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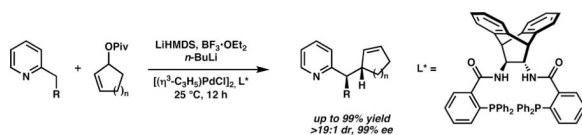
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Palladium-Catalyzed Regio-, Diastereo-, and Benzylic Allylation of 2-Substituted Pyridines

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Abstract



We report a new method for the highly regio-, diastereo-, and enantioselective palladium-catalyzed allylic alkylation of 2-substituted pyridines that allows for the formation of homoallylic stereocenters containing alkyl, aryl, heteroaryl, and nitrogen substituents. When the reaction is conducted with asymmetric acyclic electrophiles, both linear and branched products may be obtained exclusively by selecting the appropriate regioisomeric starting material and ligand, an example of the “memory effect.” Deuterium-labeling studies reveal that though no such phenomenon occurs with racemic cyclic electrophiles, the chiral ligand employed reacts kinetically faster with the enantiomer of substrate for which it is “matched,” and yet eventually converts all “mismatched” substrate to product.

The development of palladium-catalyzed asymmetric allylic alkylations (AAAs) continues to be a productive area of research.¹ Still, there are only a few examples of such reactions that form an adjacent stereocenter diastereoselectively, and these are almost exclusively limited to enolate nucleophiles.² This narrow substrate scope reflects the inherent challenge of simultaneously forming vicinal stereocenters selectively. After reporting a method for employing 2-methylpyridines in palladium-catalyzed AAAs,³ we wondered whether an analogous reaction with higher-order 2-substituted pyridines could be effected in a diastereo- and enantioselective fashion (Scheme 1, **A**). We hypothesized that, upon coordination of the pyridyl nitrogen atom with BF₃, benzylic deprotonation would provide a nucleophile that would exist as a single geometric isomer because of the steric demands imposed by the Lewis acid. If such control were possible, alkylation products might be obtained with both high diastereo- and enantiocontrol.

Unfortunately, when 2-ethylpyridine (**1**) was reacted with allylic carbonate **2** under the previously optimized conditions,³ ¹H NMR revealed no desired product and partial decomposition of **2** (Scheme 1, **B**). Replacing the *tert*-butyl carbonate ester with the more robust pivalate ester provided an electrophile that was completely stable to the reaction conditions, and with this substrate the desired alkylation product (**3a**) could be obtained in 15% yield, >19:1 dr, and 95% ee. Although the reaction conversion was low, the excellent diastereo- and enantioselectivity validated our hypothesis. Disappointingly, higher yields

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

could not be obtained by heating the reaction or by using other strong bases (e.g. LiTMP, *t*-BuOK, KHMDS, or *n*-BuLi).

The breakthrough came when a single equivalent of *n*-BuLi was added to the nucleophilic complex generated with three equivalents of LiHMDS; under these conditions, **3a** was now isolated in 85% yield, >19:1 dr, and 94% ee. Presumably, the introduction of *n*-BuLi quantitatively deprotonates the equivalent of HMDS formed in the initial deprotonation event, driving the reaction to completion.

Other 2-substituted pyridines that underwent reaction with cyclohex-2-enyl pivalate were identified (Table 1). A range of 2-alkyl- and 2-aryl-substituted pyridines performed well, as did the corresponding five-membered ring electrophile (see **3b**). Large substituents generally provided the highest level of stereocontrol; for example, 2-(naphthalene-2-ylmethyl)pyridine gave **3g** in 90% yield, >19:1 dr, and 98% ee.⁴ Heteroaryl substitution was also tolerated (**3h**), as was an aryl bromide (**3i**), which did not undergo oxidative addition by palladium(0) or lithium-halogen exchange with *n*-BuLi. Finally, a nitrogen-containing stereocenter could also be established (**3j**).⁵ The relative and absolute stereochemistry of the products was assigned by analogy to **3d**, which was bromocyclized to provide single crystals of the corresponding pyridinium cation suitable for X-ray diffraction (Scheme 2).⁶

The alkylation is sensitive to the steric nature of the nucleophile. When additional substituents were placed either at the benzylic (e.g. 2-isopropylpyridine) or homobenzylic (e.g. 2-neopentylpyridine) positions, no desired product was observed. Conversely, if the 2-pyridyl substituent is insufficiently sterically demanding for the two possible geometric configurations of the nucleophile to be adequately differentiated, the product is formed with low diastereocontrol (e.g. when 2-(methoxymethyl)pyridine was employed, the product was obtained in 78% yield but 3:2 dr).

