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Chasing the Proton Culprit from Palladium-Catalyzed Allylic Amination

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Transition-metal-catalyzed allylic amination has long been an area of intense research.[1] Allylamines have previously been prepared using iridium[2] and rhodium[3] catalysts with high selectivities for the branched products. On the other hand, the use of palladium in this chemistry has been known to produce linear allylamines with few notable exceptions.[4] This phenomenon has been obscure for some time. The goal of this contribution is to shed light on this long-standing problem and to evaluate ways of exercising control over selectivity with palladium catalysts.

We recently demonstrated an instructive aberration in palladium-catalyzed allylic amination: unsubstituted aziridines were found to give preferential formation of branched allylated products.[5] Mechanistic investigations indicate that amines other than aziridines undergo branched/linear (b/l) isomerization to form the thermodynamically more stable linear products.[5,6] It was found that protic acid generated during the reaction is the prerequisite for product isomerization.[5] Palladium coordination to the double bond of the protonated allylamine initiates ionization of the kinetically favored branched product (Figure 1). We consequently sought conditions under which the proton can be scavenged without detrimental effect on catalytic turnover such that the linear product formation can be suppressed.

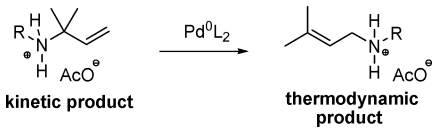

Figure 1. Branched-to-linear isomerization in allylic amination.

Extensive screening of a variety of bases was performed in order to affect the b/l ratio (see Supporting Information). Irrespective of their pK_a values, the majority of these additives either destroyed the starting acetate, arrested catalytic turnover, or had no effect. Delightfully, DBU struck the right balance: it produced branched products with high selectivities and without detrimental effects. Table 2 shows b/l ratios and yields for secondary as well as primary aliphatic amines. The developed conditions are well suited for challenging nonhindered aliphatic amines, known to exhibit low selectivities.[5a] In our system, benzylamine proved to be among the most interesting substrates: in the absence of DBU, a linear bisallylated product **3g** was formed, while in the presence of DBU, the branched isomer **3f** was the major product with no bisallylation byproducts (Figure 2). The latter fact supports the idea that in the absence of DBU the kinetic branched product has to undergo isomerization before it can react with another equivalent of allyl acetate. When DBU is present, the branched monoallylated product does not isomerize.[2b,7] The use of a substoichiometric amount of DBU (25%) was found to preferentially give the linear product.

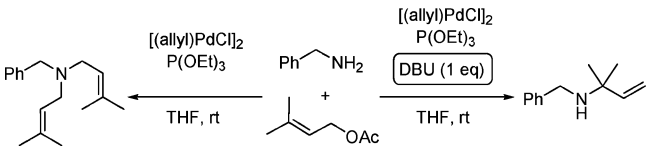

Figure 2. Base effect on selectivity in allylic amination.

Table 1. Ligand Screen for Benzylamine and Acetate **2b**

entry	ligand	b/l
1	$P(OEt)_3$	6:1
2	*rac*-BINAP	1:2
3	Cy_2P(*o*-biphenyl)	99:1

While it appeared possible to control the b/l ratio with trisubstituted allyl acetates, the reaction outcome with disubstituted substrates was not as straightforward. The presence of DBU is a necessary but not a sufficient requirement to favor the formation of branched products from disubstituted allyl acetates. The reaction outcome strongly depends on both the ligand and the amine. Triethylphosphite, which favors the formation of branched product with prenyl acetate **2a** (Table 1), gives a 6:1 b/l ratio with acetate **2b**. Bidentate ligands give lower b/l ratios with **2b**. Luckily, 2-(dicyclohexyl)biphenyl phosphine[8] significantly improved selectivity giving greater than 99:1 b/l ratio for this challenging substrate. Allyl acetate **2c** gave lower selectivity (entry 3, Table 2), but the same general trend prevailed.

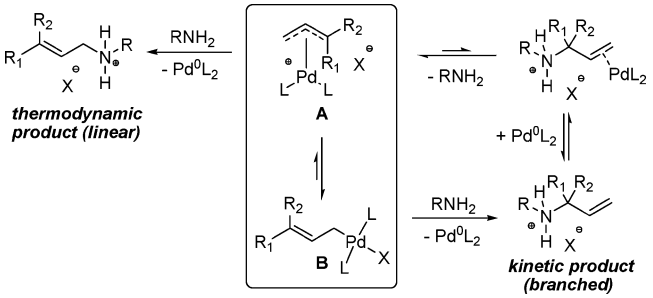

Figure 3. Pd(II) intermediates in the course of allylic amination.

