

A Powerful Palladium-Catalyzed Multicomponent Process for the Preparation of Oxazolines and Benzoxazoles

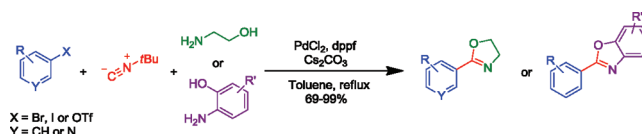
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ABSTRACT



Efficient and convenient three-component couplings of an aryl halide, isocyanide, and an amino alcohol under palladium catalysis provide a range of oxazolines and benzoxazoles in excellent yield.

The search for novel methods for the preparation of new and interesting molecules with a greater degree of efficiency is of utmost importance in the continuous development of synthetic chemistry. As the molecular targets increase in complexity the effectiveness of the methods required to construct these molecules also has to increase, often with multiple bond-making and/or bond-breaking processes taking place in one transformation. Multicomponent reactions¹ allow for the introduction of atoms originating from three or more different starting materials into a final molecule and have long been seen as a way of incorporating a large degree of diversity into molecular scaffolds in a single synthetic step.

The benefit of carrying out multicomponent reactions over conventional multistep sequences includes savings in the costs of reagents and solvents, along with other materials required for purification and isolation. An additional advantage is the removal of the need to isolate, often unstable, intermediates making these one-pot processes far more powerful than their multistep equivalents.

The use of transition metal complexes as catalysts in multicomponent processes adds an extra dimension to these reactions. Due to the wide range of transformations

(1) For some selected examples: (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–416. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126–129. (c) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181–189. (d) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 373–388. (e) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 9–22. (f) Sunderhaus, D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. (g) Shaabani, A.; Maleki, A.; Maghimi-Rad, J. *J. Org. Chem.* **2007**, *72*, 6309–6311. (h) Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Synthesis* **2008**, 1688–1702. (i) Sakhno, Y. I.; Desenko, S. M.; Shishkina, S. V.; Shishkin, O. V.; Sysoyev, D. O.; Groth, U.; Kappe, C. O.; Chebanov, V. A. *Tetrahedron* **2008**, *64*, 11041–11049. (j) Scheffekaar, R.; Paravidino, M.; Muilwijk, D.; Lutz, M.; Spek, A. L.; de Kanter, F. J. J.; Orru, R. V. A.; Ruijter, E. *Org. Lett.* **2009**, *11*, 125–128. (k) Brioché, J.; Masson, G.; Zhu, J. *Org. Lett.* **2010**, *12*, 1432–1435.

(2) For some relevant reviews: (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111. (b) Balme, G.; Bouyssi, D.; Monteiro, N. *Pure Appl. Chem.* **2006**, 231–239. (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (d) Bouyssi, D.; Monteiro, N.; Balme, G. *Beilstein J. Org. Chem.* **2011**, *7*, 1387–1406.

(3) For some recent examples: (a) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585–1587. (b) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813. (c) Stonehouse, J. P.; Chekmarev, D. S.; Ivanova, N. V.; Lang, S.; Paireau, G.; Smith, N.; Stocks, M. J.; Sviridov, S. I.; Utkina, L. M. *Synlett* **2008**, 100–104. (d) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903–1906. (e) Saito, N.; Katayama, T.; Sata, Y. *Org. Lett.* **2008**, *10*, 3829–3832. (f) Mannathan, S.; Jegannathan, M.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192–2195. (g) Staben, S. T.; Blaquié, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325–328. (h) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 2410–2413. (i) Yoshida, Y.; Murakami, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 8878–8879. (j) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590–13591. (k) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784–5787.

that these species mediate, this strategy has attracted considerable interest.^{2,3}

