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Intramolecular Aminocyanation of Alkenes by Cooperative Palladium/Boron Catalysis

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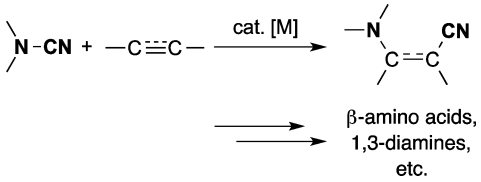
Supporting Information

ABSTRACT: A cooperative palladium/triorganoboron catalyst to accomplish the intramolecular aminocyanation of alkenes through the cleavage of N−CN bonds is reported. 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) is found to be crucial as a ligand for palladium to effectively catalyze the transformation with high chemo- and regioselectivity. A range of substituted indolines and pyrrolidines with both tetra- or trisubstituted carbon and cyano functionalities are readily furnished by the newly developed cyanofunctionalization reaction. A preliminary example of enantioselective aminocyanation is also described.

Cyanofunctionalization reactions across unsaturated carbon−carbon bonds have been studied extensively because of their utility in accessing highly functionalized nitriles, which are found in a number of pharmaceutical drugs, agrochemicals, and optoelectronic materials as well as synthetic intermediates for carboxylic acids, esters, amides, and amines. Starting from simple and readily available substrate sets, silylcyanation,[1] germylcyanation,[2] stannylcyanation,[3] borylcyanation,[4] carbocyanation,[5] thiocyanation,[6] bromocyanation,[7] and most recently oxycyanation[8] of alkynes and/or alkenes have been realized by metal catalysis to give nitriles having a functional group at the position β to the cyano group. We report herein the intramolecular aminocyanation of alkenes through N−CN bond activation by cooperative palladium/boron catalysis. We also demonstrate the first catalytic enantioselective aminocyanation reaction. Aminocyanation had never been achieved until the very recent report on the three-component coupling of alkenes, *N*-fluorobenzenesulfonimide, and Me_3SiCN by copper catalysis to achieve net aminocyanation.[9] The transformation serves as an ideal protocol to directly give β-aminonitriles, which function as synthetic precursors for highly important building blocks such as β-amino acids and 1,3-diamines (Scheme 1).

Scheme 1. Aminocyanation of Unsaturated Compounds



A key to realizing aminocyanation is the activation of N−CN bonds of cyanamides by metal catalysts. Indeed, the catalytic cleavage of N−CN bonds has been reported only very recently,[10] whereas the reactivity of cyanamides and their use in synthetic organic chemistry have been studied extensively,[11] wherein very harsh reaction conditions are required for the cleavage of the unreactive N−CN bonds.[12] We have demonstrated that the use of Lewis acid cocatalysts significantly affects the rate of nickel-catalyzed carbocyanation[13] and palladium-catalyzed oxycyanation[8] reactions, possibly by promoting the oxidative addition of C−CN[14] and O−CN bonds through coordination of a cyano group to a Lewis acid catalyst in an η^1 fashion. Therefore, we examined the reaction of *N*-cyano-*N*-[2-(2-methylallyl)phenyl]-acetamide (**1a**)[15] to ascertain the viability of the aminocyanation reaction through N−CN bond activation by taking advantage of cooperative catalysis. Screening of several combinations of metal complexes, ligands, and Lewis acids led us to find that reaction conditions very similar to those for the intramolecular oxycyanation[8] employing CpPd(allyl) (10 mol %), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos)[16] (10 mol %), and BEt_3 (40 mol %) allowed the intramolecular insertion of the double bond of **1a** into the N−CN bond in a 5-exo-trig manner to give 2-(1-acetyl-2-methylindolin-2-yl)-acetonitrile (**2a**) in 82% yield after 3 h in toluene at 80 °C (reaction scheme in Table 1). BPh_3 also showed good activity. As in the case of oxycyanation, the Pd/Xantphos/triorganoboron catalysts are exceptionally effective; poor to modest yields were obtained with the related bisphosphine ligands DPEphos (entry 1) and Nixantphos (entry 2), whereas other mono- and diphosphanes gave no trace amounts of **2a**. In many cases, modest to good conversions of **1a** were noted; however, reaction quenching by filtration through a silica gel pad resulted mainly in protodecyanation of **1a**. The use of other Lewis acids such as $B(C_6F_5)_3$ (entry 3) and $AlEt_3$ (entry 4) and the absence of a Lewis acid catalyst (entry 5) were futile. Nevertheless, the prolonged reaction with $B(C_6F_5)_3$ in the absence of CpPd(allyl) at a higher temperature gave a small amount of **2a** (entry 6), while BPh_3 alone did not show any detectable amount of product (entry 7). The preliminary but interesting reactivity observed with $B(C_6F_5)_3$ would be an issue for further investigation. Other palladium sources were far less effective than CpPd(allyl) (entries 8−11). Palladium(II) sources such as $PdCl_2$ and $Pd(OAc)_2$ are reluctant to be reduced to palladium(0) species under these reaction conditions, partly because of the inability of

