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Efficient coupling reactions of lithium alkynyl(triisopropoxy)borates with aryl halides: application to the antifungal terbinafine synthesis

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Abstract

Thermally stable lithium alkynyl(triisopropoxy)borates were reacted with several aryl halides in the presence of palladium catalysts to give the corresponding cross-coupling products in excellent yields. The present methodology has been successfully applied to the antifungal terbinafine synthesis.

Keywords: palladium; alkyne; antifungal agent; terbinafine.

The palladium-catalyzed cross-coupling reaction has become a powerful tool in synthetic organic chemistry. Tremendous development of the mechanistically related variants has drawn profit from mechanistic insights into these cross-coupling reactions.[1] In 1975, three different research groups reported independently that disubstituted acetylenes were synthesized by reaction of 1-alkynes with aryl halides in the presence of a palladium catalyst and an organic base such as diethyl amine.[2] The mechanism of these coupling reactions appears to involve oxidative addition of the aryl halide to palladium(0), followed by alkynylation of the intermediate organopalladium halide and reductive elimination to the disubstituted alkyne. A major problem with these reactions is the formation of the dimerized byproducts, 1,4-disubstituted-1,3-butadiynes.[3] In order to exclude such dimerization, modification of the alkynes to the alkynylmetallic species involving Mg, Cu, Zn, Sn, Si and B has been developed.[4] In 1978, Negishi reported that the 1-alkynyl group in lithium 1-hexynyl(tributyl)borate was selectively coupled with iodobenzene through a palladium-catalyzed addition–elimination sequence.[5] We thought that replacement of the alkyl (butyl) groups in lithium 1-hexynyl(tributyl)borate by alkoxy (isopropoxy) groups could provide even more efficient alkynyl transfer reagents due to their thermal stability as well as their reactivity. Here we wish to report our preliminary results on

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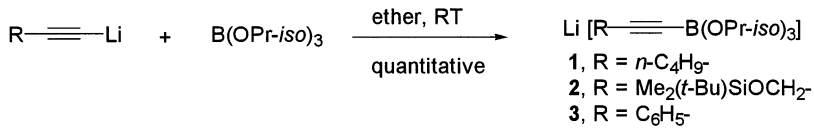
cross-coupling reactions of lithium 1-alkynyl(triisopropoxy)borates with a variety of enones and aryl halides.[6]

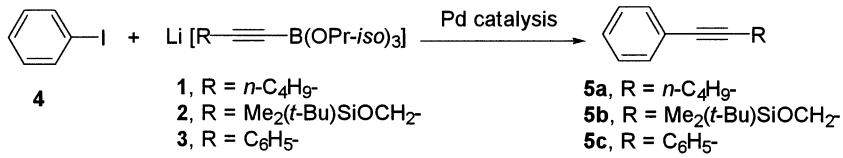
Treatment of commercially available triisopropoxyborane with alkynyllithiums at 0°C, generated in situ from 1-alkynes plus *n*-butyllithium in ether, yielded lithium 1-alkynyl(triisopropoxy)borates as white precipitates, which were filtered and dried under reduced pressure. The characterization of lithium 1-alkynyl(triisopropoxy)borates was confirmed by ^{1}H NMR.[7] These compounds were quite stable in a refrigerator for several months.



Next, we investigated cross-coupling reactions of these lithium 1-alkynyl(triisopropoxy)borates with iodobenzene under various catalytic conditions as summarized in Table 1.

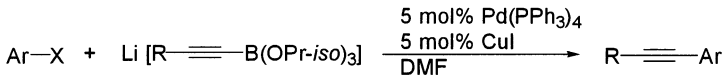
The following results could be drawn from these data. First, all three lithium 1-alkynyl(triisopropoxy)borates were reacted with iodobenzene in the presence of a palladium catalyst to give the coupled products without formation of any dimerized byproducts. Second, concurrent use of a palladium compound and copper(I) iodide as a cocatalyst dramatically improved the reaction efficiency, although the exact role of copper iodide is not clear. These coupling reactions in various other solvents such as dichloromethane, THF, 1,4-dioxane, toluene and acetonitrile did occur in moderate yields. As a result, we could choose the optimal conditions for these coupling reactions: a mixture of $Pd(PPh_3)_4$ and CuI as a cocatalyst and DMF as an optimal solvent. We then applied these conditions to a wide variety of aryl halides. The results are summarized in Table 2.

