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Acetone Cyanohydrin as a Source of HCN in the Cu-Catalyzed Hydrocyanation of α-Aryl Diazoacetates

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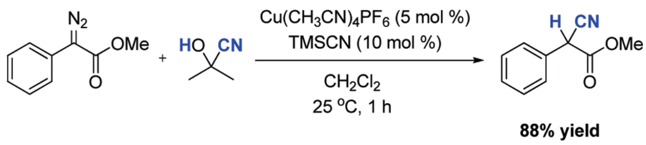
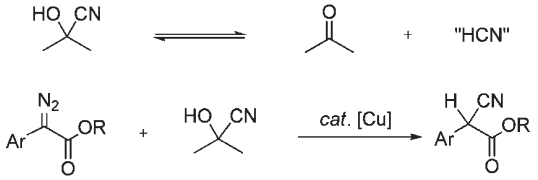


A procedure for the Cu-catalyzed hydrocyanation of α-aryl diazoesters has been developed using acetone cyanohydrin as a source of hydrogen cyanide (HCN). It was found that the addition of trimethylsilyl cyanide (TMSCN) significantly accelerates the conversion presumably by delivering free cyanide ion in situ, thus producing various types of α-aryl cyanoacetates in high yields under mild conditions.

Metal-mediated C−H insertion of α-diazoacetates has been developed as one of the most representative synthetic tools for the formation of C−C bonds by taking advantage of excellent reactivity of the resultant carbenoids.[1] In more recent years, insertion reactions of heteroatomic nucleophiles X-H (X = N, O, S, etc) into α-diazocarbonyls have also been actively investigated using various catalytic systems.[2] On the other hand, hydrocyanation of α-diazocarbonyls has been much less investigated although α-cyanoester products have an important synthetic utility as a bifunctional building unit.[3] Although hydrogen cyanide (HCN) can be regarded as the most straightforward reagent for the hydrocyanation reaction, its toxic and volatile property makes its widespread and practical applications in organic synthesis quite difficult.[4]

SCHEME 1. New Source of Hydrogen Cyanide for the Hydrocyanation of α-Aryl Diazoesters



As a result, there have been investigations of developing surrogates of hydrogen cyanide.[5] Among those candidate compounds, acetone cyanohydrin can be regarded as one of mild, cheap, and environmentally friendly species.[6] In line with our recent interest in the development of new reactions of α-diazocarbonyl compounds,[7] we envisioned development of a hydrocyanation reaction using acetone cyanohydrin as a source of hydrogen cyanide (Scheme 1).

We initiated our study of the hydrocyanation reaction of methyl α-diazo-α-phenylacetate using acetone cyanohydrin under various conditions (Table 1). It was immediately found that while copper(I) chloride catalyzed the reaction only with low efficiency (entry 2), its cationic species notably improved the conversion at room temperature (entry 3). Interestingly, whereas the addition of KCN to the CuCl catalyst system completely inhibited the reaction (entry 4), a much increased product yield was obtained upon addition of the same additive (KCN) to the cationic copper system (entry 5).[8]

The main reason for the additive effects of KCN was postulated to generate free cyanide ion (CN^-) from the combined copper cocatalyst system, in which in situ generated cyanide accelerates the hydrocyanation reaction.[9] This reasoning led us to further investigate the optimization processes. Indeed, whereas the additional coadditive of a crown ether to the above system of entry 5 resulted in almost

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(1) For reviews on the C−H insertion of carbenoids, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270. (d) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109. (e) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.

(2) For recent reports on the enantioselective X-H (X = N, O, S, etc) insertion into α-diazocarbonyl compounds, see: (a) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594. (b) Ge, M.; Corey, E. J. *Tetrahedron Lett.* **2006**, *47*, 2319. (c) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066. (d) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 932. (e) Zhang, Y.-Z.; Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Zhou, Q.-L. *Chem. Commun.* **2009**, 5362.

(3) (a) Hocková, D.; Holý, A.; Masojídková, M.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2003**, *46*, 5064. (b) Kozlowski, M. C.; DiVirgilio, E. S.; Malolanarasimhan, K.; Mulrooney, C. A. *Tetrahedron: Asymmetry* **2005**, *16*, 3599. (c) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

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(6) (a) Mori, A.; Inoue, S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 983−994. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (c) Ming, Y.; Xu, Q.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 845. (d) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.

