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Transition-Metal-Catalyzed Uninterrupted Four-Step Sequence to Access Trisubstituted Isoxazoles

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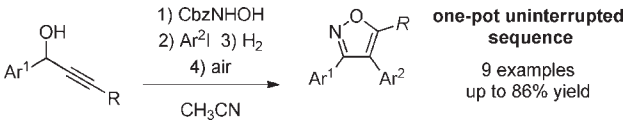
ABSTRACT



We describe herein a novel uninterrupted four-step sequence to access trisubstituted isoxazoles from readily available propargylic alcohols using sequentially iron and palladium catalytic systems. The advantages of such a strategy are illustrated by the high overall yields and the time-saving procedure that are reported.

Increasing research efforts are directed toward the development of new methodologies with high synthetic efficiency and atom economy. To achieve this goal, synthetic chemists have shown great interest for one-pot, multistep sequences of reactions, due to the inherent efficiency of avoiding operations of isolation and purification of intermediates generated from traditional iterative synthetic methods.[1] Clarke et al. recently disclosed the principle of "pot economy", which is defined as the aim "to complete an entire multi-step, multi-reaction synthesis in a single pot".[2] On the basis of this concept, Hayashi et al. have, for instance, reported the synthesis of several drugs using an "uninterrupted sequence of reactions" strategy allowing solely the removal of various volatiles by distillation: reactive wastes, excess of reagents, solvents, etc.[3] In this communication, we report our efforts to build up an uninterrupted multistep, one-pot sequence to obtain fully substituted isoxazoles from readily available propargylic alcohols using Fe and Pd catalysts.

Isoxazoles exert interesting biological activities and are core components of many pharmaceutically valuable compounds.[4] Typical regio- and chemoselective syntheses of 3,4-diarylisoxazoles consist of a stepwise approach based on a palladium-catalyzed cross-coupling between a preformed (and purified) 4-iodo-,[5] 4-silicon-,[6] or 4-boron-isoxazole derivative[7] and the appropriate aryl coupling partner.[8] We recently described a Fe(III)-catalyzed one-pot synthesis of 3,5-disubstituted isoxazolines and isoxazoles from propargylic alcohols **1** via N-protected propargyl hydroxylamines as key intermediates.[9] Our next move

(1) For a recent highlight on this topic, see: Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2.

(2) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438.

(3) (a) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304. (b) Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem.—Eur. J.* **2010**, *16*, 12616. (c) Ishikawa, H.; Honma, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 2824.

(4) (a) Sperry, J.; Wright, B. *Curr. Opin. Drug Discovery Dev.* **2008**, *8*, 723. (b) Giomi, D.; Cordero, F.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Katriski, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Joule, J., Eds.; Elsevier: Oxford, U.K., 2008; Vol. 4, p 365. (c) Sutharchanadevi, M. In *Comprehensive Heterocyclic Chemistry II*; Katriski, A. R., Rees, A. R., Scriven, E. F. V., Shinkai, I., Eds.; Elsevier: Oxford, U.K., 1996; Vol. 3, p 221.

(5) (a) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203. (b) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643. (c) Crossley, J. A.; Browne, D. L. *J. Org. Chem.* **2010**, *75*, 5414. (d) Waldo, J. P.; Metha, S.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 658. (e) Okitsu, T.; Potewar, T. M.; Wada, A. *J. Org. Chem.* **2011**, *76*, 3438.

(6) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839.

(7) (a) Davies, M. W.; Wybrow, R. A. J.; Johnson, C. N.; Harrity, J. P. A. *Chem. Commun.* **2001**, 1558. (b) Kumar, J. S. D.; Ho, M. M.; Leung, J. M.; Toyokuni, T. *Adv. Synth. Catal.* **2002**, *344*, 1146. (c) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707.