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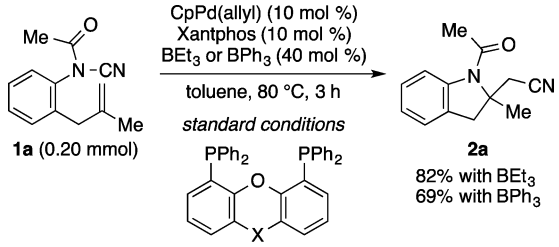
Table 1. Intramolecular Aminocyanation of Alkenes with 1a: Effect of Reaction Parameters



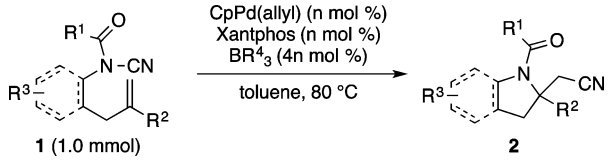
entry	variation from the standard conditions	yield (%)[a]
1	DPEphos instead of Xantphos (with BPh_3)	6
2	Nixantphos instead of Xantphos (with BPh_3)	45
3	$B(C_6F_5)_3$ instead of BR_3	1
4	$AlEt_3$ instead of BR_3	<1
5	without BR_3	2
6[b,c]	$B(C_6F_5)_3$ instead of BR_3 without CpPd(allyl)	11
7	without CpPd(allyl) (with BPh_3)	<1
8	$[PdCl(allyl)]_2$ instead of CpPd(allyl) (with BPh_3)	<1
9	$PdCl_2$ instead of CpPd(allyl) (with BPh_3)	<1
10	$Pd(OAc)_2$ instead of CpPd(allyl) (with BPh_3)	19
11	$Pd(dba)_2$ instead of CpPd(allyl) (with BPh_3)	24
12[b,d]	$Ni(cod)_2$ instead of CpPd(allyl) (with BPh_3)	1

