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Rhodium(ı)-catalyzed N–CN bond cleavage: intramolecular β-cyanation of styrenes[†]

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We report herein the first example of intramolecular cyanation of a styrene by a rhodium(ı)-catalyzed N–CN cleavage reaction. Substituents on the arenes or the styrene alpha-position are tolerated. Our results demonstrate that alkene cyanation can indeed be atom economical.

Transition metal catalyzed activation of traditionally inert bonds such as unactivated C-H, C-C and C-O not only make synthetic routes simpler but also more efficient and, consequently, this field has attracted enormous attention recently.¹ Of particular interest is C-C activation given the central role of this bond in organic chemistry and the challenge of selective manipulation. An important variant of C-C bond activation, i.e., C-CN activation,² has already been demonstrated in the DuPont's adiponitrile process using catalytic nickel. The first example of carbocyanation reaction was realized in 2004 by Hiyama and co-workers. Subsequently, Chatani, Hiyama and Jacobsen et al. reported several key results for the generation of C-H,³ C-Si,⁴ C-C^{4b,5} and C-B⁶ bonds *via* activation of the C-CN bond following Hiyama's precedent.^{5b} Generally, metals such as Fe and Rh are utilized in tactical combination with organic silicon reagents or metal-Lewis acid bifunctional catalysis.^{5g,7} Only a few cases involving O-CN⁸ activation have been realized recently while N-CN9 cleavage is even more rare. Herein, we report that Rh(I) can activate the N-CN bond under mild conditions and the resultant intermediate is utilized in the intramolecular cyanation of styrenes to give 3-arylacrylonitriles (cinnamonitriles) in good yields. 3-Arylacrylonitriles find numerous applications in the preparation of pharmaceutical, agrochemical, and material science/optoelectronic compounds.¹⁰ The conjugated alkene is readily functionalized¹¹⁻¹⁵ whereas the nitrile¹⁶ is a useful precursor for a wide range of functionalities, e.g., aldehydes, acids, amides, amines and so on. 3-Arylacrylonitriles are commonly prepared by the reaction

of stoichiometric metal-cyano reagents and pre-activated (substituted) alkenes (X = Br, Cl, I, OTf, etc.) in the presence of a transition metal catalyst (Scheme 1, eqn (1)).¹⁷ Alternatively, there has been considerable progress towards synthesis of 3-arylacrylonitriles from boronic acids.^{9a,18} In 2006, Liebeskind reported the palladium-catalyzed, copper(1)-mediated coupling of boronic acids and benzyl thiocyanate to provide alkenyl nitriles.^{18a} Later, Hartwig disclosed an iridium-catalyzed borylation of arene C-H bonds followed by a copper-mediated cyanation of the formed arylboronate esters using $Zn(CN)_2$ to access 3-arylacrylonitriles.18b Recently, Hu and Cheng et al. reported a simple copper(1)-mediated procedure for the cyanation of boronic acids with CuCN and TMSCN.^{18c} Additionally, Yamamoto and co-workers reported a copper-catalyzed stereoselective hydroarylation of 3-aryl-2-propynenitriles with arylboronic acid, which provided a different route for the synthesis of 3,3-diarylacrylonitriles (Scheme 1, eqn (2)).^{18e,19} Most recently, Jiao and co-workers reported a strategy which relies upon activated C(sp³)-N coupling reactions, *i.e.*, transformation of alkyl arenes or alkenes with TMSN₃ to the corresponding alkenyl nitriles catalyzed by inexpensive and nontoxic iron(II) chloride (Scheme 1, eqn (3)).²⁰ All of these methods exploited pre-activated precursors for high atom economy.²¹



Scheme 1 Strategies for the synthesis of 3-arylacrylonitriles.

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However, one of the most straightforward approaches to 3-arylacrylonitrile synthesis, *i.e.*, transition metal catalyzed cyanation of unactivated styrenes, has received scant attention (Scheme 1, eqn (4)).²² Due to the high affinity of many metals for cyano ligands and the moderate nucleophilic nature of cyanide, transition metal mediated insertion or addition of cyanide to alkenes is quite challenging.²³ Considering these difficulties, we initiated our research using a model compound **1a**.

We initially screened different rhodium complexes along with a suitable ligand (Table 1, entries 1-4). It was found that $[RhCl(COD)]_2$ (COD = cyclooctadiene) combined with the DPEphos ligand gave a promising outcome with a 65% isolated vield of 1b under unoptimized conditions, and only trace amount of a double bond isomer was detected. Other Rh(I) species such as [RhOH(COD)]₂, [RhBF₄(COD)]₂ or Wilkinson's catalyst were no better than the original catalyst. Although the conversion of the reaction was almost quantitative, the major by-product was 1c, derived from simple de-cvanation. Subsequently optimization attempts via (i) water-exclusion (added 4 Å sieves or MgSO₄), (ii) alternative metal catalyses (Table 1, entries 5 and 6) and (iii) different solvents (Table 1, entries 7 and 8) proved to be disappointing. Palladium species afforded low yields while solvents such as dichloroethane and acetonitrile afforded no better yields than the original reaction conditions. We also tried various phosphine ligands. For example, triphenylphosphine was not effective while dppf gave a high conversion but relatively low yield compared with the DPEphos ligand (Table 1, entries 9-11). To seek whether the reaction is catalyzed by metal or phosphine, 1a was heated to 120 °C in the absence of the metal (Rh(1)) or the catalyst (DPEphos) for 24 h, and the starting material was recovered. Also, the Ts group is necessary for this transformation. Finally, improvements in the yield of 1b were realized when the catalyst loading was increased

