ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Pd-Catalyzed Alkynylation of 2-Chloroacetates and 2-Chloroacetamides with Potassium Alkynyltrifluoroborates

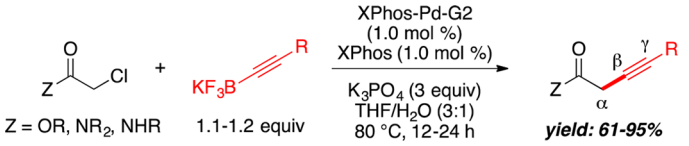
Gary A. Molander* and Kaitlin M. Traister

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

gmolandr@sas.upenn.edu

Received August 20, 2013

ABSTRACT



The synthesis of β,γ-alkynyl esters and amides using air-stable potassium alkynyltrifluoroborates as nucleophilic partners in a mild Suzuki–Miyaura cross-coupling reaction has been achieved. Propargyl esters and amides were obtained in high yields using a low catalyst loading, and the substrate scope of the reaction has been significantly improved over previous methods.

Significant exploration has taken place toward the synthesis of β,γ-alkynyl esters and amides, and yet because of the challenges associated with preparing these nonconjugated structures, several limitations persist. Most synthetic routes involve the Pd-catalyzed cross-coupling of an α-halo carbonyl compound with an alkynylmetallic species. One major obstacle with such pathways is that, after oxidative addition of the α-halo carbonyl species to Pd(0), both the halide and the enolate serve as good leaving groups from Pd. This can result in double transmetalation of the alkynyl species, promoting formation of the diyne product. Reactions of this type have been optimized to take advantage of homocoupling to gain access to diynes through similar transformations.[1]

Another major hurdle associated with such routes that limits these methods from widespread use is the instability of many alkynylmetallic species. Oshima et al. have established a radical process in which alkynylgallium species are added to α-bromo and α-iodo esters and amides.[2] Similarly, a photochemical process that allows alkynylindium species to be added to α-iodo esters has been reported by Hirashita et al.[3] Although both of these methods allow formation of the desired structures, they require *in situ* generation of an alkynylmetallic species that cannot be isolated.

To solve this problem, Lei et al. developed a protocol for the Pd-catalyzed cross-coupling of alkynylstannanes with α-bromo carbonyl compounds in the presence of XantPhos.[4] As an extension of this work, Connell and Kang devised a method for a similar Stille-type coupling to proceed with secondary bromides.[5] Both esters and amides were successfully obtained in moderate yields, although the substrate scope was limited by the use of phenylethynylstannane as the sole nucleophilic coupling partner. Although alkynylstannanes are stable enough to be isolated, many still require storage under an inert atmosphere, and their use is less than ideal because of safety concerns surrounding tin.[6]

Another noteworthy approach to the synthesis of β,γ-alkynyl esters and amides has been carried out by

(1) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969.
(2) (a) Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2687. (b) Takami, K.; Usugi, S.; Yorimitsu, H.; Oshima, K. *Synthesis* **2005**, *5*, 824.
(3) Hirashita, T.; Hayashi, A.; Tsuji, M.; Tanaka, J.; Araki, S. *Tetrahedron* **2008**, *64*, 2642.
(4) Shi, W.; Liu, C.; Yu, Z.; Lei, A. *Chem. Commun.* **2007**, 2342.
(5) Kang, J. Y.; Connell, B. T. *J. Org. Chem.* **2011**, *76*, 6856.
(6) Graf, G. G. Tin, Tin Alloys, and Tin Compounds. *Encyclopedia of Industrial Chemistry*. Wiley-VCH: Weinheim, 2000.

10.1021/ol402391z

Fu, who demonstrated a functional-group compatible, Cu(I)-catalyzed addition of terminal alkynes to diazoesters and diazoamides.[7] This method, while greatly improving the substrate scope of the alkynyl partner, only illustrated the compatibility of two electrophilic partners.

An additional major concern surrounding the previously utilized methods is the cost of producing the alkynylating species. To access the reactive intermediates, a terminal alkyne is typically reacted with one of the reagents shown in Table 1.[8] Although compared to Ga and In, Sn is a major improvement in terms of cost, the lack of atom ecomony associated with the use of Bu_3SnCl represents yet another disadvantage. Likewise, the use of diazoesters and diazoamides in the Cu-catalyzed method is limited by the lack of commercial availability of these reagents, most of which must be prepared from tosyl azide.

Table 1. Cost Comparison of Commonly used Metal Reagents in Alkynylation Reactions

substance	cost ($/mol)	relative cost
$B(OMe)_3$	9	1
$GaCl_3$	1775	204
$InCl_3$	1340	155
Bu_3SnCl	160	18

We envisioned a route that would allow the use of commercially available 2-chloro carbonyl reagents in the presence of an air-stable alkynylmetallic species that could be prepared easily from inexpensive materials. The low relative cost of $B(OMe)_3$ as compared to other commonly employed metal reagents (Table 1) makes the use of alkynylboron species appealing in this context.