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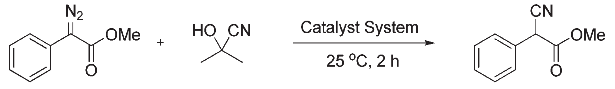
TABLE 1. Optimization of the Hydrocyanation Reaction[a]



1a

entry	catalyst system	solvent	yield[b] (%)
1	none	CH_2Cl_2	< 1
2	CuCl	CH_2Cl_2	15
3	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	47
4	CuCl/KCN	CH_2Cl_2	< 1
5	$Cu(CH_3CN)_4PF_6$/KCN	CH_2Cl_2	68
6[c]	$Cu(CH_3CN)_4PF_6$/KCN/18-C-6	CH_2Cl_2	4
7	$Cu(CH_3CN)_4PF_6$/TMSCN	CH_2Cl_2	88 (87)[d]
8	$Cu(CH_3CN)_4BF_4$/TMSCN	CH_2Cl_2	65
9	$Cu(CH_3CN)_4PF_6$/TMSCN	CH_3CN	5
10	$Rh_2(OAc)_4$	CH_2Cl_2	3
11	$Rh_2(OAc)_4$/TMSCN	CH_2Cl_2	3

[a] Methyl α-diazo-α-phenylacetate (0.5 mmol), acetone cyanohydrin (1.5 mmol), catalyst (5 mol %), and additive (10 mol %) in solvent (5.0 mL) at 25 °C for 2 h. [b] NMR yield of **1a** using 1,2-methylenedioxybenzene as an internal standard. [c] Each additive was employed by 10 mol %. [d] Number in parentheses is the isolated yield.

complete inhibition (entry 6), substitution of KCN with a more soluble organic cyanide species, trimethylsilyl cyanide (TMSCN), provided the product in excellent yield (entry 7).

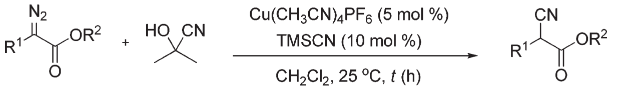
Interestingly, it turned out that the counteranions of the ionic copper catalysts also played a role on the reaction efficiency. For instance, the change of counteranion from PF_6^- to BF_4^- resulted in reduced product yield (entry 8).

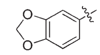
After screening various reaction media, dichloromethane was selected as the solvent of choice. On the other hand, rhodium catalyst systems which are known to be highly effective for the X-H insertion into α-diazocarbonyls[10] displayed very poor efficiency in this hydrocyanation reaction using acetone cyanohydrin. In fact, almost no product was obtained when $Rh_2(OAc)_4$ catalyst was employed regardless of the presence of TMSCN coadditive (entries 10 and 11).

With the optimized reaction conditions, we explored the substrate scope of various α-aryl diazoesters for the hydrocyanation with the use of acetone cyanohydrin (3 equiv) as a hydrogen cyanide source (Table 2). In general, the reaction proceeded smoothly and was not much effected by the steric and/or electronic variation on the aryl substituents. Alternation of alkoxy moiety in the α-diazoesters did not much affect the reaction efficiency. In fact, the hydrocyanation of methyl, *tert*-butyl, or benzyl esters of α-diazophenylacetic acid gave the corresponding α-cyanophenylacetates in high yields (entries 1, 2, and 3, respectively).

Next, the reaction efficiency was examined upon the variation of the aryl moiety of diazo substrates. The presence of various substituents at the *para* position of methyl α-diazo-α-phenylacetates displayed little effect on the product yields (entries 4−6). In addition, halo substituents on the phenyl moiety were completely tolerated under the present reaction conditions. However, a trifluoromethyl group decreased the reaction rate, and satisfactory product yield could be obtained only after prolonged reaction time with higher loading of the copper catalyst (entry 8).

