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Two-Step Cyanomethylation Protocol: Convenient Access to Functionalized Aryl- and Heteroarylacetonitriles

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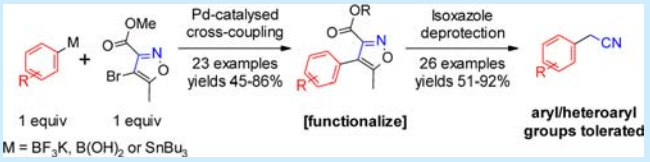
Supporting Information

ABSTRACT: A two-step protocol has been developed for the introduction of cyanomethylene groups to metalated aromatics through the intermediacy of substituted isoxazoles. A palladium-mediated cross-coupling reaction was used to introduce the isoxazole unit, followed by release of the cyanomethylene function under thermal or microwave-assisted conditions. The intermediate isoxazoles were shown to be amenable to further functionalization prior to deprotection of the sensitive cyanomethylene motif, allowing access to a wide range of aryl- and heteroaryl-substituted acetonitrile building blocks.



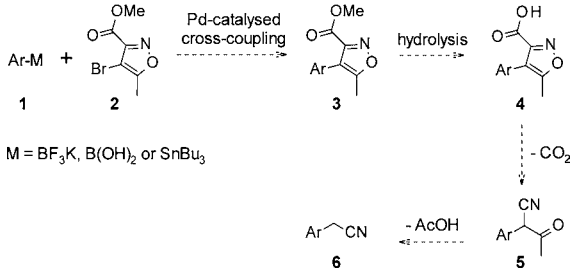
Arylacetonitriles serve as versatile intermediates in organic synthesis due to their ability to undergo a broad range of functional group transformations. The methylene protons are reactive toward electrophiles by virtue of their acidity,[1] while the cyano group can be readily transformed into various other functionalities, including amides, amines, ketones, and acids.[2] The arylacetonitrile motif itself can also be used as a building block in the construction of heterocycles.[3] In addition to their popularity as synthetic intermediates, substituted arylacetonitriles have appeared in several pharmaceutically active molecules recently.[4]

Classically, the α-aryl nitrile motif has been installed by (i) nucleophilic substitution reactions involving cyanide and benzyl halides,[5] (ii) photolytic reactions,[6] (iii) dehydrations,[7] and (iv) nucleophilic aromatic substitution reactions followed by decarboxylation.[8] More recently, several methods have emerged that employ the coupling of functionalized acetonitriles with aryl halides under the action of palladium catalysis. Since Migita and co-workers demonstrated the coupling of cyanomethyltributyltin with aryl bromides in 1984,[9] this methodology has been extended to include the coupling of aryl metal reagents with bromoacetonitrile,[10] the coupling of trimethylsilylacetonitrile with aryl bromides in the presence of ZnF_2,[11] and the decarboxylative coupling of cyanoacetate salts with aryl halides and triflates.[12] These methods have the potential to suffer from overarylation, where the initially formed arylacetonitriles might undergo further arylation. However, judicious choice of reaction conditions enabled the selective formation of monoarylated products, including a single heterocyclic example (3-thiopheneacetonitrile).[12] A deaminative metal-free approach was also recently reported.[13]

In 2011, a conceptually different approach was realized by the group of Velcicky and Schmalz,[14] where they showed that isoxazole 4-boronic acid pinacol ester could undergo efficient cross-coupling with aryl halides to furnish arylacetonitriles directly. Because of the acidic nature of the 3- and 5-positions of 4-substituted isoxazoles, their cross-couplings are often complicated by side reactions and decomposition pathways, but Velcicky and Schmalz successfully harnessed this feature to access a range of α-aryl nitriles, including a single heterocyclic example (2-pyridylacetonitrile).

