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Enantioselective Palladium-Catalyzed Diamination of Alkenes Using *N*-Fluorobenzenesulfonimide

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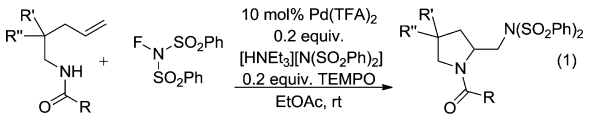
Supporting Information

ABSTRACT: An enantioselective Pd-catalyzed vicinal diamination of unactivated alkenes using *N*-fluorobenzenesulfonimide as both an oxidant and a source of nitrogen is reported. The use of Ph-pybox and Ph-quinox ligands afforded differentially protected vicinal diamines in good yields with high enantioselectivities. Mechanistic experiments revealed that the high enantioselectivity arises from selective formation of only one of four possible diastereomeric aminopalladation products of the chiral Pd complex. The aminopalladation complex was characterized by X-ray crystallography.

Chiral 1,2-diamines are important moieties found in biologically active compounds, organocatalysts, asymmetric ligands, and auxiliaries.[1,2] Direct difunctionalization of unactivated alkenes constitutes a valuable and powerful method for creating such useful chiral 1,2-diamine motifs. Despite the many uses of asymmetric 1,2-diamine scaffolds, efficient methods for their direct synthesis from alkenes are limited in comparison with conceptually similar dihydroxylation and aminohydroxylation transformations.[3] Though several transition-metal-catalyzed diamination reactions have recently been developed,[4] enantioselective variants are still rare. Notable examples include the intermolecular enantioselective diaminations reported by Muñiz[5,6] and Shi.[7] Although these methods provide high yields and enantioselectivities, there are still limitations on these transformations, particularly that they require stoichiometric amounts of osmium[5] or chiral iodine reagent[6] or are limited to diene substrates.[7]

We recently disclosed a novel palladium-catalyzed diamination of alkenes using *N*-fluorobenzenesulfonimide (NFBS) as both an oxidant and a source of nitrogen.[8] This method is useful for the generation of a variety of differentially protected cyclic 1,2-diamines (Scheme 1). Herein we report a highly enantioselective version of this reaction using chiral oxazolines as ligands along with the results of mechanistic experiments that shed light on the origin of the enantioselectivity in this system.

Scheme 1. Pd-Catalyzed Diamination Using NFBS



The development of an enantioselective diamination reaction began with a screen of the chiral pyridinebis(oxazoline) (pybox) ligands depicted in Figure 1 under standard

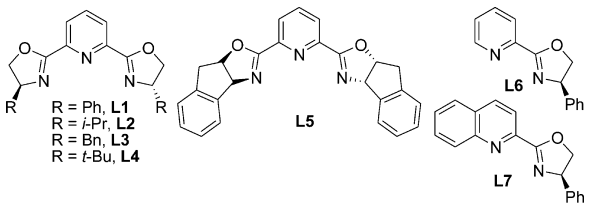


Figure 1. Chiral ligands.

Table 1. Chiral Ligand Screen and Optimization

R = Ph, **1a**
R = Me, **3a**

R = Ph, **2a**
R = Me, **4a**

entry	alkene	ligand	cond.[a]	% yield	% ee[b]
1	**1a**	(*R*,*R*)-**L1**	A	75	92
2	**1a**	(*S*,*S*)-**L2**	A	56	−32
3	**1a**	(*S*,*S*)-**L3**	A	62	−10
4	**1a**	(*S*,*S*)-**L4**	A	59	−20
5	**1a**	(*S*,*S*)-**L5**	A	60[c]	−62
6	**1a**	(*R*)-**L6**	A	42	36
7	**1a**	(*R*)-**L7**	B[d]	80	80
8	**3a**	(*R*)-**L7**	B	66	93
9	**3a**	(*R*,*R*)-**L1**	A	50	80

[a]Conditions A: 15 mol % ligand, 10 mol % $Pd(TFA)_2$, 20 mol % TEMPO, EtOAc, reflux. Conditions B: 12 mol % ligand, 10 mol % $Pd(TFA)_2$, 20 mol % TEMPO, 1,4-dioxane, rt. [b]Determined by chiral HPLC. [c]^{1}H NMR yield versus an internal standard. [d]NFBS was added over a 3 h period.