The reaction is not limited to cyclic electrophiles. Indeed, when 2-benzylpyridine (**4**) was reacted with pivalate **5**, linear product **7** was obtained in 74% yield and 89% ee (Table 2, entry 1). Unexpectedly, when the reaction was instead conducted with regioisomeric pivalate **6**, a mixture of linear and branched products (**7** and **8**) was formed (entry 2). This is an example of the “memory effect,” in which the regiochemistry of the electrophile influences the regiochemistry of the product.⁷ When the reaction was performed with **5** in benzene with **L2**, the linear product was again formed, but with little enantiocontrol (entry 3). However, with **6**, the branched product could be obtained in 64% yield and 63% ee⁸ (entry 4). Thus either regioisomeric product may be obtained exclusively by choosing the appropriate allylic ester and ligand.

To assess whether such an effect was occurring with cyclic electrophiles, deuterated substrate **9** was prepared (Table 3). When the reaction was conducted with **4** and racemic ligand, regioisomer **11** was obtained with high selectivity (entry 1), while nonracemic ligands gave an equal mixture of **10** and **11** (entries 2 and 3). These results show: (1) no “memory effect” is operative, since no bias for nucleophilic attack is observed with the (*S,S*)- or (*R,R*)-ligand alone, (2) when placed in competition, each ligand is able to perform a near-perfect kinetic resolution of the electrophile, since each reacts fastest with the enantiomer of **9** for which it is “matched” (providing **11** as the common product of “matched” ionization pathways), and (3) despite this high degree of chiral recognition, a single enantiomer of ligand is capable of converting both “matched” and “mismatched” substrate to product.

In summary, we have reported a new method for the highly regio-, diastereo-, and enantioselective allylic alkylation of 2-substituted pyridines. Investigations of the reaction

mechanism, the role of lithium aggregates, and applications of this strategy to other nucleophilic classes are ongoing.

Supplementary Material

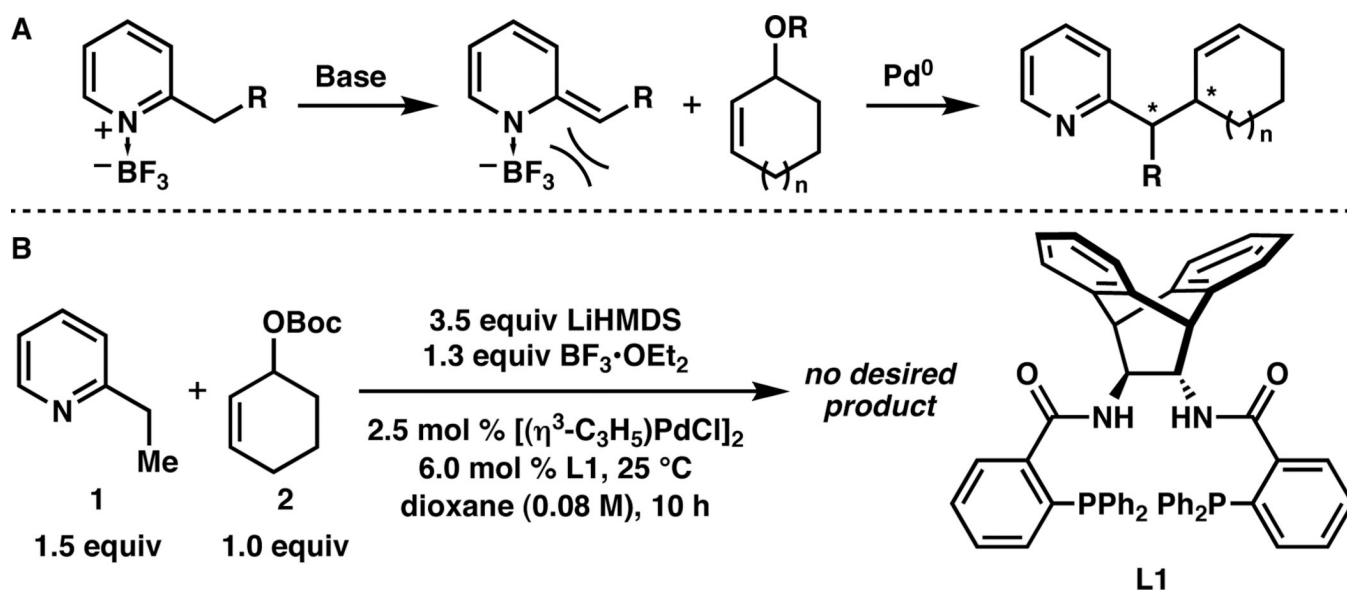
Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