We were intrigued by the possibility of introducing acetonitrile units into aromatic molecules through the intermediacy of 3,5-disubstituted isoxazoles. This additional substitution might allow us to more readily intercept the cross-coupled intermediates bearing an intact isoxazole group **3**, which could then undergo further functionalization, prior to isoxazole deprotection. We postulated that functionalized aryl reagents **1** could be coupled to bromoisoxazole **2**,[15] bearing an ester group in the 3-position, and then deprotected in a separate step via intermediates **4** and **5** to reveal the target arylacetontriles **6** (Scheme 1). The ester function would serve to both (i) protect the molecule toward mildly basic conditions (typically employed in cross-coupling reactions) and (ii) trigger a hydrolysis/decarboxylation cascade sequence under more forcing conditions.[16] We anticipated that loss of carbon dioxide would result in spontaneous N−O bond cleavage, leading to arylcyanoacetates **5** after tautomerization. Loss of acetic acid would then deliver the α-aryl nitriles **6**.

Scheme 1. Proposed Route to Arylacetonitriles 6



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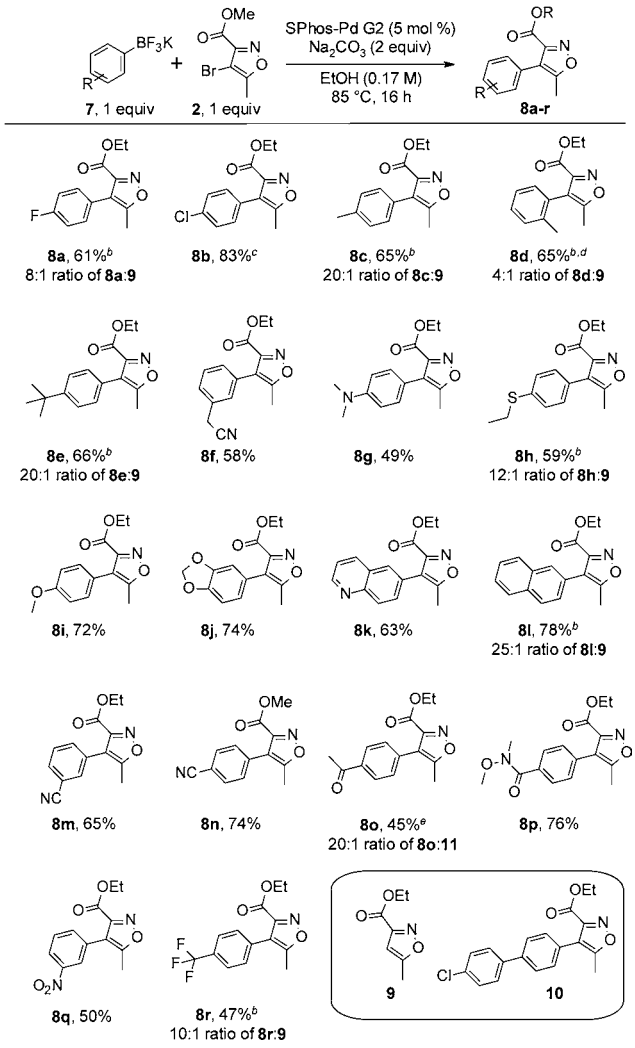
To test this hypothesis, bromoisoxazole **2** was coupled with a range of substituted aryl boron and tin compounds **1**. We were pleased to find that this cross-coupling could be readily accomplished under palladium-catalyzed conditions with a range of commercially available potassium aryltrifluoroborate salts **7** in yields of 45−78% (with concomitant transesterification)[17] using conditions similar to those developed by Molander and co-workers for the coupling of 3,5-dimethylsubstituted isoxazoles (Scheme 2).[18,19]

