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Chemoselective Palladium-Catalyzed Cyanation of Alkenyl Halides

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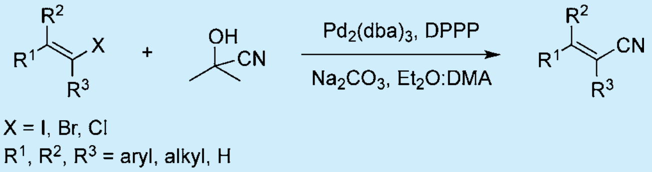
Supporting Information

ABSTRACT: A palladium-catalyzed cyanation of alkenyl halides using acetone cyanohydrin is described. A number of structurally diverse alkenylic nitrile containing compounds was prepared in one step under optimized conditions. The reaction proved to be efficient, chemoselective, easy to perform, and tolerant of a number of functional groups.



The alkenyl-nitrile[1] functional group is highly versatile and widely represented in several important dyes, herbicides, and natural products.[2] A number of important pharmaceutical agents also comprise a crucial *α,β*-unsaturated nitrile group: the anticancer agents trilostane and CC-5079; the Parkinson's disease drug entacapone; and the potent anti-HIV non-nucleoside reverse transcriptase inhibitor, rilpivirine (Figure 1).[3] A number of synthetic routes to alkenyl nitriles are known,[4] which include the following: amide dehydration reactions,[5] carbocyanation of alkynes,[6] Wittig/Horner–Emmons[7,8] type phosphorus, and silicon-based Peterson[9,10] olefinations, although many suffer from poor yields and/or limited stereocontrol.

Transition metal (Ni, Pd)-catalyzed alkenyl cyanation reactions are an attractive option, although their application has been somewhat restricted to the synthesis of substituted cinnamonitriles.[11] Hazards associated with the handling and disposal of metal cyanide waste, coupled with the significant problem of catalyst deactivation due to the presence of excess dissolved cyanide ion, are also unwelcoming.[12]

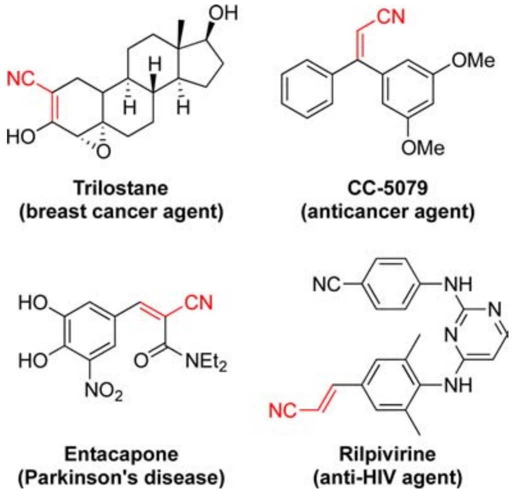
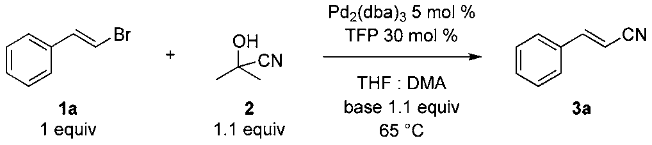


Figure 1. Representative examples of clinically important alkenyl-nitrile containing pharmaceuticals.

Table 1. Screening Conditions for the Palladium-Catalyzed Cyanation of Alkenyl Bromide 1a



entry	base	additive	ACH addition	time	yield[a]
1	Na_2CO_3	–	15 min	6 h	23%
				15 h	23%
				10 min	trace[b]
2	Na_2CO_3	–	one portion	6 h	24%
3	Na_2CO_3	–	17 h	1 h (18 h total)	trace[b]
4	Na_2CO_3	Bu_3SnCl_{cat}	15 min	6 h	15%
5	TlOEt	H_2O	15 min	6 h	–
		after 6 h		15 h[c]	

[a]Isolated yield. [b]Determined by analysis of the crude ^1H NMR; product not isolated. [c]After reacting for 6 h, a drop of H_2O was added to form TlOH *in situ*. After another 15 h reaction time, there was still no reaction and no starting material consumption.

