterocycle, a process that would then be both diastereo- and enantioselective. To our delight, submitting 5,6,7,8-tetrahydroquinoxaline to the optimized reaction conditions delivers desired tricycle **12** in 99% yield, 4.3:1 dr, and >99% ee (Scheme 3).

In summary, we have demonstrated that polynitrogen-containing aromatic heterocycles are competent cross-coupling partners for enantioselective palladium catalysis. Importantly, no substrate prefunctionalization or preactivation is required prior to the AAA event. The mesityl ester, a new leaving group in allylic alkylation chemistry, was singularly effective for the desired transformation, an observation that highlights its particular robustness under strongly basic reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.

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