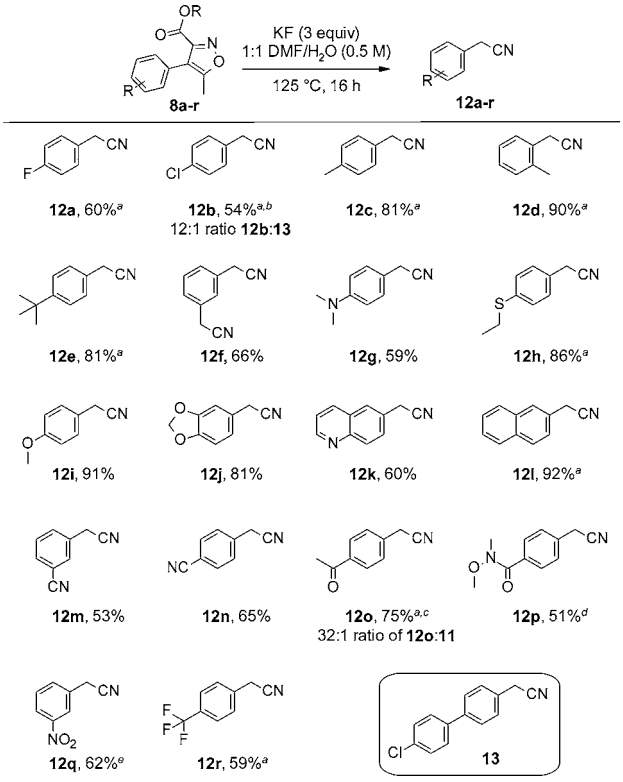
Scheme 2. Cross-Coupling of Potassium Aryltrifluoroborates 7 with Isoxazole Bromide 2[a]



[a]Reactions performed in sealed vials. [b]Material contained compound **9** as an impurity after flash column chromatography. [c]Material contained compound **10** as an impurity after flash column chromatography. [d]XPhos-Pd G2 (5 mol %) utilized in place of SPhos-Pd G2. [e]Material contained 4,4′-diacetylbiphenyl **11** as an impurity after flash column chromatography (see the Supporting Information).

While both fluoro- (**8a**, 61% yield) and chloro-substitution (**8b**, 83% yield) were tolerated in the 4-position, the corresponding coupling with potassium 4-bromophenyltrifluoroborate did not yield any of the desired product under the reaction conditions. In fact, the chloro product **8b** underwent further cross-coupling to a small extent with the starting trifluoroborate salt under the reaction conditions to give biphenyl **10** (at this stage the ratio of products could not be quantified accurately, but a 12:1 ratio of **12b**:**13** was observed after deprotection of the isoxazole; see Scheme 3 below).

Scheme 3. Deprotection of Cross-Coupled Isoxazoles 8 To Give Arylacetonitriles 12



[a]Starting material contained compound **9** as an impurity. [b]Material contained compound **13** as an impurity after flash column chromatography. [c]Material contained 4,4′-diacetylbiphenyl **11** as an impurity after flash column chromatography. [d]Reaction performed in NMP/H_2O (0.5 M) at 175 °C for 20 min under microwave irradiation. [e]Reaction performed in NMP/H_2O (0.5 M) at 200 °C for 20 min under microwave irradiation (see the Supporting Information).

A range of other functional groups were also found to be tolerated under the reaction conditions (see **8c−r**). It was necessary to utilize a boronic acid to synthesize 4-cyano-substituted compound **8n** (74% yield), as the corresponding potassium 4-cyanophenyltrifluoroborate salt failed to generate the desired product under the standard reaction conditions.

With a broad range of cross-coupled compounds **8** bearing the substituted isoxazole unit in hand, we set out to investigate the deprotection step to reveal the target arylacetonitriles **12** (Scheme 3). A range of bases and solvents were screened to accomplish this transformation, and gratifyingly, we found that the desired compounds could be formed by heating the cross-coupled intermediates in a mixture of DMF and water in the presence of potassium fluoride.[14] Cross-coupled compounds that were carried into this isoxazole deprotection step containing minor amounts of debrominated material **9** (see Scheme 2) gave clean arylacetonitriles after purification by flash column chromatography, presumably because **9** decomposed to volatile components under the reaction conditions.[17]

Interestingly, the Weinreb amide **8p** and 3-nitro substrate **8q** did not give good conversion to the intended products **12p** and **12q** under the standard deprotection conditions. Further

