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

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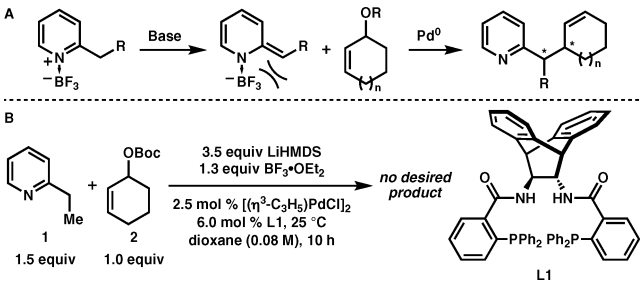
The development of palladium-catalyzed asymmetric allylic alkylations (AAAs) continues to be a productive area of research.[1] Still, there are only a few examples of such reactions that form an adjacent stereocenter diastereoselectively, and these are almost exclusively limited to enolate nucleophiles.[2] 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 BF_3, 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.

Scheme 1. Reaction Hypothesis and Initial Result

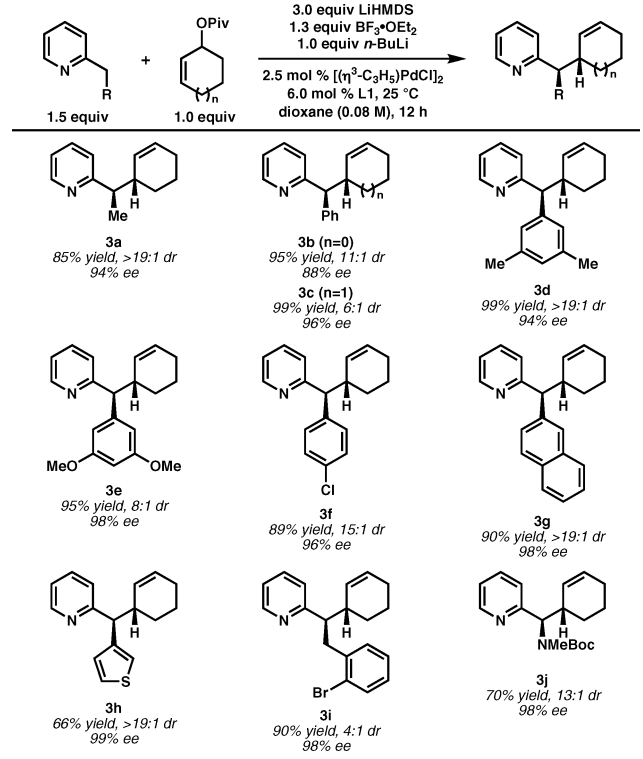


Unfortunately, when 2-ethylpyridine (**1**) was reacted with allylic carbonate **2** under the previously optimized conditions,[3] ^{1}H NMR revealed no desired product and partial decomposition of **2** (Scheme 1, **B**). Replacing the *tert*-butyl carbonate ester with the more robust pivalate ester 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 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 3 equiv 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

Table 1. AAA Reactions with 2-Substituted Pyridyl Nucleophiles[a]



[a] Yield reflects combined isolated yield of both diastereomers; dr and ee determined by ^{1}H NMR analysis of the crude reaction mixture and chiral HPLC, respectively.

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 at either 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).

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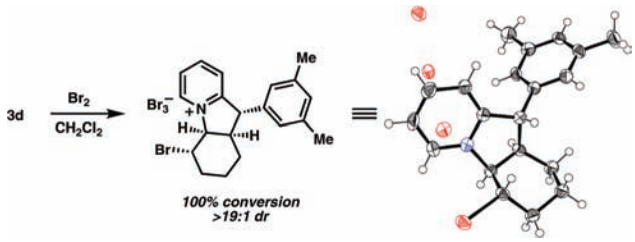
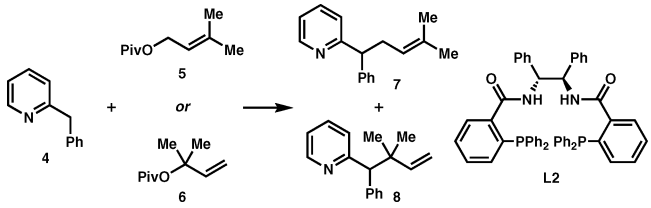
Scheme 2. Bromocyclization of **3d**



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% ee[8] (entry 4). Thus either regioisomeric product may be obtained exclusively by choosing the appropriate allylic ester and ligand.

Table 2. "Memory Effect" Observed with Linear Electrophiles[a]

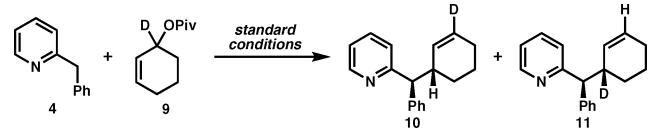


entry	substrate	ligand	solvent	**7**:**8**[b]	yield (%)[c]	ee (%)[d]
1	**5**	**L1**	dioxane	>19:1	74	89
2	**6**	**L1**	dioxane	1:1.6	71	**7**:64 **8**:17
3	**5**	**L2**	PhH	>19:1	32	3.6
4	**6**	**L2**	PhH	<1:19	64	63

[a] Reactions run under standard conditions. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Combined isolated yield of both regioisomers. [d] Determined by chiral HPLC.

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 a 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 the following: (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.

Table 3. AAA Reactions with Deuterated Substrate **9**



entry	ligand	**10**:**11**[a]	yield (%)[b]	dr[c]	ee (%)[d]
1	(*S*,*S*)- + (*R*,*R*)-**L1**	1:19	97	9:1	−
2	(*S*,*S*)-**L1**	1:1	93	9:1	+90
3	(*R*,*R*)-**L1**	1:1	99	9:1	−91

[a] Determined by ^{1}H NMR of the product mixture. [b] Combined isolated yield of both regioisomers. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral HPLC.

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.

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Note Added after ASAP Publication. A word was inadvertently omitted from the title in the version published ASAP July 31, 2009. The corrected version was published August 7, 2009.

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

References

(1) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.
(2) Ketones: (a) Braun, B.; Laicher, F.; Meier, T. *Angew. Chem.* **2000**, *112*, 3637. (b) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2004**, *11*, 174. (c) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (d) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (e) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2008**, *130*, 11852β-keto esters: (f) Trost, B. M.; Sacchi, K. L.; Schroeder, G. M.; Asakawa, N. *Org. Lett.* **2002**, *4*, 3427. Imino esters: (g) Baldwin, I. C.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1515. (h) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. Azalactones: (i) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (j) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818. Nitroalkanes: (k) Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 6291.
(3) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092.
(4) Interestingly, the 1-naphthyl analog of **3g** could be obtained in 100% conversion by ^{1}H NMR but only 2:1 dr.
(5) No reaction was observed with the unmethylated carbamate or the corresponding phthalimide-protected aminopyridine.
(6) (a) Szychowski, J.; Wróbel, J. T.; Leniewski, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1980**, *28*, 9. (b) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138.
(7) (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70. (b) Lloyd-Jones, G. C.; Stephen, S. C. *Chem.—Eur. J.* **1998**, *4*, 2539.
(8) No racemization was observed under the reaction conditions.

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