diamination conditions using substrate **1a** (Table 1). It was immediately clear that among the pybox ligands **L1**−**L5**, only the phenyl-substituted pybox ligand **L1** gave sufficiently high enantioselectivity (entry 1). Although ligand **L1** gave a good yield of product **2a**, it (like all of the pybox ligands) resulted in a substantial decrease in catalyst reactivity. Though the

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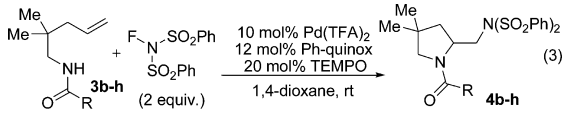
conversion in the absence of ligand was rapid at room temperature, in the presence of a tridentate ligand, complete consumption of the starting material was seen only upon refluxing in EtOAc overnight. This drop in reactivity was also apparent in the attempted reaction of substrate **3a** using ligand **L1**, which gave the desired product in a yield of only 50% (entry 9). We reasoned that perhaps the tridentate ligands donate too much electron density to the metal center and therefore decrease the rate of aminopalladation. If this hypothesis was true, the use of a bidentate ligand should alleviate this problem. Gratifyingly, the use of an analogous bidentate ligand, the phenyl-substituted quinolineoxazoline (quinox) ligand **L7**, resulted in a much more active catalyst with only slighly diminished enantioselectivity. After a short optimization (see the Supporting Information), we found that the use of **L7** allowed the reaction to be run at room temperature while giving higher yields and very high ee (entry 8).

Amide and carbamate protecting groups were tested under the optimized reaction conditions (Table 2). For amides

Table 2. Scope of the Amine Protecting Group



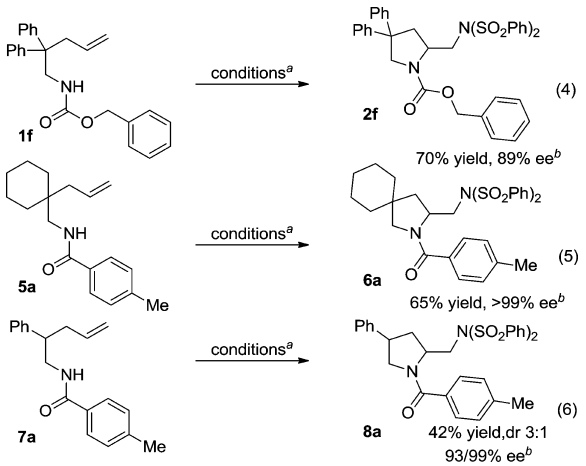
entry	alkene	R	% yield	% ee[a]
1	**3b**	Ph	75	91
2	**3c**	*p*-MeOC$_6$H$_4$	71	96
3	**3d**	*p*-BrC$_6$H$_4$	70	94
4	**3e**	CH$_3$	71	91
5	**3f**	OBn	60	93
6	**3g**	O*t*-Bu	34	82
7	**3h**	OCH$_2$CCl$_3$	50	91

[a]Determined by chiral HPLC.

(entries 1–4), both electron-withdrawing and -donating groups gave high enantioselectivities and yields similar to that for substrate **3a**. Carbamates (entries 5–7) also afforded high enantioselectivities, albeit with somewhat lower yields compared with the amides. Substrates with different substitution patterns were also subjected to the optimized conditions (Scheme 2). Products with geminal disubstitution on the backbone (**2f**, **6a**) could generally be made in good yields with high enantioselectivity. Monosubstituted substrate **7** also gave excellent enantioselectivity, but the yield and diastereoselectivity were modest.

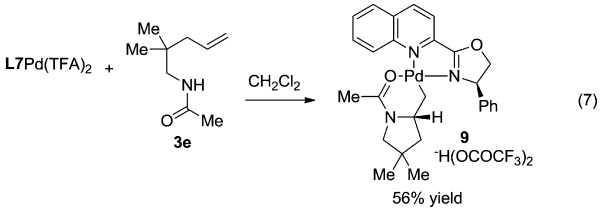
In our previous mechanistic work on the diamination reaction,[9] an intermediate alkylpalladium complex was isolated by trapping with a bipyridine ligand. To learn more about the origin of the enantioselectivity in this reaction, a Pd(Ph-quinox) complex was generated by mixing Pd(TFA)$_2$ (TFA = trifluoroacetate) and ligand **L7** and treating the mixture with substrate **3e** (Scheme 3). Full conversion to alkylpalladium complex **9** was observed.[10] Remarkably, only one of the four possible stereoisomeric products could be detected by ^{1}H NMR spectroscopy. Complex **9** was isolated in 56% yield, crystallized, and analyzed by X-ray crystallography (Figure 2). The structure of **9** shares several important features with our previously reported bipy–Pd–alkyl complex,[9] including the strong chelation of the amide carbonyl to the Pd center and the presence of the H(OCOCF$_3$)$_2$ complex counterion. The very