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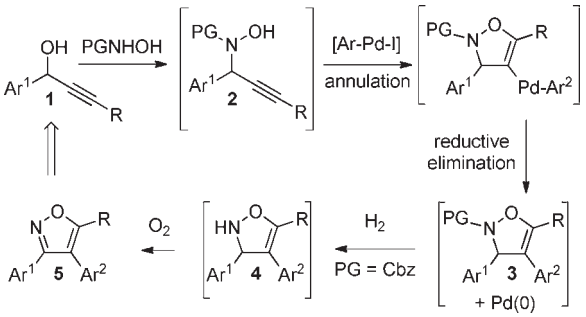
was to develop an efficient and selective one-pot strategy to access trisubstituted 3,4-diarylisoxazoles from **1**. We anticipated that the introduction of another aryl group (Ar^2) could be performed through an annulation/cross-coupling reaction that could ideally be followed, in the same sequence, by the removal of the nitrogen protecting group to lead to trisubstituted isoxazoles **5** (Scheme 1). Whereas the direct propargylic alcohol substitution by N-protected hydroxylamine to give **2** is now well-precedented, the crucial step in this sequence appears to be the annulation/cross-coupling reaction. We envisioned that an in situ generated electrophilic aryl−palladium(II) complex would allow the activation of the triple bond, and the resulting vinylic organopalladium intermediate would undergo a reductive elimination to provide the trisubstituted isoxazoline **3**. In this sequence, the presence of a palladium complex could be advantageously exploited for protecting group removal (Scheme 1, PG = Cbz), to give isoxazoline **4**, which could undergo an aerobic aromatization to yield isoxazole **5** (Scheme 1).

Scheme 1. Annulation/Cross-Coupling and Deprotection Strategy



First, our objective was to validate the palladium-catalyzed annulation/cross-coupling key step using **2a** (PG = Cbz, R = *n*Bu, Ar^1 = *p*-tol) as a model compound.[10] Arcadi et al. disclosed the first example of an annulation/cross-coupling cascade reaction promoted by in situ generated aryl−palladium complexes for the construction of 2,3-disubstituted benzofuran derivatives, in moderate yields.[11] More recently, Yang et al. revisited this methodology and use a Pd(0)/bipyridine complex as the catalytic system, to allow for the efficient preparation of various 2,3-diarylbenzo[*b*]furans.[12,13]

Under Yang conditions [PhI (2 equiv), $Pd_2(dba)_3$ (5 mol %), bipyridine (bpy, 10 mol %), and K_2CO_3 (4 equiv) in freshly distilled CH_3CN under an argon atmosphere], **2a** was converted selectively to isoxazoline **3a** in a 85% isolated yield after 72 h at 50 °C (see Table 1, entry 1). Heating the reaction mixture to reflux had a detrimental effect, yielding **3a** along with two new products whose structures have been assigned to the disubstituted isoxazoline **6a** and the enone **7a** (**3a**/**6a**/**7a**: 4/1/1 ratio, entry 2). Some complementary experiments have been carried out to better understand the formation of these side products. When **2a** was heated at 50 °C over 20 h in CH_3CN with K_2CO_3 (4 equiv) in the absence of a palladium catalyst, enone **7a** was cleanly obtained in 89% isolated yield with no detectable amount of **6a** in the crude mixture (entry 3). Moreover, no reaction occurred when **6a** was submitted to the same reaction conditions [K_2CO_3 (4 equiv), CH_3CN, 50 °C, 20 h], which indicates that (1) **7a** is formed through a palladium-free process, (2) **6a** is not an intermediate product of **7a**, and (3) K_2CO_3 itself is not able to promote the formation of **6a**.[14] Intriguingly, when **2a** was submitted to $Pd_2(dba_3)$/bpy and K_2CO_3 at 50 °C without PhI, **6a** was obtained as the main product (73% yield), along with low traces of enone **7a** (7%, entry 4), showing that **6a** is generated through a Pd(0)-catalyzed process. We thus investigated the influence of the nature of the palladium ligands (L) on the course of the transformation. Moving to $Pd(PPh_3)_4$ results in the formation of disubstituted isoxazoline **6a** as the major compound and enone **7a** in the presence (or not) of PhI in the reaction mixture (entries 5 and 6). We next examined the role of the base and noticed that no reaction occurred when $Pd(PPh_3)_4$ or Pd_2dba_3/bpy were used in the absence of K_2CO_3 or when DMAP, imidazole (Imd), or propylene oxide[15] were used as a base or scavenger with $Pd_2(dba_3)$/bpy (entries 7−11). However, Et_3N can be employed instead of K_2CO_3 with the $Pd_2(dba_3)$/bpy catalytic system without significant impact on the yield of **3a** (entry 12). The presence of a base with $pK_a > 10$ appears to be necessary for the annulation process.