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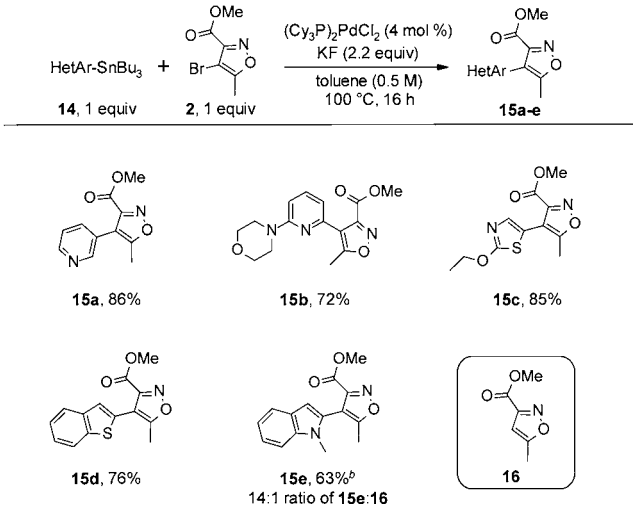
investigation of these problematic substrates revealed that microwave-assisted reaction conditions at higher temperatures were required to facilitate the smooth deprotection of **8p** to **12p** in 51% yield and of **8q** to **12q** in 62% yield.

Having shown that both potassium aryltrifluoroborates and arylboronic acids were competent coupling partners for isoxazole bromide **2**, we turned our attention to the cross-coupling of heteroaryl compounds (Scheme 4). Although we were unable to effect the cross-coupling of potassium heteroaryltrifluoroborates or heteroarylboronic acids efficiently with isoxazole bromide **2**, we were able to successfully carry out the analogous cross-couplings with stannanes under the action of palladium catalysis using conditions inspired by those of Fu and co-workers.[20] Thus, pyridines **15a** and **15b**, thiazole **15c**, benzothiophene **15d**, and indole **15e** were formed in yields of 63−86% from the corresponding stannane reagents.

Scheme 4. Cross-Coupling of Heteroarylstannanes 14 with Isoxazole Bromide 2[a]



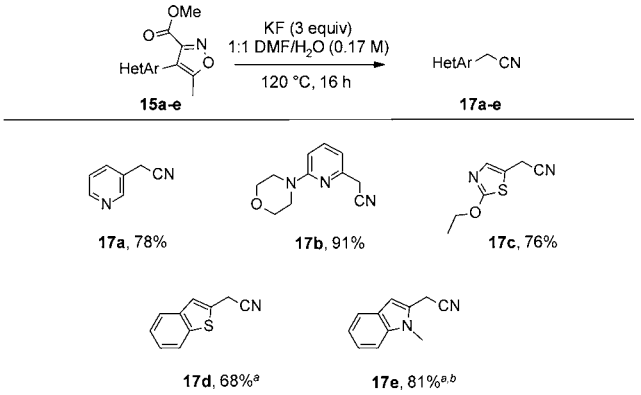
[a]Reactions performed in sealed vials. [b]Material contained compound **16** as an impurity after flash column chromatography (see the Supporting Information).

Next, we investigated the conversion of these heteroaryl cross-coupled compounds **15a−e** to the corresponding heteroarylacetonitriles **17a−e** under similar reaction conditions as before (Scheme 5). We observed that acetontriles **17a**, **17b**, and **17c** formed in good yields under thermal conditions, while the benzothiophene **17d** and indole **17e** required microwave-assisted reaction conditions at higher temperatures to generate the requisite products in 68% and 81% yields, respectively.