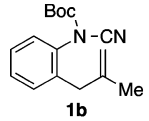
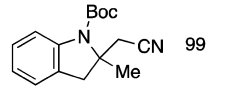
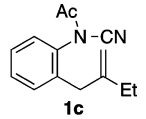
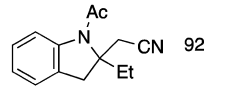
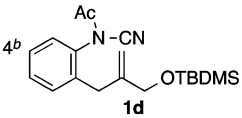
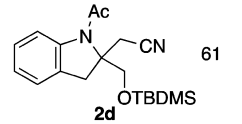
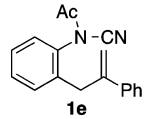
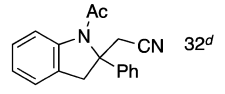
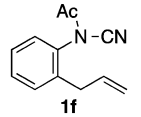
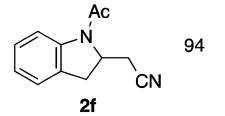
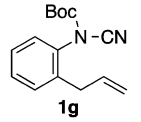
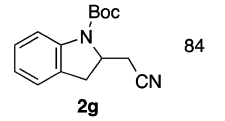
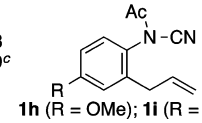
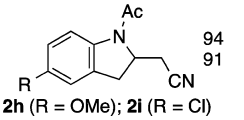
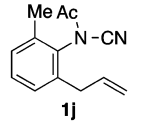
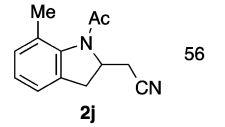
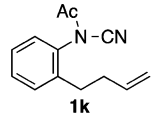
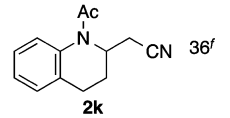
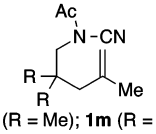
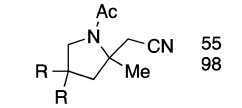
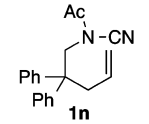
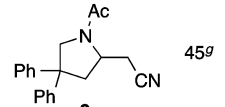
[a]Yields estimated by GC. [b]Run on a 0.10 mmol scale. [c]Run at 80 °C for 39 h and then at 120 °C for 47 h. [d]Run for 16 h.

the triorganoboranes to achieve the reduction in the absence of nucleophilic and/or basic additives. Although $Pd(OAc)_2$ could be reduced by Xantphos, this would give oxidized ligands, leading to an insufficient amount of an active catalyst species and thus resulting in poor conversion. On the other hand, CpPd(allyl) has been known to undergo reductive elimination of the Cp and allyl groups upon coordination of phosphorus ligands to give a palladium(0) species.[17] The observed poor activity of $Pd(dba)_2$ can be ascribed to the dibenzylideneacetone (dba) ligand, which inhibits the reaction in a manner yet to be identified. The reaction under the optimized reaction conditions with BEt_3 in the presence of added dba (20 mol %) gave **2a** in 29% yield after 6 h. Finally, a nickel catalyst was completely ineffective (entry 12).

The standard reaction conditions on a 1.0 mmol scale for 6 h gave **2a** in 93% yield, even with a decreased amount of the catalysts (5 mol % Pd/Xantphos; 20 mol % BEt_3), after purification by medium-pressure column chromatography on silica gel (Table 2, entry 1). *N*-Boc variant **1b** underwent the reaction in even higher yield when BPh_3 was used (entry 2). Substituents on the double bond in **1** can be varied; ethyl (entry 3) and (*tert*-butyldimethylsilyloxy)methyl (entry 4) were tolerated, whereas the aminocyanation across a conjugated double bond was sluggish (entry 5).[18] Unlike oxycyanation,[8] the cyclization of *N*-(2-allylphenyl)-*N*-cyanoacetamide (**1f**) and its Boc variant **1g** proceeded smoothly to give **2f** and **2g** having a trisubstituted carbon (entries 6 and 7), without possible *β*-hydride elimination (vide infra). 4-Methoxy-, 4-chloro-, and 2-methyl-substituted variants **1h–j** also underwent the aminocyanation (entries 8–10). While a range of 2,2-disubstituted and 2-monosubstituted indolines were successfully accessed by the present protocol, 2-substituted tetrahydroquinoline **2k** was obtained in modest yield through a seemingly reluctant 6-exo-trig cyclization (entry 11). On the other hand, the use of BPh_3 as