(8) For selected examples of isoxazole synthesis by other methods, see: (a) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775. (b) Di Nunno, L.; Vitale, P.; Scilimati, A.; Tacconelli, S.; Patrignani, P. *J. Med. Chem.* **2004**, *47*, 4881. (c) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594. (d) Burhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5379. (e) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664.

(9) (a) Debleds, O.; dal Zotto, C.; Vrancken, E.; Campagne, J. M. *Adv. Synth. Catal.* **2009**, *351*, 1991. (b) Gayon, E.; Debleds, O.; Nicouleau, M.; Lamaty, F.; Vand der Lee, A.; Vrancken, E.; Campagne, J. M. *J. Org. Chem.* **2010**, *75*, 6050. (c) Debleds, O.; Gayon, E.; Ostaszuk, E.; Vrancken, E.; Campagne, J. M. *Chem.—Eur. J.* **2010**, *16*, 12207. (d) Debleds, O.; Gayon, E.; Vrancken, E.; Campagne, J. M. *Beilstein J. Org. Chem.* **2011**, *7*, 866.

(10) **2a** is easily obtained in good isolated yield (91%) by refluxing **1a** and CbzNHOH in the presence of FeCl3 (10 mol %) in DCM according to the Zhan et al procedure: Zhan, Z.-P.; Yu, J.-L.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P *J. Org. Chem.* **2006**, *71*, 8298–8301.

(11) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

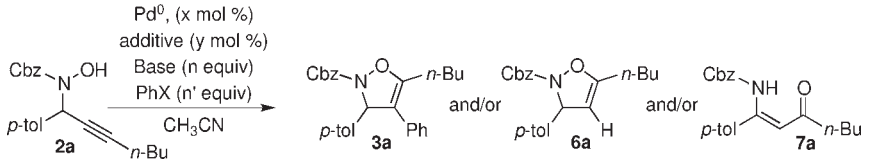
(12) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235.

(13) For an application of this strategy to the synthesis of indolizinone, see: Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500.

(14) The obtention of analogues of **7a** through the N−O bond cleavage of isoxazolines has already been described: (a) Lopez-Callen, E.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2003**, 1438. (b) Lager, M.; Dietrich, D.; Weinrich, D.; Rück-Braun, K. *Heterocycles* **2007**, *74*, 743. To the best of our knowledge, the direct transformation of propargylic hydroxylamines to enones is unknown.

(15) (a) Moreau, X.; Campagne, J.-M. *J. Organomet. Chem.* **2003**, *687*, 322. (b) Moreau, X.; Campagne, J.-M.; Meyer, G.; Jutand, A. *Eur. J. Org. Chem.* **2005**, 3749. (c) Tong, Z.; Gao, P.; Deng, H.; Zhang, L.; Xu, P.; Zhai, H. *Synlett* **2008**, 3239.

Table 1. Palladium-Catalyzed Annulation/Cross-Coupling Sequence (Product Distribution and Conditions)



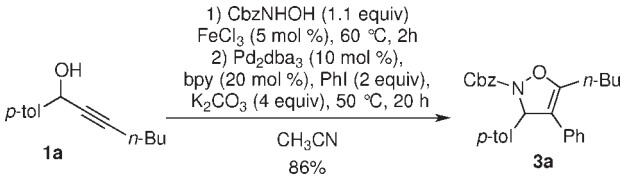
entry	catalytic system	ArX (2 equiv)	additive (4 equiv)	temperature and time	**3a/6a/7a** (yield, %)[a]
1	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	K_2CO_3	50 °C, 72 h	1/0/0 (85/-/-)
2	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	K_2CO_3	Reflux, 1 h	4/1/1 (33/5/13)
3	none	none	K_2CO_3	50 °C, 20 h	0/0/1 (-/-/89)
4	Pd_2dba_3 (5 mol %), bpy (10 mol %)	none	K_2CO_3	50 °C, 20 h	0/9/1 (-/73/7)
5	$Pd(PPh_3)_4$ (10 mol %)	PhI	K_2CO_3	50 °C, 20 h	0/3/1 (-/58/19)
6	$Pd(PPh_3)_4$ (10 mol %)	none	K_2CO_3	50 °C, 20 h	0/1.5/1 (-/41/30)
7	$Pd(PPh_3)_4$ (10 mol %)	PhI	none	50 °C, 72 h	no reaction
8	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	none	50 °C, 72 h	no reaction
9	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	DMAP	50 °C, 72 h	no reaction
10	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	Imd	50 °C, 72 h	no reaction
11	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	propylene oxide	50 °C, 72 h	no reaction
12	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhI	Et_3N	50 °C, 40 h	1/0/0 (75/-/-)
13	Pd_2dba_3 (5 mol %), bpy (10 mol %)	PhBr	K_2CO_3	50 °C, 40 h	0/4.5/1 (-/50/11)
14	Pd_2dba_3 (10 mol %), bpy (20 mol %)	PhI	K_2CO_3	50 °C, 20 h	1/0/0 (86/-/-)

