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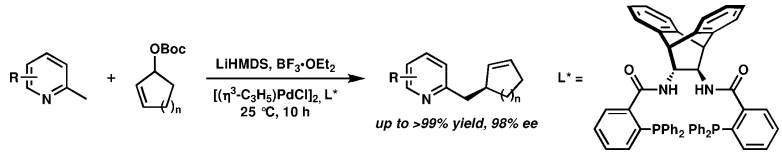
J. Am. Chem. Soc., **2008**, 130 (43), 14092-14093 • DOI: 10.1021/ja806781u • Publication Date (Web): 01 October 2008



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Published on Web 10/01/2008

Strategy for Employing Unstabilized Nucleophiles in Palladium-Catalyzed Asymmetric Allylic Alkylations

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Received August 27, 2008; E-mail: bmtrost@stanford.edu

Palladium-catalyzed asymmetric allylic alkylations (AAA) have found extensive application in the enantioselective construction of stereogenic centers, enabling the synthesis of a broad diversity of complex molecules.[1] This family of reactions includes a vast array of stabilized or "soft" carbon and heteroatom nucleophiles (those from conjugate acids with a pK_a less than 25). While nonenantioselective palladium-catalyzed allylic substitution reactions with unstabilized or "hard" nucleophiles (those from conjugate acids with a pK_a greater than 25) are known,[2] there are no reports of such reactions proceeding with high enantioselectivity.[3] One significant difference between these two classes of nucleophiles is the distinct mechanistic pathways through which each undergoes transition metal-catalyzed allylic substitution reactions: "soft" nucleophiles externally attack the allylic ligand outside the metal's coordination sphere to directly afford the product,[4] while "hard" nucleophiles internally attack the metal to form a neutral complex that liberates the product by reductive elimination.[5]

The importance of pyridine and related heterocycles, both as common structural motifs in natural products and pharmaceutical agents and as synthetic building blocks, led us to consider using metalated 2-methylpyridine, a "hard" nucleophile, in palladium-catalyzed AAA reactions. Not unexpectedly, when the 2-methylpyridyl anion generated with *n*-BuLi was employed in an AAA reaction, no desired product was observed. In considering ways to "soften" this nucleophile, we were attracted to the BF_3 complex of 2-methylpyridine, which has not heretofore been metalated stoichiometrically to serve as a nucleophile in any type of alkylation reaction.[6]

Initial experiments studied the reaction catalyzed by $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and ligand **L1** (Figure 1) of *tert*-butyl cyclopent-2-enyl carbonate with the complex generated *in situ* from 2-methylpyridine and $BF_3{\bullet}OEt_2$ (Table 1, entry 1). From the bases examined, LiHMDS emerged as the optimal reagent, although several equivalents were required for the reaction to proceed to full conversion. Similar observations have been made for lithium amide bases employed in palladium-catalyzed AAA reactions with ketone enolates,[7] a requirement that suggests lithium aggregates may be forming.[8] Conducting the reaction above or below ambient temperature proved deleterious to both the yield and the observed enantioselectivity (Table 1, entries 2−4). Of the chiral ligands tested (Figure 1), **L4** provided the desired product in the highest yield and enantiomeric excess (Table 1, entries 1, 5−7). Using a noncoordinating solvent substantially decreased the efficiency and selectivity of the reaction (Table 1, entry 9). Of the solvents surveyed, dioxane was differential, delivering the desired product in 86% yield and 95% ee (Table 1, entries 7−10).[9]

Subsequent experiments began to define the substrate scope of this reaction (Table 2). Five-, six-, and seven-membered allylic carbonates were all competent electrophilic partners for the reaction with 2-methylpyridine (Table 2, entries 1−3). Attempts to conduct an analogous AAA reaction with 4-methylpyridine provided only