Having explored the scope and limitations of this two-step cyanomethylation protocol, we examined the possibility of functionalizing the intermediate cross-coupled isoxazole **8f** prior to the deprotection step. We hoped to differentiate two cyanomethylene groups in the same molecule by utilizing the *protected* nature of the substituted isoxazole unit, which would allow functionalization of the remaining *unprotected* group. To this end, cross-coupled isoxazole **8f** was converted to the ester **18** in 91% yield (Scheme 6). Subjection of ester **18** to our standard thermal deprotection conditions furnished the corresponding α-aryl nitrile **19** in 74% yield (with concomitant hydrolysis of the ester function to the acid).[21]

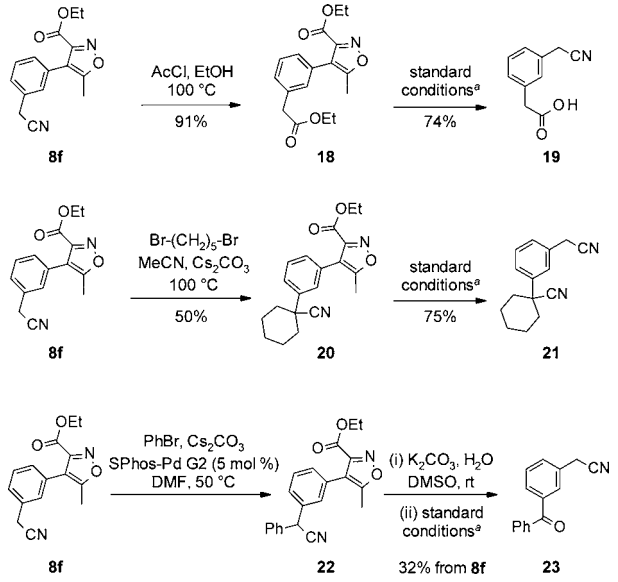
Next, we attempted further differentiation through the alkylation and arylation of cross-coupled isoxazole **8f**. Thus,

Scheme 5. Deprotection of Cross-Coupled Isoxazoles 15 To Give Heteroarylacetonitriles 17



[a]Reaction performed in NMP/H_2O (0.5 M) at 200 °C for 20 min under microwave irradiation. [b]Starting material contained compound **16** as an impurity (see the Supporting Information).

Scheme 6. Functionalization of Cross-Coupled Isoxazole 8f



[a]Standard conditions: KF (3 equiv), 1:1 DMF/H_2O (0.5 M), 125 °C, 16 h.

alkylation of **8f** with 1,5-dibromopentane led to functionalized product **20** in 50% yield, which was deprotected to give arylacetonitrile **21** (75% yield). Likewise, α-arylation of **8f** led to the formation of diphenylacetonitrile **22**, which was observed to be prone to oxidation to the corresponding benzophenone.[22] With this in mind, the diphenylacetonitrile **22** was oxidized under basic conditions and subsequently subjected to the standard deprotection protocol to generate α-aryl nitrile **23** in 32% yield over three steps from **8f**. In contrast, the alkylation and α-arylation of 1,3-phenylenediacetonitrile under reaction conditions similar to those shown in Scheme 6 led to mixtures of compounds that were challenging to purify.

Finally, we examined whether our two-step cyanomethylation protocol could be carried out in a one-pot manner (Scheme 7). Thus, reaction of trifluoroborate salt **24** and bromide **2** was followed by the addition of potassium fluoride, DMF, and water and further heating to give arylacetonitrile **12l** in 63% overall yield.

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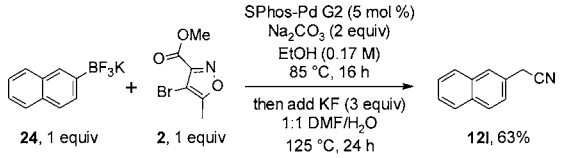
Scheme 7. One-Pot Formation of Arylacetonitrile 12l[a]



[a]Reactions performed in sealed vials.