[a] Isolated yield.

Some observations can be brought forward from this first study: In this transformation, three different pathways, respectively, leading to **3a**, **6a**, and **7a** are in competition. Among them, the one leading to enone **7a** is promoted by K_2CO_3 and appears to be the slowest one. The two other reaction pathways are Pd-catalyzed, and both lead to annulation products: the disubstituted isoxazoline **6a** with Pd(0) and the trisubstituted **3a** with Pd(II). The rate difference between these two processes strongly depends on the nature of the ligand. With PPh_3, the Pd(0) way is faster than the Pd(II) one, although the oxidative addition (OA) step into the Ar–I bond is known to occur easily under these reaction conditions. In strong contrast, the Pd(II) way is preferred when using bpy. It is worth noting that the use of PhBr instead of PhI in the Yang conditions leads to the exclusive formation of **6a** (entry 13). Surprisingly, Pd(0) appears to be able to activate a triple bond toward an internal nucleophile, whereas Pd(II) sources are generally used for the π-activation of double/triple C–C bonds. In some particular cases during this study, the catalytic cycle using Pd(0) appears to be more efficient than the corresponding Pd(II) one (compare entries 1, 5, and 6).[16]

Nevertheless, under Yang conditions, **3a** can be selectively obtained and the reaction time can be shortened by increasing the amount of Pd_2dba_3 to 10 mol %, leading to **3a** in 86% isolated yield (entry 14) over 20 h. For practical reasons, these conditions were thus chosen as standard reaction conditions for the rest of this study.

Scheme 2

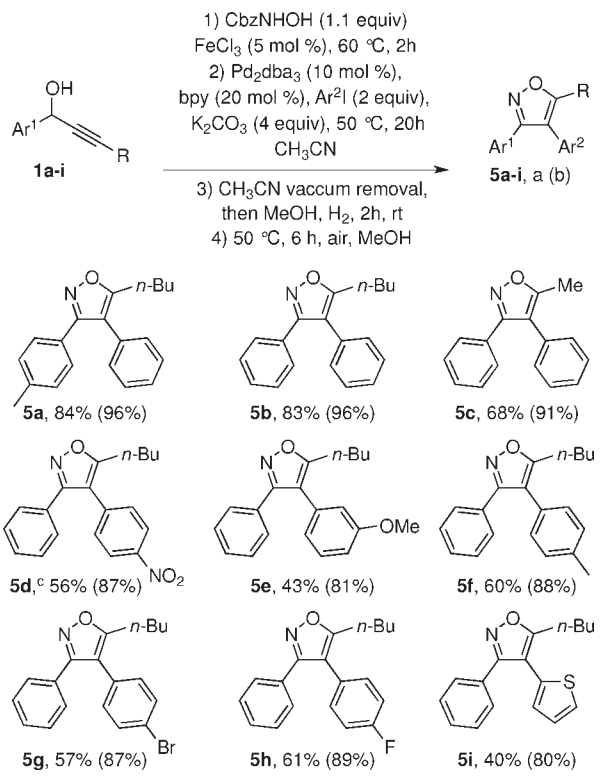


With these conditions in hand, we next turned our attention to the development of a one-pot direct propargylic alcohol substitution/annulation/cross-coupling sequence: **1a** → [**2a**] → **3a**. Initial attempts to promote direct formation of **3a** from **1a** in the presence of a Pd(II) catalyst were unsuccessful with full recovery of the starting material. We then envisioned that the use of $FeCl_3$ would first promote the propargylic substitution.[9,10] **1a** and CbzNHOH were thus treated by $FeCl_3$ (5 mol %) in CH_3CN at 60 °C. After complete conversion of **1a** to **2a** (as judged by TLC),[17] PhI, $Pd_2(dba)_3$, K_2CO_3, and bpy were added and the reaction was heated at 50 °C over 20 h. Gratifyingly, **3a** was selectively obtained in a 86% isolated yield,