TABLE 2. Cu-Catalyzed Hydrocyanation of α-Aryl Diazoacetates[a]



Entry	R^1	R^2	*t* (h)	Product	Yield (%)
1	Ph	Me	1	**1a**	88
2	Ph	$C(CH_3)_3$	1	**1b**	77
3	Ph	CH_2Ph	2	**1c**	77
4	$(4\text{-Me})C_6H_4$	Me	1	**1d**	71
5	$(4\text{-F})C_6H_4$	Me	2	**1e**	73
6	$(4\text{-Cl})C_6H_4$	Me	3	**1f**	75
7	$(4\text{-Br})C_6H_4$	Me	2	**1g**	64
8[b,c]	$(4\text{-CF}_3)C_6H_4$	Me	20	**1h**	52
9		Me	1	**1i**	50
10	$(3\text{-MeO})C_6H_4$	Me	3	**1j**	84
11[b]	$(3\text{-Me})C_6H_4$	Me	1	**1k**	82
12[b]	$(3\text{-Cl})C_6H_4$	Me	12	**1l**	73
13[b]	$(3\text{-Br})C_6H_4$	Me	12	**1m**	67
14	$(3,4\text{-Cl})C_6H_3$	Me	24	**1n**	69
15	$(2\text{-Me})C_6H_4$	Me	2	**1o**	79
16	$(2\text{-Cl})C_6H_4$	Me	1	**1p**	81
17	$(2\text{-Br})C_6H_4$	Me	2	**1q**	78
18	1-Naphthyl	Me	2	**1r**	54
19	2-Naphthyl	Me	1	**1s**	93
20	Methyl	CH_2Ph	24	**1t**	< 1

[a] α-Aryl diazoacetate (0.5 mmol), acetone cyanohydrin (1.5 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol %), and TMSCN (10 mol %) in CH_2Cl_2 (5.0 mL) at 25 °C for the indicated time. [b] 2.5 mmol of acetone cyanohydrin was used. [c] 10 mol % of $Cu(CH_3CN)_4PF_6$ was used.

Hydrocyanation reaction of methyl α-diazo-α-phenylacetates bearing *meta* substituents proceeded smoothly to afford the desired products in respectable yields (entries 10−14). Quite interestingly, the reaction efficiency was not significantly influenced by the steric bulkiness of the phenyl substituents as evidenced in entries 15−17. Not only simple phenyl but also condensed α-aryl diazoacetates were facile substrates for the hydrocyanation (entries 18 and 19). However, α-diazo-α-alkyl esters did not undergo the hydrocyanation under the developed conditions (entry 20).

In order to test a possibility of the diastereoselective hydrocyanation reaction, optically active α-aryl diazoacetates were prepared in high yield by a conventional two-step procedure starting from phenylacetic acid: esterification of

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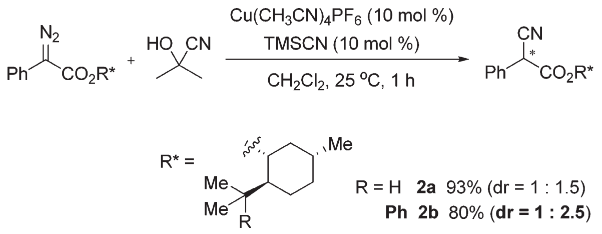
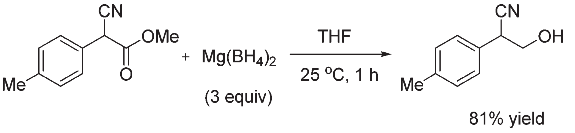
(10) For recent reports of the rhodium-catalyzed carbenoid formation, see: (a) Huang, H.; Wang, Y.; Chen, Z.; Hu, W. *Adv. Synth. Catal.* **2005**, *347*, 531. (b) Wong, F. M.; Wang, J.; Hengge, A. C.; Wu, W. *Org. Lett.* **2007**, *9*, 1663. (c) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555.