Alkynyltrifluoroborates can be readily prepared from alkynyl boronates by a simple quench using aqueous KHF_2. Potassium alkynyltrifluoroborates offer the advantages of being air-stable compounds capable of being stored on the bench for extended periods of time, and also of being able to be prepared from terminal alkynes in a simple and cost-effective manner.

Based on the conditions recently developed for the α-arylation[9] and α-alkenylation[10] of 2-chloro esters and amides, we sought to apply similar conditions to the desired transformation. Screening was begun on the reaction of *N*-benzyl-2-chloroacetamide with potassium phenylethynyltrifluoroborate using the XPhos-Pd-G2 preformed catalyst (Figure 1) in the presence of K_2CO_3 and Cu_2O. Although a minimal amount of the desired product was observed under these initial conditions, the reaction showed a significant conversion to the diyne product. Attempts to reduce homocoupling by changing the base or solvent were unsuccessful, and it was determined that completely eliminating Cu from the reaction served to suppress the homocoupling side reaction. SPhos and RuPhos were tested in addition to XPhos under the unoptimized reaction conditions, but only minimal conversion to product (< 5%) was observed with these ligands. Because of the reported success of XantPhos for a similar reaction,[4] a number of bidentate phosphine ligands were also investigated, but XPhos remained the best ligand for the desired transformation.

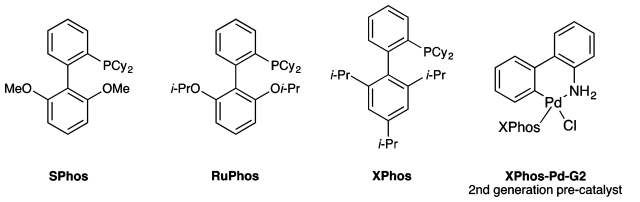


Figure 1. Structures of SPhos, RuPhos, and XPhos ligands and XPhos-Pd-G2 pre catalyst.

The base in Suzuki–Miyaura reactions is often critical because of its effects on the rate of trifluoroborate hydrolysis and of Pd(0) formation.[11] Table 2 shows the results of a small screening of bases under preliminary reaction conditions.

Table 2. Base Screening in Reaction of *N*-Benzyl-2-chloroacetamide with Potassium Phenylethynyltrifluoroborate

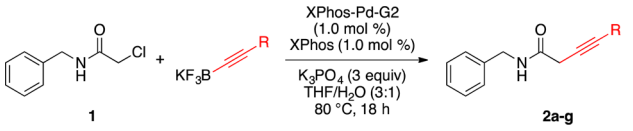
base	product	homocoupling
K_2CO_3	36	2
Cs_2CO_3	48	14
K_3PO_4	74	6
$(n\text{-}Bu_4N)H_2PO_4$	4	3
$(NH_4)_2CO_3$	6	24
$(n\text{-}Bu_4N)OH$	0	1

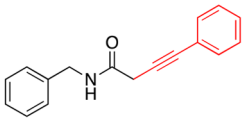
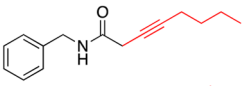
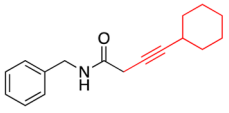
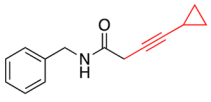
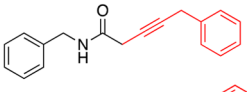
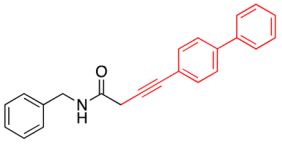
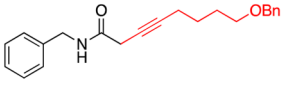
Given the promising results of K_3PO_4, we continued the optimization with this base. Increasing the amount of base to 5 equiv or decreasing it to 1 equiv was detrimental to the reaction. It was found that homocoupling reactions were more prevalent at a higher temperature (100 °C), while at a lower temperature (60 °C), a large amount of starting material was still present after 24 h.

With nearly optimized conditions, several organic solvents were tested in combination with various amounts of water[12] to determine an ideal solvent system, and a 3:1 toluene/H_2O ratio was found to be optimal. Under these conditions, addition of a second equivalent of XPhos (relative to Pd) was found to push the reaction further to completion.

(7) Suarez, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3580.
(8) Prices obtained from SigmaAldrich Web site.
(9) Molander, G. A.; Traister, K. M.; Barcellos, T. *J. Org. Chem.* **2013**, *78*, 4123.
(10) Molander, G. A.; Barcellos, T.; Traister, K. M. *Org. Lett.* **2013**, *15*, 3342.
(11) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.—Eur. J.* **2012**, *18*, 6616.
(12) Lennox, A. J. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 7431.