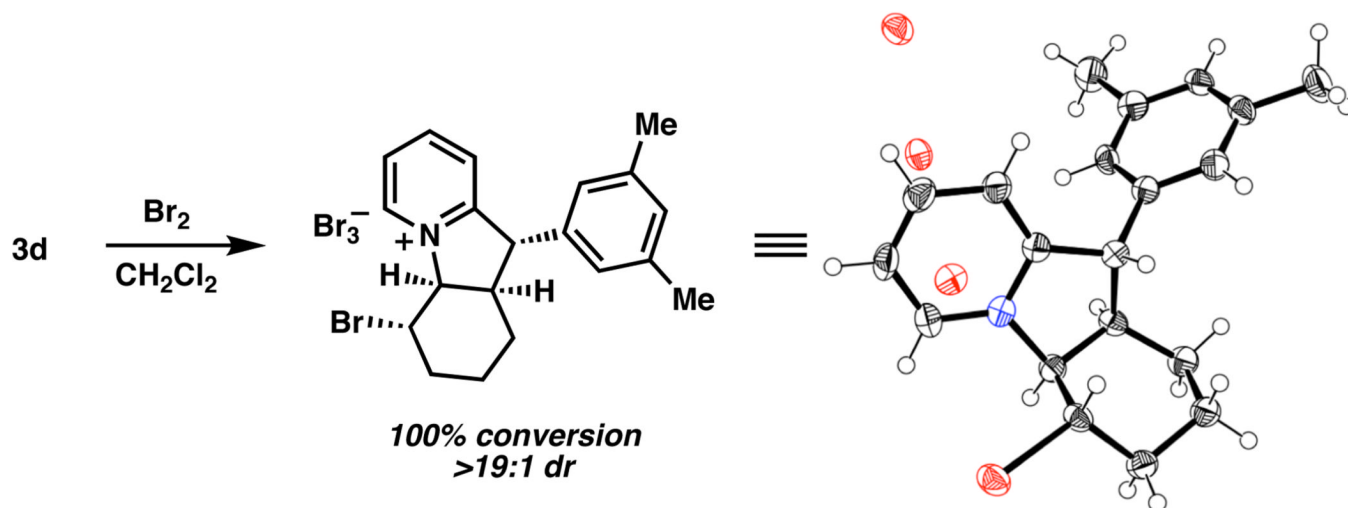
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References

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3. Trost BM, Thaisrivongs DA. *J. Am. Chem. Soc.* 2008; 130:14092. [PubMed: 18826305]
4. Interestingly, the 1-naphthyl analog of **3g** could be obtained in 100% conversion by ^1H NMR but only 2:1 dr.
5. No reaction was observed with the unmethylated carbamate or the corresponding phthalimide-protected aminopyridine.
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8. No racemization was observed under the reaction conditions.