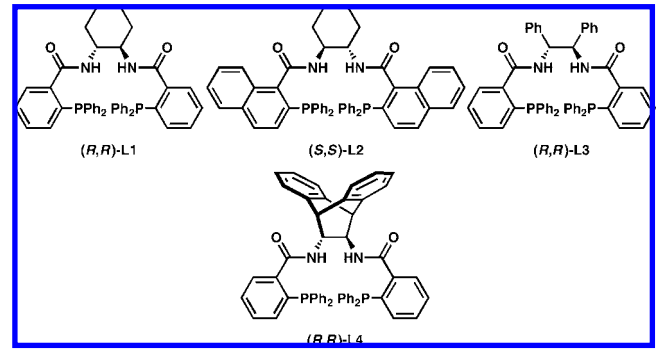
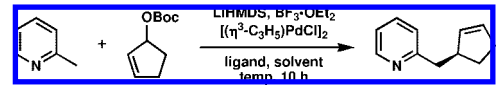


Figure 1. Chiral ligands used in optimization experiments.

Table 1. Selected Optimization Experiments[a]



entry	ligand	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	**L1**	THF	25	13	−30[d]
2	**L1**	THF	40	11	1.0
3	**L1**	THF	4	68	−8.4
4	**L1**	THF	−25	18	−4.0
5	**L2**	THF	25	55	−20
6	**L3**	THF	25	15	−43
7	**L4**	THF	25	70	86
8	**L4**	DME	25	50	94
9	**L4**	toluene	25	31	59
10	**L4**	dioxane	25	86	95

[a] Reactions run on a 0.16 mmol scale at 0.08 M using 1.0 equiv *tert*-butyl cyclopent-2-enyl carbonate, 1.5 equiv 2-methylpyridine, 1.3 equiv $BF_3{\bullet}OEt_2$, 3.5 equiv LiHMDS, 2.5 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and 6.0 mol % ligand. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Negative ee value signifies that the opposite enantiomer of the product as drawn was formed.

trace amounts of the desired adduct. When 2,4-lutidine was employed in a competition experiment between the 2- and 4-position of pyridine, substitution was observed exclusively at the 2-position (Table 2, entry 4). In contrast, when 2,6-lutidine was employed under the optimized conditions, no reaction was observed; presumably 2,6-disubstitution inhibits efficient coordination of the nitrogen atom with boron. Substitution at the 3-, 4-, and 5-positions was tolerated, even for sterically bulky alkyl and aromatic groups (Table 2, entries 5−10). Notably, aryl chlorides are not susceptible to oxidative addition by the palladium(0) species presumably generated during the reaction and potentially competitive coordination of dibenzofuranyl ethers to BF_3 does not inhibit the reaction (Table 2, entries 9 and 10, respectively). Finally, 1-methylisoquinoline also underwent the desired transformation, although longer reaction times were needed for full conversion (Table 2, entry 11).

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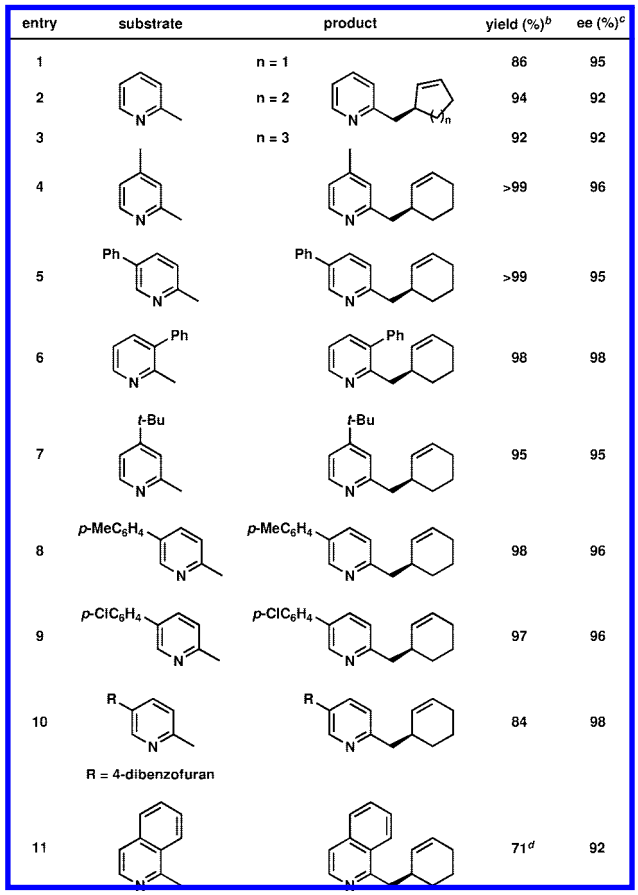
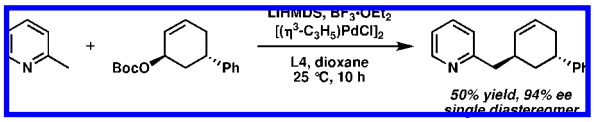
Table 2. AAA Reactions with 2-Methylpyridyl Nucleophiles[a]