Beller et al. pioneered the use of acetone cyanohydrin (ACH) for the palladium-catalyzed cyanation of aryl and heteroaryl halides.[13] Using continuous slow addition of liquid ACH *via* syringe pump allowed the controlled *in situ* release of the cyanide ion, thereby overcoming the problem of catalyst deactivation. We here report our development of a chemoselective procedure for the palladium-catalyzed cyanation of alkenyl halides using ACH as the cyanide source.[14]

Our studies commenced with (*E*)-*β*-bromostyrene (**1a**) and the addition of ACH over 15 min in the presence of the catalyst mixture [$Pd_2(dba)_3$, tri(2-furyl)phosphine (TFP)] at 65 °C.

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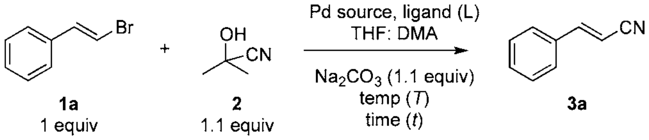
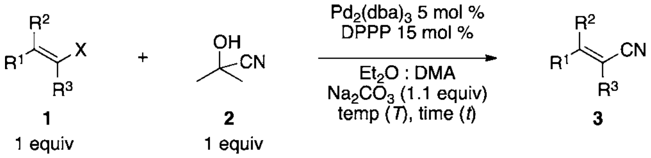
Table 2. Optimization of the Reaction Conditions for the Cyanation Reaction of Alkenyl Bromide **1a**



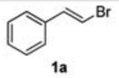
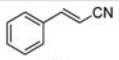
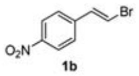
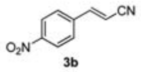
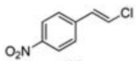
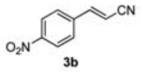
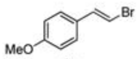
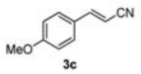
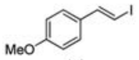
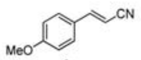
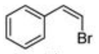
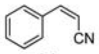
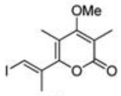
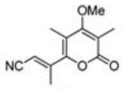
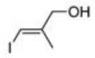
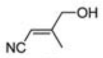
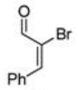
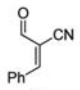
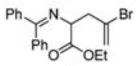
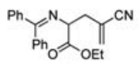
entry	Pd[a]	L	P/Pd	T (°C)	t (h)[b]	yield[e]
1	Pd$_2$(dba)$_3$	TFP	3:1	rt	6	trace[f]
2	Pd$_2$(dba)$_3$	TFP	3:1	100	6[c]	38%
3	Pd$_2$(dba)$_3$	TFP	3:1	100	3	trace[f]
4	Pd$_2$(dba)$_3$	DPPP	3:1	65	6	38%
5	Pd$_2$(dba)$_3$	DPPP	3:1	100	2[c,d]	70%
6	Pd$_2$(dba)$_3$	PPh$_3$	3:1	100	6	–
7	Pd$_2$(dba)$_3$	PCy$_3$	3:1	100	6	trace[f]
8	Pd$_2$(dba)$_3$	DPPP	4:1	100	3[d]	49%
9	Pd$_2$(dba)$_3$	DPPP	6:1	100	3[c,d]	51%
10	Pd(OAc)$_2$	TFP	3:1	100	3	trace[f]
11	Pd(OAc)$_2$	DPPP	3:1	100	1.5[c,d]	63%
12	Pd(OAc)$_2$	DPPP	4:1	100	1.5[c,d]	73%
13	Pd(OAc)$_2$	DPPP	6:1	100	1.5[c,d]	37%
14	–	DPPP	–	100	6	–[g]

[a] 5 mol % Pd$_2$(dba)$_3$, 10 mol % Pd(OAc)$_2$ used.
[b] Reactions were quenched after the indicated time period.
[c] No remaining starting material detected by crude ^{1}H NMR.
[d] Homocoupled product observed as a minor byproduct: the ratio of homocoupled product/desired product ~0.04:1 by crude ^{1}H NMR.
[e] Isolated yield.
[f] Determined by analysis of the crude ^{1}H NMR; product not isolated.
[g] Et$_2$O/DMA used as solvent, 15 mol % DPPP.