Table 1	Optimization of reac				
		Rh or Pd ligand additive	Me		
	N Ts	conditions CN NHTs			
	1a			1b	
Entry ^a	$Catalyst^{b}$	Ligand	Solvent ^c	Yield ^d [%]	
1	[RhCl(COD)] ₂	DPEphos	Toluene	65	
2	$[RhBF_4(COD)]_2$	DPEphos	Toluene	51	
3	$RhCl(PPh_3)_3$	None	Toluene	50	
4	[RhOH(COD)] ₂	DPEphos	Toluene	40	
5	$Pd_2(dba)_3$	Dppe	Toluene	31	
6	$PdCl_2(dppf)_2$	None	Toluene	42	
7	[RhCl(COD)] ₂	DPEphos	DCE	43	
8	[RhCl(COD)] ₂	DPEphos	CH ₃ CN	44	
9	[RhCl(COD)] ₂	PPh_3	Toluene	53	
10	[RhCl(COD)] ₂	Dppe	Toluene	48	
11	RhCl(COD)	Dppf	Toluene	60	
12	[RhCl(COD)]	DPEphos	Toluene	81	

^{*a*} Entries 1–11: Rh catalyst 5 mol%, ligand 10 mol%, 0.1 M **1a**, 90 °C, 12 h. Entry 12: Rh catalyst 10 mol%, ligand 10 mol%, 0.1 M **1a**, 120 °C, 48 h. ^{*b*} Reduced catalyst loadings led to low conversions. ^{*c*} All solvents were freshly purified. ^{*d*} Isolated yield after silica gel flash chromatography, **1c** was isolated in approximately 5% yield. Configuration of **1b** was confirmed using COSY and NOESY, see ESI.

from 5 mol% to 10 mol%, the reaction temperature from 90 $^{\circ}$ C to 120 $^{\circ}$ C and the reaction time from 12 h to 48 h (Table 1, entry 12).

With optimised conditions in hand, we examined the scope of cyanation of styrenes (Table 2). Alkyl substituents in the olefinic alpha position led to acrylonitriles 2b-5b in good yields (Table 2, entries 1-4), although the influence of the increasing steric bulk was evident in somewhat decreased yields. With substituted arenes in the olefinic α -position, the cyanation reaction gave 6b-11b in moderate yields (Table 2, entries 5-10), whether it contained electron-donating groups or electronwithdrawing groups. Importantly, we also found that a substituent in the alpha position of the alkene is necessary for the cyanation to occur. Substrates without an alpha substituent or with a betaposition (either electron-rich or poor) substituent failed to give acrylonitrile.²⁴ Various arene substituents (12a-15a) were also examined and, in most cases, afforded moderate yields (Table 2, entries 11-14); electron-rich arenes (12a and 14a) resulted in higher yields (Table 2, entries 11 and 13) than electron-deficient arenes (13a and 15a) (Table 2, entries 12 and 14). The low yield of 13b might be the consequence of a competitive reaction between the chloro-substituent and the metallic catalyst.²⁵

To demonstrate the potential synthetic utility of the above styrene cyanation, **1b** was transformed into indole **1d** in 70%



 a Conditions: Rh catalyst 10 mol%, ligand 10 mol%, 0.1 M xa, 120 °C, 48 h. b Xantphos was replaced by DPEphos. DPEphos as a ligand gave less than 10% yield. Xantphos = 4,5-bis(diphenyl phosphino)-9,9-dimethylxanthene.



Scheme 2 2,3-Substituted indole building block synthesis.



yield (Scheme 2). Given the rapid route for the synthesis of 2-cyano-3-substituent indole **1d** and the versatile access to other functionalities from cyano-derivatives,²⁶ we believe that this building block in particular and our synthetic process in general will find many useful applications.

To gain an insight into the reaction mechanism, we investigated the reaction of $[D_2]$ -**9a** (80 carbon atom% D). Under standard reaction conditions, we obtained *N*-tosyl aniline ($[D_2]$ -**9b**) with 68% D content. The result indicated that an intramolecular process existed, *i.e.*, the Rh(1) mediated cyano group transferred from a nitrogen atom to the terminal alkene (Scheme 3).

In conclusion, we report the first example of intramolecular cyanation of a styrene by a rhodium(I)-catalyzed N–CN cleavage reaction. Substituents on the arenes or the styrene alphaposition are tolerated. Our results demonstrate that alkene cyanation can indeed be atom economical. Furthermore, the cyanation product, **1b**, underwent an additional intramolecular C–N coupling to afford 3-Me-2-CN indole **1d**. This synthetic route provides an efficient construction of 3-alkyl/aryl-2-CN indole derivatives. Current efforts are focused on discovering intermolecular cyanation and/or with other cascade reactions to expand the utility of this methodology.

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