Table 2. Intramolecular Aminocyanation of Alkenes Catalyzed by Pd/BR_3



entry	substrate	R^4	n	time (h)	product	yield (%)[a]
1	**1a**	Et	5	6	**2a**	93
2	 **1b**	Ph	5	3	 **2b**	99
3	 **1c**	Et	5	9	 **2c**	92
4[b]	 **1d**	Ph	10	10	 **2d**	61
5[c]	 **1e**	Et	10	48	 **2e**	32[d]
6	 **1f**	Et	5	6	 **2f**	94
7[e]	 **1g**	Ph	10	5	 **2g**	84
8	 **1h** (R = OMe); **1i** (R = Cl)	Et	5	6	 **2h** (R = OMe); **2i** (R = Cl)	94
9[c]		Et	10	3		91
10[b]	 **1j**	Et	10	2	 **2j**	56
11[c]	 **1k**	Ph	10	6	 **2k**	36[f]
12[c]	 **1l** (R = Me); **1m** (R = Ph)	Ph	10	3	 **2l** (R = Me); **2m** (R = Ph)	55
13		Ph	5	12		98
14[c]	 **1n**	Ph	10	48	 **2n**	45[g]

[a]Isolated yields. [b]Run on a 0.30 mmol scale. [c]Run on a 0.50 mmol scale. [d]82% conversion of **1e**. [e]Run on a 0.20 mmol scale. [f]91% conversion of **1k**. [g]91% conversion of **1n**.

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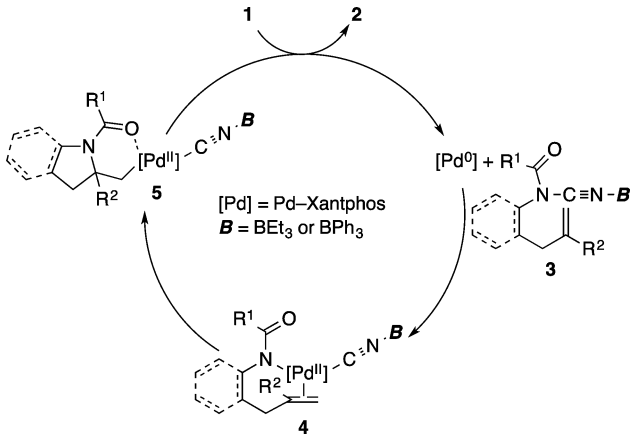
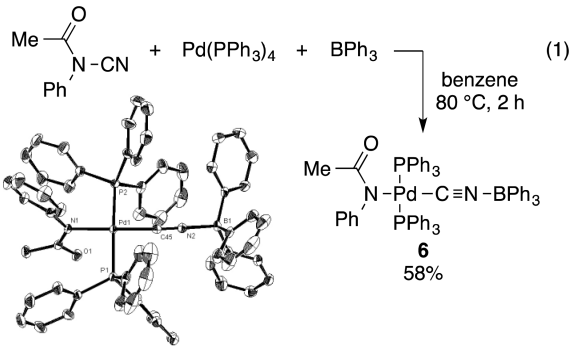
the Lewis acid allowed the N−CN bond activation of cyanamides derived from aliphatic amines to afford variously substituted pyrrolidines in modest to good yields (entries 12−14). We found that decyanation competed as a byproduct-forming process, resulting in modest yields of the aminocyanation products (entries 5, 11, and 14). In addition, a mixture of cyclic products lacking a cyano group, which were likely derived from β-hydride elimination before C−CN bond-forming reductive elimination (vide infra), was also noted (entries 11 and 14).