(16) (a) Pd(II) complexes are generally used for the activation of π systems; see: Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, p 2193. (b) For a rare study on the possible use of Pd(0) in this type of reaction, see: Ahlquist, M.; Fabrizi, G.; Cacchi, S.; Norrby, P.-O. *Chem. Commun.* **2005**, 4196–4198.

(17) For a paper dealing with the association of Pd and Fe in a catalytic process, see: Terrasson, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 5332.

Scheme 3. [a,b,c]



[a] Isolated yield. [b] Yields in parentheses are average yields per step. [c] *p*-Bromonitrobenzene was used as aryl halide.

identical to the one observed when starting from **2a** (Scheme 2).

With these encouraging results, we next screened various conditions to develop a one-pot, four-step sequence to access the trisubstituted isoxazoles **5** (Scheme 3). The hydrogenolysis of the Cbz can be performed directly after the previous sequence by addition of a H_2 balloon, provided that the acetonitrile is removed under vacuum with no particular precautions and replaced by MeOH.[18] After 2 h at room temperature (TLC monitoring), the H_2 balloon was removed and the reaction mixture was stirred for 6 h at 60 °C under an air atmosphere. Isoxazole **5a** was then obtained in 84% isolated yield from **1a** in a one-pot, 4-step uninterrupted sequence (Scheme 3), which represents an average yield of 96% per step. This average yield is greater than the yield observed for the sole Pd-catalyzed annulation/cross-coupling reaction from **2a** to **3a**, illustrating the overall benefits of performing an uninterrupted sequence of reactions for the general efficiency of this transformation.

We next studied the scope and limitations of this 4-step sequence, with regard to variously substituted aryl iodides and propargylic alcohols. Using our optimized conditions (Scheme 3), the reaction proceeds cleanly and isoxazoles **5b**–**5i** were obtained in good-to-excellent yields no matter the nature of the substituent on the Ar^2 group (Scheme 3). Electron-withdrawing or electron-donating groups are well-tolerated. Interestingly, the presence of an orthogonal bromide at the para position of Ar^2 is allowed (see compound **5g**), despite the use of the palladium catalyst, which potentially allows for further functionalization. Using 2-iodothiophene, isoxazole **5i** was obtained in a modest 40% overall yield (80% per step), which may be partially explained by the intrinsic instability of **4i**. The main limitation was observed when starting from propargylic alcohols bearing a phenyl group on the acetylenic position (R = Ph). Only the corresponding diaryl enone could be observed by ^{1}H NMR analysis of the crude reactions mixtures. In this case, these highly conjugated compounds are formed faster than the usual cyclization product.

In conclusion, we have developed an access to trisubstituted isoxazoles from readily available propargylic alcohols through a one-pot substitution/annulation/cross-coupling/hydrogenolysis/oxidation uninterrupted sequence. This approach is solvent- and time-saving since no intermediate workups or purification operations are needed. High overall yields in the formation of various fully substituted isoxazoles are thus granted by this operational simplicity and by the high efficiency of each individual step (nine examples, up to 84% overall yield). Interestingly, the palladium source mediates most of the processes of the synthetic sequence. Finally, we have also observed an unusual, ligand-controlled Pd(0)/Pd(II) competition in the π-activation of disubstituted triple bonds. This offers interesting perspectives for the development of new domino sequences, and applications are currently underway.

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Supporting Information Available. Experimental procedure and characterization data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Alternative solvents (AcOEt, $MeNO_2$, DMF...) for the whole sequence, that is, able to promote the substitution/cyclization and the hydrogenolysis steps, were also examined but did not lead to any satisfactory results.