

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

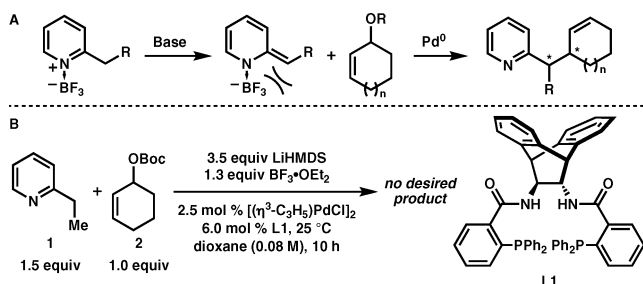
Barry M. Trost* and David A. Thaisrivongs

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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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 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.

Scheme 1. Reaction Hypothesis and Initial Result



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 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

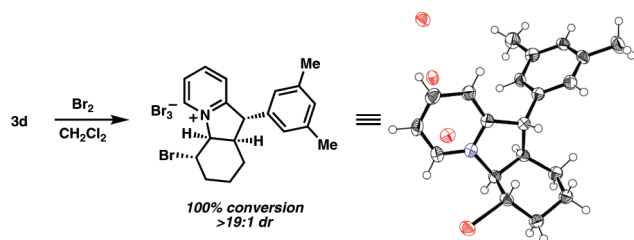
 3a 85% yield, >19:1 dr 94% ee	 3b (n=0) 95% yield, 11:1 dr 88% ee	 3c (n=1) 99% yield, 6:1 dr 96% ee
 3d 99% yield, >19:1 dr 94% ee	 3e 95% yield, 8:1 dr 98% ee	 3f 89% yield, 15:1 dr 96% ee
 3g 90% yield, >19:1 dr 98% ee	 3h 66% yield, >19:1 dr 99% ee	 3i 90% yield, 4:1 dr 98% ee
 3j 70% yield, 13:1 dr 98% ee		

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

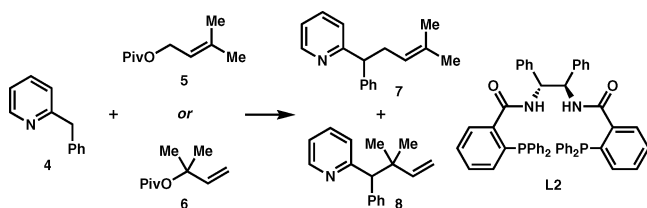
substituents generally provided the highest level of stereocontrol; for example, 2-(naphthalene-2-ylmethyl)-pyridine gave **3g** in 90% yield, >19:1 dr, and 98% ee.⁴ Heteroaryl substitution was also tolerated (**3h**), as was an aryl bromide (**3i**), which did not undergo oxidative addition by palladium(0) 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).

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% ee⁸ (entry 4). Thus either regioisomeric product may be obtained exclusively by choosing the appropriate allylic ester and ligand.

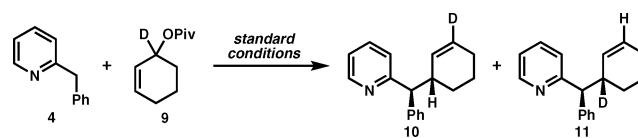
Table 2. “Memory Effect” Observed with Linear Electrophiles^a

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 ¹H 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	(<i>S,S</i>)- + (<i>R,R</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

^a Determined by ¹H NMR of the product mixture. ^b Combined isolated yield of both regioisomers. ^c Determined by ¹H 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>.

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- (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.

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