In summary, we have developed a two-step cyanomethylation protocol whereby bromoisoxazole **2** was shown to couple effectively with potassium aryltrifluoroborate salts to give aryl isoxazoles that were deprotected to give the target α-aryl nitriles. Notably, five heteroarylacetonitriles were also accessed via their corresponding heteroarylstannanes, offering considerable advantage over existing cyanomethylation methodologies. The cross-coupled isoxazole intermediates were also shown to be amenable to functionalization prior to deprotection, allowing facile access to challenging molecular scaffolds bearing two differently substituted cyanomethylene units.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization. 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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■ REFERENCES

(1) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321.
(2) (a) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1. (b) Trivedi, B. K.; Holmes, A.; Stoeber, T. L.; Blankey, C. J.; Roark, W. H.; Picard, J. A.; Shaw, M. K.; Essenburg, A. D.; Stanfield, R. L.; Krause, B. R. *J. Med. Chem.* **1993**, *36*, 3300. (c) Xi, F.; Kamal, F.; Schenerman, M. A. *Tetrahedron Lett.* **2002**, *43*, 1395. (d) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.
(3) Friedrich, K.; Wallenfels, K. *The Chemistry of the Cyano Group*; Wiley-Interscience: New York, 1970.
(4) (a) Milani, M.; Jha, G.; Potter, D. A. *Clin. Med. Ther.* **2009**, *1*, 141. (b) Cooper-DeHoff, R. M.; Handberg, E. M.; Mancia, G.; Zhou, Q.; Champion, A.; Legler, U. F.; Pepine, C. J. *Expert Rev. Cardiovasc. Ther.* **2009**, *7*, 1329. (c) Brogden, R. N.; Benfield, P. *Drugs* **1994**, *47*, 93. (d) For a review of nitrile groups in pharmaceuticals, see: Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
(5) (a) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; Deshong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171. (b) Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573.
(6) (a) Yoshida, H.; Fujimura, Y.; Yuzawa, H.; Kumagaia, J.; Yoshidab, T. *Chem. Commun.* **2013**, *49*, 3793. (b) Kurz, M. E.; Lapin, S. C.; Mariam, A.; Hagen, T. J.; Qian, X. Q. *J. Org. Chem.* **1984**, *49*, 2728.
(7) Narsaiah, A. V.; Nagaiah, K. *Adv. Synth. Catal.* **2004**, *346*, 1271.
(8) Stazi, F.; Maton, W.; Castoldi, D.; Westerduin, P.; Curcuruto, O.; Bacchi, S. *Synthesis* **2010**, 3332.
(9) Kosugi, M.; Ishiguro, M.; Negishi, Y.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1511.
(10) (a) Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40. (b) Yang, Y.; Tang, S.; Liu, C.; Zhang, H.; Suna, Z.; Lei, A. *Org. Biomol. Chem.* **2011**, *9*, 5343.
(11) (a) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.
(12) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470. For a related intramolecular decarboxylative α-allylation reaction of nitriles, see: Recio, A., III; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5630.
(13) Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 10510.
(14) Velcicky, J.; Soicke, A.; Steiner, R.; Schmalz, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 6948.
(15) For the preparation of methyl 4-bromo-5-methylisoxazole-3-carboxylate (**2**), see: Imanshi, Y.; Awai, N.; Hirai, M.; Hosaka, T.; Kono, R. Patent Appl. 037271, 2005.
(16) For examples of the decarboxylative opening of isoxazoles, see: (a) Zhoua, P.; Natalea, N. R. *Synth. Commun.* **1998**, *28*, 3317. (b) Perez, C.; Janin, Y. L.; Grierson, D. S. *Tetrahedron* **1996**, *52*, 987. (c) Ciller, J. A.; Seoane, C.; Soto, J. L. *Heterocycles* **1984**, *22*, 1989.
(17) In some cases, compound **9** was observed in the crude reaction mixtures and it was not always possible to separate this from the products. The amount of **9** was quantified by analysis of the ^{1}H NMR spectra, and the mixture of compounds was taken through into the isoxazole deprotection step.
(18) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973.
(19) SPhos-Pd G2 = chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) and XPhos-Pd G2 = chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II).
(20) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.
(21) The enzymatic hydrolysis of 1,3-phenylenediacetonitrile has previously been reported: Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.* **1990**, *31*, 7223.
(22) For the oxidative decyanation of diphenylacetonitriles, see: Kulp, S. S.; McGee, M. J. *J. Org. Chem.* **1983**, *48*, 4097.

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