Although detailed mechanistic studies have yet to be undertaken, the reaction would be initiated by oxidative addition of the N−CN bond in **1**, which is coordinated to the boron Lewis acid catalyst through a cyano group, to a Pd(0)−Xantphos complex (Scheme 2). Syn aminopalladation[19] in an exo-trig

Scheme 2. Plausible Catalytic Cycle

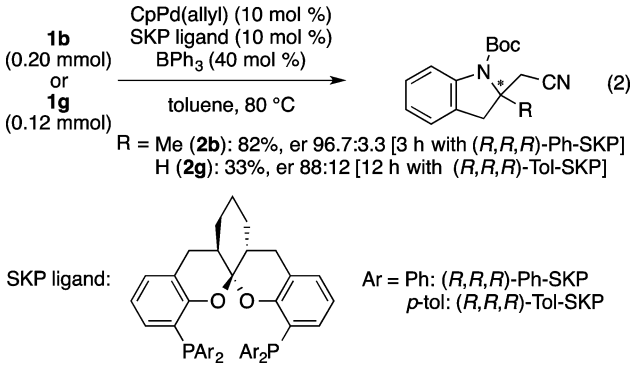


fashion is followed by C−CN bond-forming reductive elimination to give boron-bound **2**, and transfer of the boron catalyst to unreacted **1** regenerates the catalytically active palladium and **1**−boron complexes. Coordination of the aminocarbonyl functionality in **1** to a boron catalyst cannot be ruled out to justify the pronounced effect of the Lewis acid. Indeed, *N*-benzyl and N-unsubstituted variants of **1a** did not undergo the cyclization. On the other hand, we have previously shown that a cyano group coordinates to a Lewis acid preferentially over an aminocarbonyl moiety in the oxidative adduct derived from cyanoformamides, $Ni(cod)_2$, and BPh_3.[20] To gain insights into the oxidative addition step, stoichiometric reactions were examined.[21] Gratifyingly, the reaction of Ph(Ac)-N−CN, $Pd(PPh_3)_4$, and BPh_3 in benzene at 80 °C gave oxidative adduct **6**, which was characterized by NMR spectroscopy and X-ray crystallography (eq 1).[22] The observed oxidative addition did



not proceed at all in the absence of BPh_3 under the same reaction conditions even after 22 h. Thus, the coordination of a cyano group to a Lewis acidic boron center is likely to induce the N−CN bond activation. Coordination of the aminocarbonyl functionality to a palladium center would be rather important to suppress competitive β-hydride elimination of alkylpalladium intermediate **5** (R^2 = H), which is the case with oxycyanation because of the lack of such O substituents.[8] The $C(sp^3)$−CN bond-forming reductive elimination can also be effected by the coordination of a cyano group to the Lewis acid[23] as well as the bidentate phosphorus ligand with a large bite angle.[16]

In view of the importance of chiral β-amino acids and indolines, the development of an enantioselective aminocyanation was sought. Although most known chiral bidentate ligands were ineffective in terms of reactivity, we identified (*R*,*R*,*R*)-Ph-SKP, which was recently developed by Wang and Ding,[24] as a promising lead for the enantioselective aminocyanation. Thus, the reaction of **1b** using the aforementioned chiral ligand instead of Xantphos allowed the cyclization to proceed in a highly enantioselective manner to give optically active indoline **2b** in good yield (eq 2). The use of (*R*,*R*,*R*)-Tol-



SKP also allowed the enantioselective aminocyanation of **1g** to give a modest yield of **2g** having a chiral trisubstituted carbon (eq 2). (*R*,*R*,*R*)-Ph-SKP gave a lower yield of **2g** (~20%) but with very similar enantioselectivity (er 89:11).

In summary, we have developed an intramolecular aminocyanation of alkenes by palladium/boron catalysis.[25] The transformation allows for simultaneous installation of a tetra- or trisubstituted carbon and a cyano group through N−CN bond activation to afford variously substituted indolines and pyrrolidines, including optically active examples, which can be of interest as synthetic building blocks. Synthetically, the aminocyanation demonstrated herein can be a CO- and/or oxidant-free alternative to alkene aminocarbonylation and other aminofunctionalization reactions catalyzed by palladium.[26] Current efforts are directed toward further development of the enantioselective aminocyanation and more detailed mechanistic studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, including spectroscopic and analytical data, and crystallographic data (CIF). 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.

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