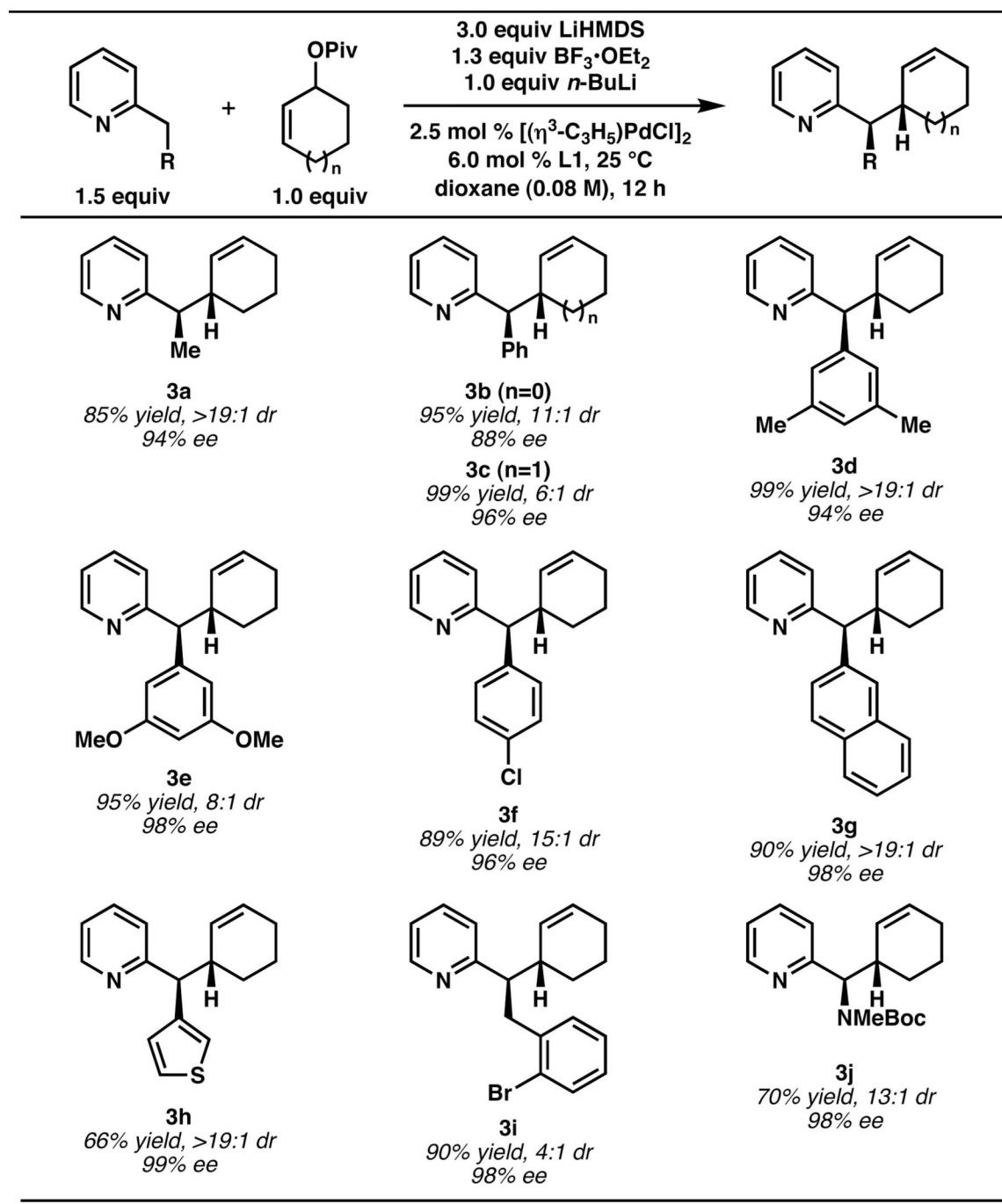


Scheme 1.
Reaction hypothesis and initial result.



Scheme 2.
Bromocyclization of **3d**.

Table 1

AAA Reactions with 2-Substituted Pyridyl Nucleophiles^a

^aYield reflects combined isolated yield of both diastereomers; dr and ee determined by ¹H NMR analysis of the crude reaction mixture and chiral HPLC, respectively.

Table 2

“Memory Effect” Observed with Linear Electrophiles^a

entry	substrate	ligand	solvent	7:8 ^b	yield (%) ^c	ee (%) ^d
1	5	L1	dioxane	>19:1	74	89
2	6	L1	dioxane	1:1.6	71	7:64 8:17
3	5	L2	PhH	>19:1	32	3.6
4	6	L2	PhH	<1:19	64	63

^aReactions run under the standard conditions.

^bDetermined by ¹H NMR of the crude reaction mixture.

^cCombined isolated yield of both regioisomers.

^dDetermined by chiral HPLC.

Table 3

AAA Reactions with Deuterated Substrate **9**

entry	ligand	10:11 ^a	yield (%) ^b	dr ^c	ee (%) ^d
1	(<i>S,S</i>)- L1	1:19	97	9:1	-
2	(<i>S,S</i>)- L1	1:1	93	9:1	+90
3	(<i>R,R</i>)- L1	1:1	99	9:1	-91

^aDetermined by ¹H NMR of the product mixture.

^bCombined isolated yield of both regioisomers.

^cDetermined by ¹H NMR of the crude reaction mixture.

^dDetermined by chiral HPLC.