Table 3. Cyanation of Alkenyl Halides



X = I, Br, Cl
R^1, R^2, R^3 = aryl, alkyl, H

entry	substrate	product	T (°C)	t (h)	yield[a]
1	 **1a**	 **3a**	100	4	79%
2	 **1b**	 **3b**	100	6	83%[b]
3	 **1b'**	 **3b**	100	6	47%
4	 **1c**	 **3c**	140[c]	2	81%
5	 **1c'**	 **3c**	140[c]	7	23%
6	 **1d**	 **3d**	100	6	55%
7	 **1e**	 **3e**	100	4	66%
8	 **1f**	 **3f**	100	2	72%
9	 **1g**	 **3g**	100	3	49%[d]
10	 **1h**	 **3h**	100	4	80%

[a] Isolated yield.
[b] Inseparable 18:1 mixture of *E*/*Z* isomers generated.
[c] A reaction temperature of 100 °C gave yields of 69% and 15% from **1c** and **1c**′, respectively.
[d] Generated as an inseparable 3.5:1 mixture with (*E*)-cinnamaldehyde.

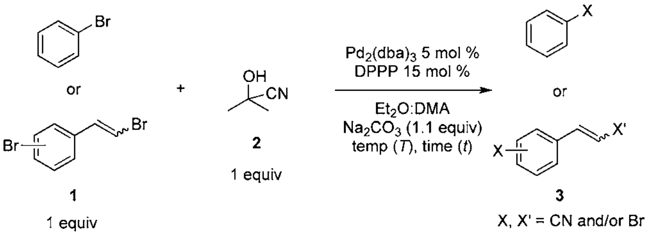
After 6 h of reaction time, the corresponding nitrile product **3a** was isolated in a modest 23% yield (Table 1, entry 1).

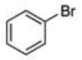
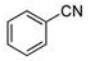
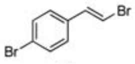
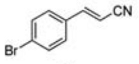
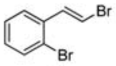
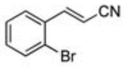
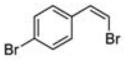
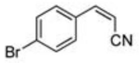
Whereas increasing the reaction time had no effect on the overall yield, stopping the reaction after 10 min resulted in a trace amount of desired product (Table 1, entry 1). Interestingly, no deterioration in the yield was observed when the ACH was added in one portion, yet syringe pump addition of ACH over a 17 h period resulted in only trace product (crude ^{1}H NMR), with most of the bromostyrene starting material remaining unreacted (Table 1, entries 2 and 3). The use of catalytic Bu$_3$SnCl (for *in situ* generation of Bu$_3$SnCN) or a soluble base such as TlOEt led only to a decrease in the reaction yield (Table 1, entries 4 and 5).

Having established that the addition of ACH in one portion was optimal for our system, we next screened a number of catalyst mixtures by systematically changing the palladium source and the ligand and by sampling various metal/ligand ratios. A selection of solvent systems, temperatures, and additives were also investigated.

The reaction temperature was found to be a very important factor. Whereas performing the reaction at room temperature resulted in only a trace amount of product, elevating the temperature to 100 °C significantly increased the yield to 38% (Table 2, entries 1 and 2). The electron-donating bidentate ligand, 1,3-bis(diphenylphosphino)propane (DPPP), emerged as the most efficient, leading to a dramatically improved yield of 70% at 100 °C (Table 2, entry 5). The source of the palladium catalyst had little effect on the overall yield: changing from Pd$_2$(dba)$_3$ to Pd(OAc)$_2$ registered an almost identical yield (70 and 73%, respectively) but required a higher ligand concentration (Table 2, entries 5 and 12). Thus, 5 mol % Pd$_2$(dba)$_3$ was selected as the preferred palladium source of choice (see Supporting Information, Table S1). A survey of reaction media (see Supporting Information, Table S2) established that polar solvents such as dimethylformamide (DMF) or dimethylacetamide (DMA) were essential to maintain higher yields. The combination of Et$_2$O/DMA (2:1) emerged as the solvent of choice (Table S2, entry 11). The use of additives such as zinc, TMEDA, CuI, and TBAB along with these standardized conditions appeared to have only a deleterious effect on yield,[15] as did the substitution of Na$_2$CO$_3$ for alternative bases (see Supporting Information, Table S3).