Scheme 1. Proposed Catalytic Cycle

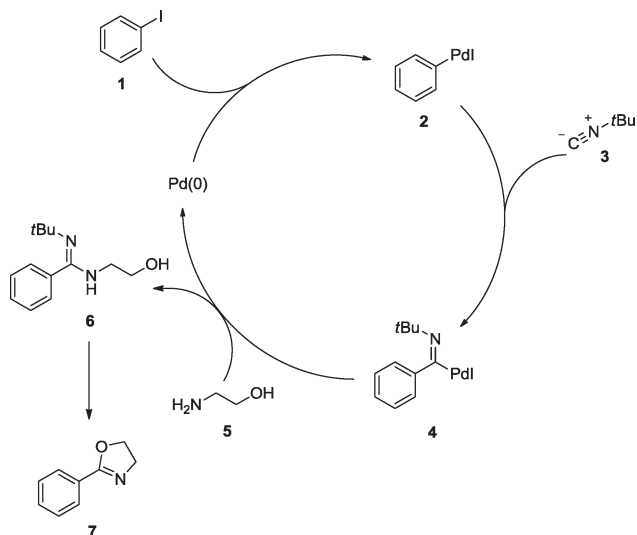


Table 1. Formation of Oxazoline **7**^a

$\text{Ar-I} + \text{tBu-N=C} + \text{H}_2\text{N-CH}_2\text{-CH}_2\text{-OH} \xrightarrow[\text{Toluene, reflux}]{\text{PdCl}_2, \text{dppf}, \text{Cs}_2\text{CO}_3} \text{Ar-Oxazoline}$			
Entry	Equiv of Aminoethanol 5	Reaction Time	Yield
1	2	2 h	56%
2	2	6 h	68%
3	2	18 h	71%
4	3	2 h	68%
5	5	2 h	80%

^a Conditions: *tert*-Butyl isocyanide (1.5 equiv), ethanolamine (see table), Cs₂CO₃ (2 equiv), PdCl₂ (5 mol %), dppf (5 mol %), toluene, reflux.

Isocyanides can be considered as isoelectronic⁴ with carbon monoxide and therefore can be used as an alternative to carbon monoxide in palladium-catalyzed carbonylations, as exploited in the report from Whitby et al.⁵ of amidines being prepared *via* a one-pot coupling of an aryl halide, isocyanide, and an amine.

(4) (a) Kosugi, M.; Ogata, T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, 1197–1200. (b) Ishiyama, T.; Oh-e, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1992**, 33, 4465–4468. (c) Saluste, C. G.; Whitby, R. J.; Furber, M. *Tetrahedron Lett.* **2001**, 42, 6191–6194. (d) Saluste, C. G.; Whitby, R. J.; Furber, M. *Org. Biomol. Chem.* **2004**, 2, 1974–1976. (e) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, 13, 1028–1031. (f) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, 13, 4604–4607.

(5) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, 39, 4156–4158.

Table 2. Preparation of Oxazolines^a

$\text{Ar-X} + \text{tBu-N=C} + \text{H}_2\text{N-CH}_2\text{-CH}_2\text{-OH} \xrightarrow[\text{Toluene, reflux, 2 h}]{\text{PdCl}_2, \text{dppf}, \text{Cs}_2\text{CO}_3} \text{Ar-Oxazoline}$			
Entry	Starting Halide	Desired Product	Yield
1	1	7	80%
2	8	7	77%
3	9	7	0%
4	10	11	72%
5	12	13	69%
6	14	13	71%
7	15	17	81%
8	16	18	88%
9	19	20	71% ^b
10	21	22	93%

^a Conditions: Aryl halide (1 equiv), *tert*-Butyl isocyanide (**3**) (1.5 equiv), ethanolamine (**5**) (5 equiv), Cs₂CO₃ (2 equiv), PdCl₂ (5 mol %), dppf (5 mol %), toluene, reflux. ^b Reaction time of 18 h required.

Taking advantage of this elegant use of an isocyanide reagent and exploiting the amidine intermediate formed in the reaction, the addition of an extra cyclization step would allow for the facile construction of a range of heterocyclic compounds *via* a novel palladium-catalyzed multicomponent cascade sequence.

Our strategy involves, rather than using a simple amine, employing an amine with a suitable second nucleophilic group such as an alcohol attached. This means that the amidine intermediate **6** can be intercepted by the nucleophilic oxygen atom resulting in an oxazoline.

The proposed transformation would involve oxidative addition of aryl halide **1** to Pd(0) giving Pd(II) species **2**. This can then undergo an insertion process with *tert*-butylisocyanide **3** to give compound **4**. The use of aminoethanol **5** allows for formation of amidine intermediate **6** and regenerates the Pd(0) catalyst.

Table 3. Preparation of Benzoxazoles^a

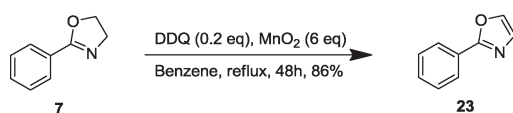
Entry	Starting Halide	Starting Aminophenol	Desired Product	Yield
1				95%
2				96%
3				98%
4				92%
5				99%

^a Conditions: Aryl halide (1 equiv), *tert*-butyl isocyanide (**3**) (1.5 equiv), amino phenol (5 equiv), Cs₂CO₃ (2 equiv), PdCl₂ (5 mol %), dppf (5 mol %), toluene, reflux.