Scheme 2. Substrate Scope



[a]Conditions: 12 mol % ligand, 10 mol % Pd(TFA)$_2$, 20 mol % TEMPO, 2 equiv of NFBS, 1,4-dioxane, rt. [b]Determined by chiral HPLC.

Scheme 3. Formation of Alkylpalladium Intermediate 9



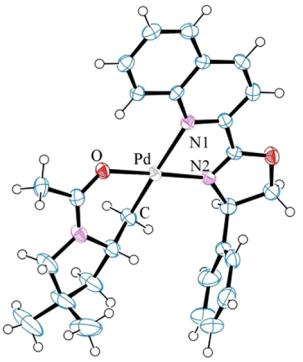


Figure 2. Crystal structure of (*R*)-Ph-quinox–Pd–alkyl complex **9**. The complex counterion has been omitted for clarity. Bond distances (Å): Pd–C, 1.998; Pd–O, 2.039; Pd–N1, 2.233; Pd–N2, 2.021.

large difference in the Pd–N bond lengths (2.02 vs 2.23 Å) in this complex is noteworthy. Two factors could be responsible for this difference. First, the large difference in trans influence by O and C should result in some lengthening of the quinoline–Pd bond. Second, the quinoline–Pd bond should also be longer because of steric interference between the peri hydrogen of the quinoline and the ligand cis to the quinoline. Two existing X-ray crystal structures confirm that both factors are operative and that the latter factor is more important. In the bipy–Pd–alkyl complex, which should be affected only by the trans influence, the Pd–N bond trans to C is only 0.07 Å longer than the Pd–N bond trans to O (2.03 vs 2.10 Å). In the (*t*-Bu-quinox)PdCl$_2$ complex reported by Yang,[11] which should display only the effects of quinoline sterics, the quinoline–Pd bond is 0.15 Å longer than the oxazoline–Pd bond (2.16 vs

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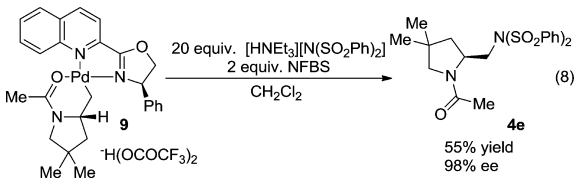
2.01 Å). The 0.21 Å difference in bond lengths in complex **9** is very nearly the sum of those two factors.[12] The failure of pyrox ligand **L6** to give high enantioselectivity (Table 1, entry 6), indicates that the steric effect of the quinoline plays a crucial role in determining the stereoselectivity.

To establish further the intermediacy of complex **9** in the catalytic diamination, **9** was treated with NFBS and triethylammonium benzenesulfonimide (Scheme 4).[13] Under

Scheme 4. Amination of the Alkylpalladium Complex



these conditions, the diamination product was isolated in 55% yield with 98% ee, which is very nearly the same as the catalytic reaction affords. Furthermore, the major enantiomer produced in this reaction matched that observed in the catalytic reaction, and its absolute configuration was determined to be *S*, matching what was observed in complex **9** (see the Supporting Information). This is consistent with aminopalladation serving as the enantiodetermining step of the catalytic cycle.

In conclusion, an enantioselective method for the diamination of alkenes to create a differentally protected diamination product has been developed. The palladium-catalyzed reaction provided products in moderate yields with up to 99% ee using the (*R*)-Ph-quinox ligand. Isolation of a single stereoisomer of the intermediate alkylpalladium complex established that aminopalladation is the enantiodetermining step of this transformation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental conditions, spectroscopic data, crystallographic information (CIF), and data for determining the enantiomeric excesses of the diamination products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(10) Previously, the stereochemistry of this step was determined to be anti. The formation of **9** also proceeds through anti-aminopalladation (see the Supporting Information).

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(12) See Table S2 in the Supporting Information for details on bond lengths.

(13) As reported in ref 8, excess benzenesulfonimide was required to prevent competitive incorporation of the trifluoroacetate counterion.