Table 1
Coupling reactions of iodobenzene with lithium 1-alkynyl(triisopropoxy)borates in DMF



	Borates	Catalyst	Temp (°C)	Time (h)	Products	Yield (%)
1	**1**	No catalyst	60	4	**5a**	0
2		5 mol% $Pd(OAc)_2$	60	4		59
3		5 mol% $Pd_2(dba)_3$	60	4		74
4		5 mol% $Pd_2Cl_2(\pi\text{-}C_3H_5)_2$	60	4		79
5		5 mol% $Pd(PPh_3)_4$	60	2		53
6		5 mol% $Pd(PPh_3)_4$, 5 mol% CuI	80	2		88
7		5 mol% $PdCl_2(PPh_3)_2$	60	4		47
8		5 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI	60	4		93
9	**2**	5 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI	60	5	**5b**	57
10		5 mol% $Pd(PPh_3)_4$, 5 mol% CuI	60	5		75
11	**3**	5 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI	60	15	**5c**	86
12		5 mol% $Pd(PPh_3)_4$, 5 mol% CuI	60	15		94

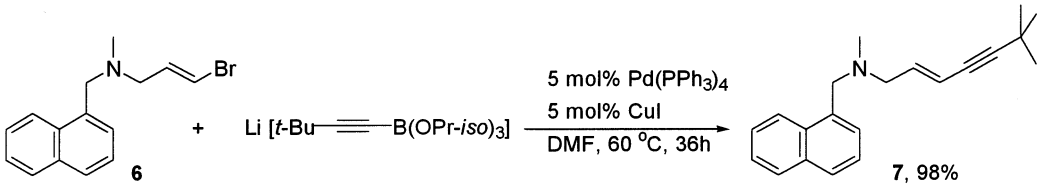
Table 2
Coupling reactions of lithium 1-alkynyl(triisopropoxy)borates with aryl halides in DMF



	Ar-X	R	Temp (°C)	Time (h)	Yield (%)
1	$(4\text{-}NO_2)C_6H_4I$	$n\text{-}C_4H_9$–	rt	24	74
2	$(4\text{-}NO_2)C_6H_4I$		80	5	97
3	$(4\text{-}CH_3)C_6H_4I$		80	5	97
4	$(2\text{-}CH_3)C_6H_4I$		80	20	80
5	$(4\text{-}CH_3O)C_6H_4Br$		80	20	90
6	$2,4,6\text{-}(CH_3O)_3C_6H_2I$		80	48	27
7	C_6H_5Br		60	10	73
8	$(4\text{-}CH_3)C_6H_4I$	$Me_2(t\text{-}Bu)SiOCH_2$–	60	24	67
9	$(2\text{-}CH_3)C_6H_4I$		60	24	55
10	$(4\text{-}CH_3O)C_6H_4Br$		80	5	34
11	C_6H_5Br		60	10	50
12	$(4\text{-}NO_2)C_6H_4I$	C_6H_5–	60	15	98
13	$(4\text{-}CH_3)C_6H_4I$		rt	24	90
14	$(2\text{-}CH_3)C_6H_4I$		60	15	96