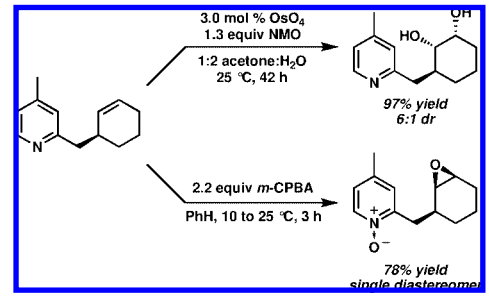
[a] Reactions run at 0.08 M in dioxane for 10 h with 1.0 equiv electrophile, 1.5 equiv nucleophile, 1.3 equiv BF_3•OEt_2, 3.5 equiv LiHMDS, 2.5 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and 6.0 mol % **L4**. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction run for 18 h; after 10 h, the product was isolated in 30% yield and 92% ee.

Scheme 1. AAA Reaction Proceeds with Retention of Configuration



To assess whether the anions generated in these palladium-catalyzed AAA reactions were indeed behaving as "soft" nucleophiles, 2-methylpyridine was reacted with an electrophile[3] designed to test whether the product obtained arose from net inversion of configuration at the allylic leaving group, which is observed with unstabilized nucleophiles, or the product of net retention of configuration, which is observed with stabilized nucleophiles (Scheme 1). Experimentally, the product of net retention of configuration was obtained as a single diastereomer by ^{1}H NMR analysis in 50% yield[10] and 94% ee. This suggests that the mechanism by which the reaction proceeds involves external attack

Scheme 2. Diastereoselective Reactions of Product Olefins



of the "soft" pyridyl nucleophile on the allylic ligand and not by an inner sphere coordination followed by reductive elimination.

Subsequent reactions of the product olefins can be rendered diastereoselective. Catalytic dihydroxylation with OsO_4 and NMO provided the corresponding diol in a diastereomeric ratio of 6:1 (Scheme 2). Alternatively, the proximity of the pyridyl nitrogen atom to the olefin can be exploited to direct reagents to one face preferentially, giving access to products with complementary diastereoselectivity. For example, epoxidation with *m*-CPBA occurred on the sterically more encumbered side of the olefin, providing the corresponding epoxide, with concomitant oxidation of the pyridyl nitrogen atom, as a single diastereomer (Scheme 2).

In summary, we have developed a way to overcome the limitation unstabilized nucleophiles present in palladium-catalyzed AAA reactions. Further investigations into the synthetic utility of these products and applications of this strategy to other "hard" nucleophiles are currently underway.

Acknowledgment. We thank the National Science Foundation for their support of our programs and Johnson Matthey for generously providing us with palladium salts.

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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(9) See Supporting Information for proof of absolute stereochemistry; that shown for all other compounds is assigned by analogy.
(10) The reaction failed to proceed to completion. The remainder of the mass balance was recovered starting material.

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