The amidine intermediate **6** can then undergo cyclization, which after loss of *tert*-butyl amine would give desired oxazoline **7** (Scheme 1).

Gratifyingly, our initial attempt at this transformation worked well, with oxazoline **7** being formed cleanly in 2 h. Increasing the reaction time to 18 h allowed formation of oxazoline **7** in an improved 71% yield (Table 1, entry 3), while increasing the number of equivalents of the aminoethanol **5** afforded the desired compound in an excellent 80% yield in the shorter 2 h reaction time (Table 1, entry 5).

The reaction also worked well when bromobenzene **8** was subjected to our reaction conditions of *tert*-butylisocyanide **3** and aminoethanol **5** using the PdCl₂–dppf catalytic system, widening the scope of halides that we could utilize for this process. However, these conditions were unsuccessful when chlorobenzene **9** is used as the aryl halide (Table 2, entries 1–3).

Scheme 2. Conversion of Oxazolines to Oxazoles

Taking advantage of the difference in reactivity between the different halides, we used chloro iodobenzene **10** in this reaction. This substrate worked as expected with selective substitution of the iodine giving compound **11** with none of the compound that would arise from substitution of the chloride being detected (Table 2, entry 4).

The reaction is also tolerant of a more demanding electron-rich aryl halide with **12** giving the desired product **13** in 69% yield, with the corresponding triflate compound **14** also allowing this compound to be isolated in 71% (Table 2, entries 5 and 6). The success of the aryl triflate as a pseudohalide increases the scope of this powerful procedure.

Further reactions with aryl bromides **15** and **16** gave their corresponding oxazolines **17** and **18** in 81% and 88% yields respectively (Table 2, entries 7 and 8). The reaction also works well with *ortho*-substituted aryl iodide **19** with oxazoline **20** being formed, although due to the increase in steric demands for this process an 18 h reaction time was required (Table 2, entry 9).

Successful preparation of oxazolines from heteroaryl halides is shown with the use of pyridyl bromide **21** yielding compound **22** in 93% yield (Table 2, entry 10).

Dehydrogenation of oxazolines leads to the corresponding oxazole product⁶ (Scheme 2), and so this

procedure should facilitate the synthesis of a wider range of products.

Building on this we wished to expand the reaction to the synthesis of benzoxazoles. Changing the nucleophile used in our palladium-catalyzed multicomponent reaction, from aminoethanol **5**, to an aminophenol derivative would afford a range of substituted benzoxazoles (Table 3).

In practice aminophenols worked well with the desired benzoxazole products being isolated in greater than 92% yields for a range of substrates. This increase in yield can be explained due to the aromatic ring locking the two nucleophilic elements into the ideal orientation to lower the activation barrier for the cyclization step compared to the case where aminoethanol **5** is used.

This process for the formation of benzoxazoles is practically convenient to carry out and offers a number of advantages compared to the similar carbonylation process reported by Perry et al.⁷ The process reported here can be

carried out at atmospheric pressure and without the need to use toxic carbon monoxide gas and affords the product heterocycle directly.

In summary, we have reported an efficient method for the preparation of oxazoline and benzoxazole containing molecules using a powerful palladium-catalyzed multicomponent process. In addition to allowing rapid access to a number of scaffolds, required for library synthesis when trying to discover new lead compounds in the pharmaceutical and agrochemical industries, this method would be particularly useful for isotopic labeling studies. The incorporation of an isotopically labeled carbon atom in the heart of this molecule could easily be achieved as the final step using a suitably labeled isocyanide, which would be useful in drug metabolism studies and for molecular imaging techniques.

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Supporting Information Available. Experimental procedures and spectroscopic data for compounds **7**, **11**, **13**, **17**, **18**, **20**, **22**, **25**, **27**, **29**, **31**, and **33** is provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(6) (a) Kashima, C.; Arao, H. *Synthesis* **1989**, 873–874. (b) Baba, D.; Fuchigami, T. *Tetrahedron Lett.* **2003**, *44*, 3133–3136. (c) Ramirez, T. A.; Zhao, B.; Shi, Y. *Tetrahedron Lett.* **2010**, *51*, 1822–1825. (d) Lui, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686–4686.

(7) Perry, R. J.; Wilson, B. D.; Miller, R. J. *J. Org. Chem.* **1992**, *57*, 2883–2887.