The strong preference for branched products in the presence of DBU can be explained by considering the palladium intermediates shown in Figure 3. After Pd(0) attack on trisubstituted prenyl acetate

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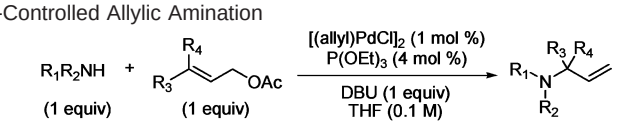
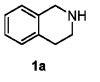
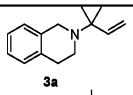
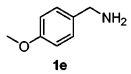
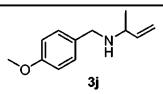
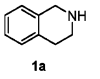
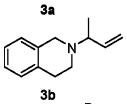
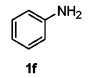
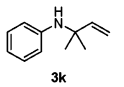
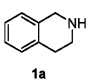
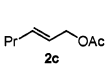
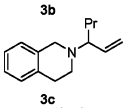
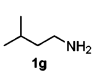
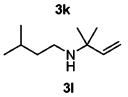
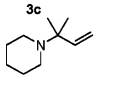
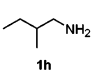
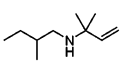
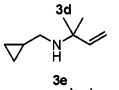
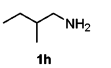
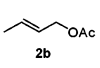
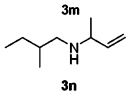
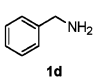
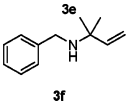
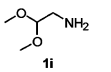
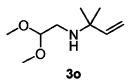
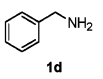
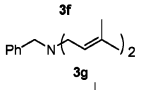
Table 2. Substrate Scope for Base-Controlled Allylic Amination



entry	amine	acetate	product	% yield (b/l)	entry	amine	acetate	product	% yield (b/l)
1	 **1a**	 **2a**	 **3a**	92 (19:1)	10	 **1e**	 **2b**	 **3j**	82[a] (19:1)
2	 **1a**	 **2b**	 **3b**	82[a] (13:1)	11	 **1f**	 **2a**	 **3k**	71 (4:1)
3	 **1a**	 **2c**	 **3c**	80[a,b] (2:1)	12	 **1g**	 **2a**	 **3l**	80 (9:1)
4	 **1b**	 **2a**	 **3d**	80 (99:1)	13	 **1h**	 **2a**	 **3m**	87 (19:1)
5	 **1c**	 **2a**	 **3e**	81[d] (19:1)	14	 **1h**	 **2b**	 **3n**	81[a] (9:1)
6	 **1d**	 **2a**	 **3f**	90 (9:1)	15	 **1i**	 **2a**	 **3o**	87 (99:1)
7	 **1d**	 **2a**	 **3g**	100[b,c] (0:100)	16	**1j**	**2a**	**3p**	61 (4:1)
8	**1d**	**2b**	**3h**	84[a] (99:1)	17	**1l**	**2a**	**3q**	76 (9:1)
9	**1e**	**2a**	**3i**	85 (19:1)					

[a] $Cy_2P(o\text{-biphenyl})$ ligand was used. [b] GC yield. [c] No DBU was added. [d] Contaminated with 10% of $P(OEt)_3$ that co-distills at 85 °C at 0.9 mmHg.

in THF, the resulting intermediate exists predominantly as the linear σ-complex **B**.[5a] The nucleophile is expected to attack in an S_N2' fashion, giving the branched allylamine as the kinetic product. DBU acts as a safeguard against a proton-driven isomerization that proceeds via π-complex formation **A**. In the case of disubstituted allyl acetates, the σ- and π-intermediates are differentiated to a smaller extent. DBU keeps the reaction under kinetic control, but achieving a high b/l ratio requires greater discrimination between isomeric allyl palladium intermediates, which is achieved through ligand control.

In summary, we have shown that the presence of DBU in palladium-catalyzed allylic amination is essential if the branched allyl amine is desired. Numerous examples with excellent yields and high b/l ratios have been documented using inexpensive ligands. Given the widespread utility of palladium-catalyzed allylic amination, we expect that these findings will be relevant in areas ranging from asymmetric catalysis to target-oriented synthesis. Finally, chasing the proton culprit from palladium catalysis using well-tuned base additives may operate in other catalytic processes. It is likely that a search for such reactions will lead to discovery of previously unobserved selectivity patterns, especially since a proton can sometimes act as the catalyst, thus veiling metal activity.[9]

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

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