Table 4. Chemoselective Cyanation of Alkenyl Halides



entry	substrate	product	*T* (°C)	*t* (h)	yield[a]
1	 **1i**	 **3i**	100	6	-[b]
2	 **1j**	 **3j**	100	4	83%
3	 **1k**	 **3k**	100	2	68%
4	 **1l**	 **3l**	100	2	67%[c]

[a] Isolated yield. [b] No reaction. [c] Inseparable mixture of *Z*/*E* isomers generated in a ratio of 11:1 respectively.

With these encouraging results in hand we were interested in the scope and limitations of our new protocol. Table 3 shows a variety of different alkenyl halides tested in the palladium-catalyzed cyanation with ACH.

The inclusion of electron-donating and -withdrawing groups on the aromatic nucleus of the bromostyrene had minimal effect on the reaction yield (Table 3, entries 2 and 4), although a higher reaction temperature was required in the case of those substrates deactivated by the electron-releasing methoxy substituent (Table 3, entries 4 and 5). Alkenyl iodides and chlorides were also found to be suitable substrates (Table 3, entries 3, 5, 7, and 8).

Furthermore, the reaction conditions proved tolerant of a number of sensitive groups including aldehyde, hydroxyl, and imine functional groups (Table 3, entries 8–10). In contrast to the (*E*)-alkenyl bromide **1a**, when the (*Z*)-alkenyl bromide **1d** was subjected to the optimized reaction conditions, it was found to be sluggish, with incomplete consumption of starting alkenyl bromide even after 6 h (Table 3, entries 1 and 6). In certain instances under the optimized reaction conditions, the low yield could be attributed to either incomplete consumption of the starting material or formation of undesired side products (see Supporting Information, Table S4).

Interestingly, bromobenzene failed to react under the standard conditions, with no trace of the aryl nitrile product being detected even after 6 h (Table 4, entry 1). This striking contrast in the reaction outcome for the aryl and alkenyl halides in the palladium-catalyzed cyanation reaction was intriguing. The fact that aryl halides required slow addition of ACH for effective cyanation to proceed,[13] while the alkenyl halides relied upon fast addition of the cyanide ion equivalent, presented an opportunity to exploit the reactivity difference.

Our new palladium-catalyzed protocol provided the ideal setting to investigate a chemoselective cyanation of alkenyl halides in the presence of aryl halides. Remarkably, when the (*E*)-1-bromo-4-(2-bromoalkenyl)benzene (**1j**) was exposed to our optimized reaction conditions, high levels of selectivity (if not specificity)[16] were observed: the corresponding alkenyl nitrile **3j** was isolated in 83% yield with no detectable formation of benzonitrile or *trans*-3-(4-cyanophenyl)acrylonitrile (Table 4, entry 2). Similarly high levels of chemoselectivity were observed when the dibromides **1k** and **1l** were employed; the corresponding alkenylnitriles **3k** and **3l** were isolated exclusively using our cyanation conditions (Table 4, entries 3 and 4, respectively). The level of chemoselectivity/specificity[16] demonstrated is unprecedented in palladium-catalyzed cyanation reactions,[17] thus establishing our method as a powerful and complementary protocol to Beller's aryl cyanation chemistry. The exact mechanistic details of the transformation are currently being investigated.[18,19]

In conclusion, we have demonstrated a straightforward access to alkenyl nitriles *via* a chemoselective palladium-catalyzed reaction of alkenyl halides and acetone cyanohydrin. The reaction demonstrated impressive functional group tolerance (alcohols, aldehydes and imines) and was amenable with sterically hindered substrates. Of particular significance was the observed chemoselective preference for the alkenyl bromide in the presence of aryl bromides.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, and copies of ^{1}H and ^{13}C NMR spectra for new compounds are included. 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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S.; Junge, K.; Beller, M. *Chem. Commun.* **2009**, 4883−4885 and references therein.

(5) For selected examples, see: (a) Maffioli, S. I.; Marzorati, E.; Marazzi, A. *Org. Lett.* **2005**, *7*, 5237−5239. (b) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett.* **2009**, *11*, 2461−2464.

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