Table 3. Cross-Coupling of *N*-Benzyl-2-chloroacetamide with Potassium Alkynyltrifluoroborates[a]



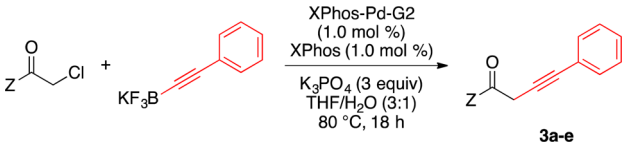
entry	product		yield (%)
1		**2a**	92, 88[b]
2		**2b**	90
3		**2c**	82
4		**2d**	92
5		**2e**	95
6		**2f**	80
7		**2g**	76

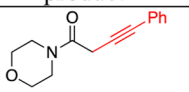
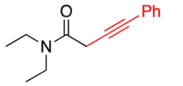
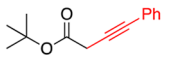
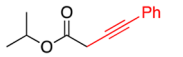
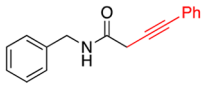
[a] Reaction conditions: 2-chloroacetamide (1.0 mmol), potassium alkynyltrifluoroborate (1.1 mmol, 1.1 equiv), K_3PO_4 (3.0 mmol, 3.0 equiv), XPhos-Pd-G2 (1 mol %), XPhos (1 mol %), solvent (3.2 mL), 80 °C. [b] 5.0 mmol scale (0.5 mol % Pd).

N-Benzyl-2-chloroacetamide was cross-coupled with a variety of alkynyltrifluoroborates under the optimized conditions, as shown in Table 3. The scope of the alkynyltrifluoroborates include those with not only aryl and straight-chain alkyl substituents but also branched alkyl (Table 3, entries 3–4), benzyl (Table 3, entry 5), and a protected alcohol unit (Table 3, entry 7). The scalable nature of the reaction was demonstrated by the ability to carry out the reaction of *N*-benzyl-2-chloroacetamide with potassium phenylethynyltrifluoroborate on a 5.0 mmol scale with the use of only 0.5 mol % Pd (Table 3, entry 1).

We next sought to expand the scope of the reaction to include various electrophilic coupling partners. Table 4 illustrates the versatility of the reaction scope in terms of the electrophile, which allows the same alkynyltrifluoroborate partner to be coupled with tertiary amides (Table 4, entries 1 and 2) and esters (Table 4, entries 3 and 4) under the same reaction conditions.

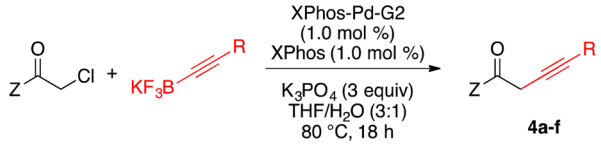
Table 4. Cross-Coupling of Potassium Phenylethynyltrifluoroborate with 2-Chloro Esters and Amides[a]

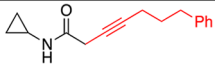
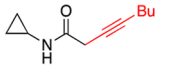
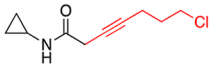
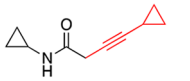
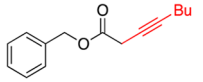


entry	product		yield (%)
1		**3a**	72
2		**3b**	77
3		**3c**	74[b]
4		**3d**	84[b]
5		**2a**	92

[a] Reaction conditions: 2-chloroacetate or 2-chloroacetamide (1.0 mmol), potassium alkynyltrifluoroborate (1.1 mmol, 1.1 equiv), K_3PO_4 (3.0 mmol, 3.0 equiv), XPhos-Pd-G2 (1 mol %), XPhos (1 mol %), solvent (3.2 mL), 80 °C. [b] 1.2 equiv of alkynyltrifluoroborate used.

Table 5. Cross-Coupling of 2-Chloro Esters and Amides with Potassium Alkynyltrifluoroborates[a]



entry	product		yield (%)
1		**4a**	75
2		**4b**	90
3		**4c**	61
4		**4d**	74
5		**4e**	89[b]
6		**4f**	76[b]

[a] Reaction conditions: 2-chloroacetate or 2-chloroacetamide (1.0 mmol), potassium alkynyltrifluoroborate (1.1 mmol, 1.1 equiv), K_3PO_4 (3.0 mmol, 3.0 equiv), XPhos-Pd-G2 (1 mol %), XPhos (1 mol %), solvent (3.2 mL), 80 °C. [b] 1.2 equiv of alkynyltrifluoroborate used.

The substrate scope of the reaction was also extended to include a variety of other nucleophilic and electrophilic coupling partners, as illustrated in Table 5. An alkynyltrifluoroborate containing a terminal chloride was successfully cross-coupled in good yield (Table 5, entry 3).

A protocol has been developed for the synthesis of β,γ-alkynyl esters and amides through mild reaction conditions using air-stable, easily prepared alkynyltrifluoroborates. This method offers advantages over current pathways in terms of cost, atom economy, functional group compatibility, and ease of starting material acquisition.

Acknowledgment. We thank the NIH (NIGMS R01 035249) and NSF (GOALI) for support of this research. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for acquisition of HRMS spectra.

Supporting Information Available. Complete experimental procedures and characterization data (^{1}H and ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.