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Substituted Alkyne Synthesis under Nonbasic Conditions: Copper Carboxylate-Mediated, Palladium-Catalyzed Thioalkyne–Boronic Acid Cross-Coupling

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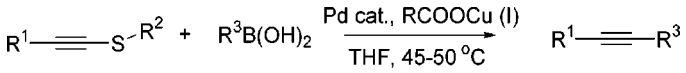
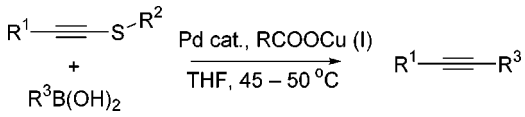
ABSTRACT



A new methodology for the synthesis of substituted alkynes is described. In the presence of copper(I) thiophene-2-carboxylate (CuTC) or copper (I) 3-methylsalicylate (CuMeSal), the palladium-catalyzed cross-coupling of thioalkyne derivatives with boronic acids affords functionalized alkynes in yields ranging from 39 to 91%. This coupling occurs efficiently under mild, nonbasic conditions with a wide variety of thioalkynes and boronic acids, providing a reaction complementary to the Sonogashira protocol.

Alkynes are important building blocks in materials science and organic synthesis.[1] We report herein a new and mild method of substituted alkyne synthesis involving the coupling of boronic acids and thioalkynes (Scheme 1) that supplements

Scheme 1. Thioalkyne−Boronic Acid Coupling



previously known methods of synthesis.[2] This new, nonbasic and general methodology is an umpolung complement to the Sonogashira protocol.[3] It improves upon the related Suzuki cross-coupling approach to substituted alkynes,[4] a route that requires the use of potentially hazardous bromo- or chloroalkyne derivatives under basic conditions.

The method takes advantage of boronic acids (widely available, mild, stable, and nontoxic reactants that are compatible with a wide variety of functional groups) and easily synthesized thioalkynes. With the exception of thioalkyne **1**, which was prepared by a literature route,[5] thioalkyne reactants **2**−**7** (Figure 1) were easily obtained from terminal alkynes and *N*-(*p*-tolylthio)succinimide, using a modification of a literature procedure.[6] Other routes to thioalkynes are known.[2,5,7] Using the indicated protocol, a wide variety of stable, storable thioalkynes were obtained in good to excellent yields.

Thioalkynes **1**−**7** reacted with boronic acids in THF at 45−50 °C to give substituted alkynes in good to excellent yields. The process is catalyzed by palladium and mediated

(1) Patai, S. *The Chemistry of the Carbon−Carbon Triple Bond*; Wiley: New York, 1978.

(2) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988.

(3) (a) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, 1998; p 198. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (c) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, *5*, 549−550. (d) Thorand, S.; Krause, N. *J. Org. Chem.* **1958**, *23*, 8551−8553.

(4) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437−3440. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980.

(5) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114* (23), 8869−8885.

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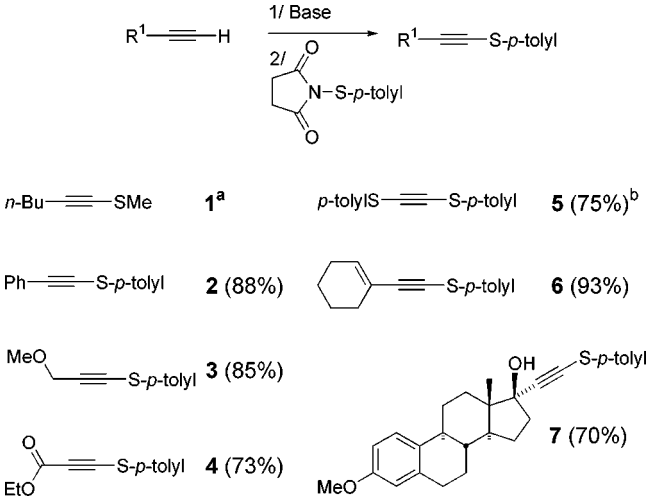
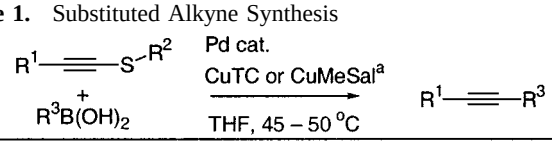