SCHEME 2. Diastereoselective Hydrocyanation



the acid with chiral alcohols followed by a diazo transfer with *p*-(acetamido)benzenesulfonyl azide.[11] When (−)-menthyl α-diazo-α-phenylacetate was allowed to react with acetone cyanohydrin under the Cu-catalytic conditions, only a low level of diastereoselectivity (60:40) was observed (Scheme 2). A more promising result was obtained by the introduction of a phenyl group at the menthyl auxiliary, thus providing improved diastereoselectivity up to 73:27. Importantly, optically pure (−)-menthyl α-cyanophenylacetate could be isolated in 48% yield after a simple recrystallization of the crude reaction mixture.[12]



(1)

The obtained products in this study, α-aryl cyanoesters, are a key precursor of *β*-cyano alcohols which can be regarded as an important building motif in organic synthesis.[13] α-Aryl cyanoesters could be readily reduced to the corresponding aryl-substituted hydroxylpropane nitrile in high yield upon treatment with magnesium borohydride under mild conditions (eq 1).[14]

Although detailed mechanistic studies are required to describe the exact catalytic pathway, some preliminary observations give mechanistic clues. For example, the fact that the addition of TMSCN accelerates the hydrocyanation most significantly in the case of using $Cu(CH_3CN)_4PF_6$ catalyst and that the type of counteranion species of the copper catalysts influences the reaction efficiency indicates that a reaction of TMSCN with hexafluorophosphate counteranion generates a free cyanide ion that can be involved in the catalytic cycle.[15,16] It can next be suggested that the initially formed copper carbenoid from the reaction of α-diazoester with copper species reacts with the in situ generated cyanide anion to afford an alkylcyano copper intermediate, and then a hydrogen transfer takes place from acetone cyanohydrin into the copper intermediate upon the regeneration of Cu(I) and cyanide species for the next catalytic cycle.[9]

In summary, we have developed a mild and efficient protocol of hydrocyanation of α-aryl diazoesters with the use of acetone cyanohydrin as a hydrogen cyanide surrogate under the copper catalyst system. The addition of TMSCN as a cocatalyst significantly improves the reaction efficiency, thus allowing a broad range of substrates to react leading to α-aryl cyanoacetates in satisfactory yields under mild conditions.

Experimental Section

Representative Procedure for the Cu-Catalyzed Hydrocyanation of α-Aryl Diazoacetates. To a Schlenk tube was added $Cu(CH_3CN)_4PF_6$ (9.3 mg, 0.025 mmol) followed by CH_2Cl_2 (5.0 mL) and TMSCN (6.3 μL, 0.05 mmol) under nitrogen atmosphere. After the reaction mixture was stirred for 5 min at room temperature, acetone cyanohydrin (137 μL, 1.5 mmol) and then methyl α-diazo-α-phenylacetate (88 mg, 0.5 mmol) were then added dropwise. The resulting mixture was stirred for 1 h at room temperature and filtered through a pad of Celite. After an organic solvent was removed under reduced pressure, flash column chromatography on silica gel (hexane/ethyl acetate, 7:1) afforded methyl (2-cyano-2-phenyl)acetate (**1a**, 77 mg, 88%): R_f 0.20 (hexane/ethyl acetate, 7:1); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.38 (m, 5H), 4.73 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 129.8, 129.3, 129.2, 127.9, 115.5, 53.9, 43.4; IR (NaCl) ν 3035, 2957, 2848, 2252, 1751, 1436, 1311, 1237, 1210, 1079 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9NO_2$ $[M]^+$ 175.0633, found 175.0635.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] See the Supporting Information for the detailed experimental procedures.

[12] Taber, D. F.; Berry, J. F.; Martin, T. J. *J. Org. Chem.* **2008**, *73*, 9334.

[13] (a) Shia, K.-S.; Jan, N.-W.; Zhu, J.-L.; Ly, T. W.; Liu, H.-J. *Tetrahedron Lett.* **1999**, *40*, 6753. (b) García Ruano, J. L.; Cifuentes García, M.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Org. Lett.* **2002**, *4*, 55. (c) Im, D. S.; Cheong, C. S.; Lee, S. H. *J. Mol. Catal. B: Enz.* **2003**, *26*, 131.

[14] For an example of a selective reduction using $Ca(BH_4)_2$, see: Narasimhan, S.; Ganeshwar Prasad, K.; Madhavan, S. *Synth. Commun.* **1995**, *25*, 1689.

[15] (a) Ong, C. W.; Chien, C. J. *Organometallics* **1993**, *12*, 241. (b) Faragalla, J.; Heaton, A.; Griffith, R.; Bremner, J. B. *Synlett* **2009**, 306.

[16] One reviewer suggested an alternative mechanistic pathway where TMSCN would be in equilibrium with TMSNC and this isocyanide can accelerate the reaction rate, acting as a similar way to cyanide ion.