The alkynylborate **1** was reacted with electronically and sterically diverse arylhalides to give the coupling products. Electron poor aryl halide, 1-iodo-4-nitrobenzene, was relatively labile toward these conditions (entries 1, 2), while electron-rich aryl halide, 4-bromoanisole, required a higher reaction temperature to complete coupling. Particularly, highly electron-rich aryl iodide, 2,4,6-trimethoxyiodobenzene, was not completely consumed even within a prolonged period of time (entry 6). The alkynylborates **2** and **3** were also reacted with aryl halides to yield the corresponding coupling products without formation of any byproducts, respectively. Bromobenzene was shown to be inferior to iodobenzene, since it required a longer reaction time (entries 7 and 11). It should be noted that these coupling reactions were slightly slowed down with sterically congested aryl halides. For example, 2-iodotoluene was coupled with the borates **1** and **2** to give the corresponding coupling products in 80 and 55% yields, while 4-iodotoluene gave the products in 90 and 67% yields, respectively. Again, while 4-iodotoluene was almost completely coupled with the borate **3** even at room temperature, 2-iodotoluene required heating for complete coupling. It is important to note from these data that the present method worked cleanly to prepare the corresponding arylalkynes from aryl iodides without formation of any byproducts.

This method was applied to the short preparation of an antifungal agent, terbinafine. Terbinafine contains the (*E*)-1,3-enyne structural moiety and exhibits strong antimycotic activity and is currently used for the treatment of skin mycoses.[8] Several syntheses have been described based on the Pd-catalyzed Stille coupling of an (*E*)-vinyl iodide with an alkynyl tin and the Sonogashira coupling of an (*E*)-vinyl chloride with *tert*-butylacetylene.[9]



We have treated the vinyl bromide **6** with *tert*-butylethynyl(triisopropoxy)borate under the above conditions. As expected, the desired terbinafine (**7**) was obtained in 98% isolated yield, implying that this present method could provide an alternative for Stille-, Sonogashira-, and Suzuki reactions.

A typical experimental procedure is as follows. In a 5 ml test tube were placed lithium *tert*-butylethynyl(triisopropoxy)borate (116.5 mg, 0.42 mmol), $Pd(PPh_3)_4$ (12.8 mg, 0.011 mmol), CuI (2.1 mg, 0.011 mmol), and then dry DMF (1.0 ml). The mixture in the test tube was purged with a slow stream of dry argon for 5 min and then treated with a solution of the halide **6** (61.1 mg, 0.21 mmol) in DMF (1.0 ml) via cannula. The resultant mixture was stirred for 36 h at 60°C, and then cooled to room temperature. Extractive workup and silica gel chromatography of the residue afforded the pure terbinafine (**7**, 60.0 mg, 98%) as a colorless liquid.[10]

In summary, we have shown that three thermally stable lithium 1-alkynyl(triisopropoxy)borates **1**–**3** were reacted with several aryl halides in the presence of palladium–copper catalysts to give the corresponding cross-coupling products in excellent yields. The present methodology has been successfully applied to the antifungal terbinafine synthesis.

Acknowledgements

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References

1. (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley & Sons, Inc.: New York, 1998. (d) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985.
2. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253–257. (c) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259–263.
3. Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 129–160.
4. Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp. 521–549.
5. Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p. 285.
6. (a) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634. (b) Negishi, E.; Lew, G.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 874–875. (c) Molander, G. A.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 3106–3108.
7. **1**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.02 (sept, $J=6.0$ Hz, 3H), 2.19 (td, $J=6.6$ Hz, 2.0 Hz, 2H), 1.61–1.30 (m, 4H), 1.21 (d, $J=6.1$ Hz, 18H), 0.92 (t, $J=7.0$ Hz, 3H); **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (s, 2H), 4.00 (sept, $J=6.0$ Hz, 3H), 1.20 (d, $J=6.1$ Hz, 18H), 0.90 (s, 9H), 0.12 (s, 6H); **3**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54–7.28 (m, 5H), 4.03 (sept, $J=6.0$ Hz, 3H), 1.21 (d, $J=6.1$ Hz, 18H).
8. Stütz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320–328.
9. (a) Rudisill, D. E.; Castonguay, L. A.; Stille, J. K. *Tetrahedron Lett.* **1988**, *29*, 1509–1512. (b) Alami, M.; Ferri, F.; Gaslain, Y. *Tetrahedron Lett.* **1996**, *37*, 57–58. (c) Kim, G.-C.; Seo, M.-J. *Bull. Kor. Chem. Soc.* **1995**, *16*, 1002–1003.
10. Satisfactory spectral data were obtained for all compounds.