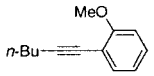
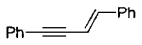
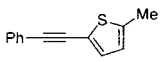
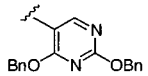
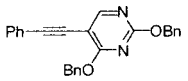
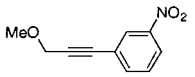
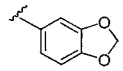
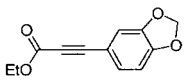
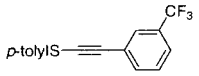
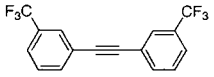
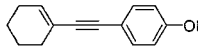
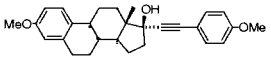
Figure 1. Thioalkyne synthesis. [a]Obtained following a literature procedure.[5] [b]Obtained by a 3-step, one-pot procedure: (i) ethynylMgCl, *N*-(*p*-tolylthio)succinimide, (ii) *n*-BuLi, (iii) *N*-(*p*-tolylthio)succinimide.

by either copper(I) thiophene-2-carboxylate (CuTC) or copper(I) 3-methylsalicylate (CuMeSal) (Table 1).[8] In accord with other recent palladium-catalyzed, copper carboxylate-mediated reactions discovered in this laboratory,[9] both the catalytic palladium and stoichiometric copper carboxylate are required for cross-coupling. Copper(I) halides (chloro, bromo, or iodo) as well as standard bases (K_2CO_3, NaOAc) were ineffective. Both the copper(I) cation and the carboxylate anion are necessary—NaTC was ineffective as a CuTC replacement. Moreover, adding K_2CO_3 to the normal coupling conditions significantly diminished the yield of product.

Different palladium sources and solvents were examined for the coupling of thioalkyne substrates. Similar results were obtained with $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ with $P(OEt)_3$ or tris-2-furylphosphine or $SbPh_3$. All reactions were completed within 3−18 h at 45−50 °C. In one case the coupling was carried out efficiently at room temperature overnight (Table 1, entry 3); other examples may proceed equally well at room temperature. Among the solvents *N*,*N*-dimethylacetamide (DMA), EtOH, dioxane, and THF, the latter two gave the best results. The nature of the sulfur substituent of the thioalkyne cross-coupling partner did not seem critical, since both an *S*-*p*-tolyl and an *S*-methyl thioalkyne could be used for the coupling. The reaction tolerated a variety of thioalkynes and boronic acids (alkenyl, heteroaryl, and aryl,

Table 1. Substituted Alkyne Synthesis



entry	S-alkyne[b]	R^3	product		yld %
1	**1**	*o*-MeOPh		**8**	68
2	**2**	(E)-β-styryl		**9**	68
3	**2**	2-Me-5-thienyl		**10**	87[c]
4	**2**			**11**	39
5	**3**	*m*-NO_2Ph		**12**	86
6	**4**			**13**	91
7	**5**	*m*-CF_3Ph		**14**	54
8	**5**	*m*-CF_3Ph		**15**	74
9	**5**	*p*-MeOPh		**16**	65
10	**6**	*p*-MeOPh		**17**	74
11	**7**	*p*-MeOPh		**18**	81

[a] CuTC: Cu^I thiophene-2-carboxylate. CuMeSal: Cu^I 3-methylsalicylate. [b] Refer to Figure 1 for thioalkyne structures. [c] Reaction carried out at room temperature.

containing both electron-donating and electron-withdrawing substituents) leading to the efficient formation of substituted alkynes, in all but one case. In that case (Table 1, entry 4), the uracil derivative moiety probably binds to the copper carboxylate and interferes with effective coordination of copper to the palladium thiolate ligand.

Particular attention is drawn to the double functionalization of the solid dithioalkyne **5**. Through appropriate choice of conditions, **5** can undergo either mono- (Table 1, entry 7) or disubstitution (Table 1, entries 8, 9).

The mechanism of the cross-coupling most likely begins with oxidative addition of Pd(0) with the carbon−sulfur bond of the thioalkyne to afford an alkynylpalladium thiolate, typified by **19** in Scheme 2.[10] Alkynylpalladium thiolate **19**

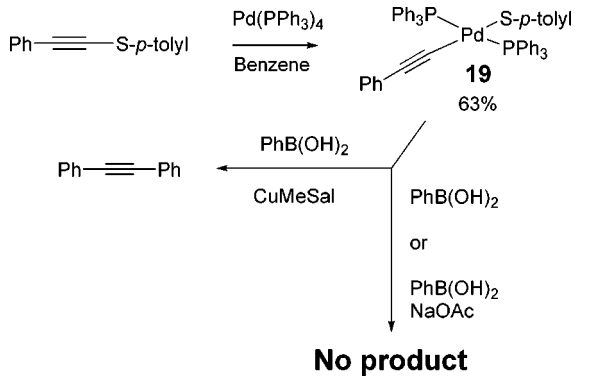
(6) Busi, E.; Capozzi, G.; Menichetti, S.; Nativi, C. *Synthesis* **1992**, *7*, 643−645.

(7) (a) Takeda, H.; Shimada, S.; Ohnishi, S.; Nakanishi, F.; Matsuda, H. *Tetrahedron Lett.* **1998**, *39*, 3701−3704. (b) Braga, A. L.; Silveira, C. C.; Reckziegle, A.; Menezes, P. H *Tetrahedron Lett.* **1993**, *34*, 8041−8042. (c) Stang, P. J.; Zhankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 4571−4576. (d) Tanaka, K.; Shiraishi, S.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, *34*, 3103−3106.

(8) Other recent copper carboxylate-mediated reactions: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

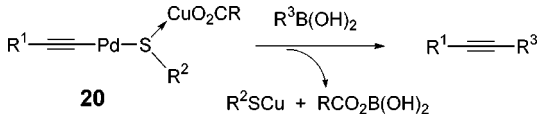
(9) Liebeskind, L. S. Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261.

Scheme 2. Cross-Coupling Mechanism



was prepared in 63% yield by mixing phenylethynyl *p*-tolyl sulfide **2** with $Pd(PPh_3)_4$ in benzene at room temperature.[11] Compound **19** was treated with $PhB(OH)_2$ under various conditions. PhC≡CPh was produced in the presence of $PhB(OH)_2$ and CuMeSal, but not with $PhB(OH)_2$ alone or with $PhB(OH)_2$ in the presence of NaOAc. These results highlight the critical role played by the copper(I) carboxylate cofactor in facilitating transmetalation from boron to palladium, which does not occur directly from boron to the alkynylpalladium thiolate. A logical intermediate is the Cu(I) carboxylate−alkynylpalladium thiolate complex **20** (Scheme 3). Transmetalation to palladium would then proceed directly from the alkynylpalladium thiolate−Cu(I) carboxylate complex or be preceded by prior boron to copper transmetalation.

Scheme 3. Transmetalation and the Copper Cofactor



The *stoichiometric* pairing of the Cu(I) cation and carboxylate anion are crucial to the success of the process. The ineffectiveness of the copper(I) halides indicates that the carboxylate counterion of the copper is clearly important in facilitating transmetalation from boron, possibly through direct coordination to trivalent boron. The requirement of a full equivalent of Cu(I) in the process is dictated by the need to scavenge thiolate as the reaction proceeds. Any readily available or easily prepared copper(I) carboxylate should suffice in this chemistry; the use of CuTC and CuMeSal was guided by a combination of low cost (of the corresponding acid) and relative air-stability of the copper carboxylate product.

In conclusion, the scope and limitations of the copper carboxylate-mediated, palladium-catalyzed cross-coupling of thioalkynes and boronic acids have been studied. The methodology allows the synthesis of unsymmetrical and symmetrical alkynes in good yields under nonbasic conditions.[12]

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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006807D

(10) Other references to C−S oxidative addition are found within Kuniyasu, H.; Ohtaka, A.; Nakazono, T.; Kinomoto, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2000**, *122*, 2375−2376.

(11) Phenylethynyl *p*-tolyl sulfide **2** (101 mg, 0.45 mmol, 1.0 equiv) was mixed with $Pd(PPh_3)_4$ (502 mg, 0.43 mmol, 1.0 equiv) in dry and degassed benzene (11 mL), at room temperature, in the dark, under argon. After 10 h, pentane (60 mL), was added and an orange solid precipitated. After filtration of the solid, the palladium complex **19** (230 mg, 0.27 mmol, 63%) was obtained as a lightly orange solid.

(12) **Typical experimental procedure:** The boronic acid (1.0−1.5 equiv), Pd catalyst (3−10%), copper salt (CuTC or CuMeSal, 1.0−1.5 equiv), and thioalkyne (1.0 equiv) were placed in a 25 mL Schlenk tube. After a vacuum and argon cycle, dry and degassed solvent was added. The reaction mixture was stirred for 3−18 h at 45−50 °C. Following the typical procedure, dry and degassed THF (2.5 mL) was added to the steroidal derivative **7** (50 mg, 0.11 mmol, 1.0 equiv), CuMeSal (26 mg, 0.12 mmol, 1.1 equiv), *p*-methoxyphenylboronic acid (20 mg, 0.13 mmol, 1.1 equiv), and $Pd(PPh_3)_4$ (7 mg, 0.01 mmol, 5%). The reaction was stirred for 14 h at 45 °C; after chromatography on an SiO_2 preparative plate (CH_2Cl_2 as eluent), **18** (37 mg, 0.09 mmol, 81%) was obtained as white crystals. Full details are contained in the Supporting Information.