

Alkoxydienes via Copper-Promoted
Couplings: Utilizing an Alkyne Effect

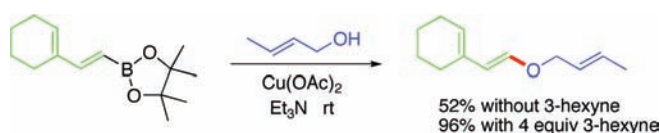
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ABSTRACT



Simple alkenes and alkynes, with 3-hexyne in particular, are found to be important π ligands for oxidative copper-based coupling (modern Ullmann) reactions. This enabled syntheses of various alkoxydienes with removable protecting groups that are valuable substrates for Diels–Alder reactions from alcohols and vinyl boronate esters. In addition to demonstrating that 3-hexyne is a ligand for copper in both stoichiometric and catalytic reactions, the reaction atmosphere was found to play a critical role.

Copper-mediated coupling reactions have emerged as important methods for C–O and C–N bond formation in recent years.¹ Major advances have been reported in both the classic Ullmann process employing aryl or vinyl halides as the electrophilic coupling partners² and the modern Ullmann coupling (oxidative) employing aryl or vinyl boronic acids.³ We recently reported a copper-promoted coupling of vinyl boronate esters and alcohols as an efficient method for the synthesis of vinyl ethers.⁴ One application of this chemistry is the synthesis of allyl vinyl ether substrates for Claisen rearrangements, and another application is the synthesis of alkoxydienes for

utilization as electron-rich dienes in Diels–Alder reactions. A general direct method to synthesize alkoxydienes would prove immensely useful. Deprotectable alkoxydienes are of even greater utility, which led us to choose 2-chloroethanol and 2-(trimethylsilyl)ethanol as suitable alcohols to couple with dienyl boronates. The resulting activated dienes can be easily deprotected after use in Diels–Alder reactions via addition of a metal(0)⁵ or fluoride source.⁶ We report herein realization of a mild alkoxydiene synthesis and the discovery of novel ligand effects in copper-mediated cross couplings.

Coupling of dienyl boronate **1** with 2-chloroethanol at rt in the presence of 2 equiv of cupric acetate and 4 equiv of triethylamine gave only a 35% yield of alkoxydiene **2a**. That being unacceptable, we sought to improve upon our initial reported copper coupling conditions by examining ligand effects that have been so critically important for recent improvements² in the classic Ullmann process. Screening phosphorus-based ligands identified tri-2-furylphosphine as a promising ligand as it provided a significant improvement to 60% (Table 1).

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








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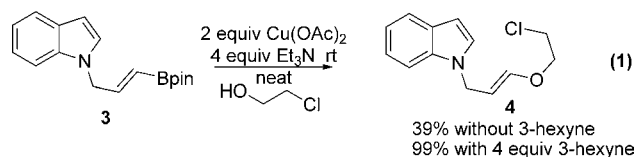
Table 1. Ligand Screening Yields

Reaction scheme for Table 1: **1** (cyclohexene derivative with Bpin) reacts with 2 equiv Cu(OAc)₂, 4 equiv Et₃N, and 4 equiv ligand in neat 2-chloroethanol to form **2a** (cyclohexene derivative with OCH₂CH₂Cl).

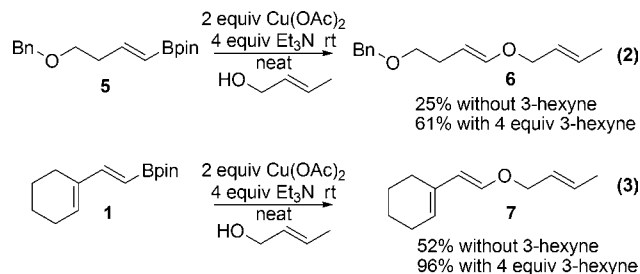
phosphines	alkenes	alkynes
No Ligand 35%	 0%	 50%
P(OPh) ₃ 14%	 34%	 62%
P(Ph) ₃ 33%	 39%	TMS-C≡C-TMS 70%
P(Bu) ₃ 33%	 45%	 64%
P(2-furyl) ₂ 60%	 59%	 80%

Our initial studies indicated that allyl alcohol was a particularly effective alcohol partner in the coupling reaction, resulting in yields higher than those using ethanol or propanol. Experiments with substituted ethyl alcohols suggested that this was not an inductive electronic effect, so we postulated that the alkene might be functioning as a π -Lewis base to copper.⁷ That indeed is the case as born out by the effect of alkene additives shown in Table 1. Interestingly, benzoquinone or dimethyl fumarate additives gave negative results, but in striking contrast to all other cases. Not only was no product formed, but the boronate ester was completely consumed and only protodeboration was detected. Electron-rich dihydropyran had no impact on coupling yield. Ring strain increased Lewis basicity⁸ as demonstrated with norbornene, which gave a 68% yield. However, alkynes were the best ligands, with 3-hexyne boosting the yield to 80%.

The 3-hexyne ligand effect was corroborated in coupling **3** with 2-chloroethanol, wherein the yield of **4** increased from 39% to 99% (eq 1).



The alkyne effect is also applicable to couplings involving other alcohols, such as crotyl alcohol (eq 2 and 3), wherein yields were nearly or more than doubled:



Although copper-alkyne complexes have been reported,⁹ this is, to the best of our knowledge, the first use of an alkyne ligand to increase the efficiency of an oxidative (modern Ullmann) coupling method.¹⁰

Several important copper-based coupling reactions have been discovered recently, in particular for C–N bond formation,¹ which we hypothesized may also benefit from this alkyne effect. To test this, coupling of phenylboronic acid with benzimidazole to yield **8** was chosen. We found that alkyne and also reaction atmosphere have a dramatic impact upon coupling yields (Table 2). 3-Hexyne was most effective in the absence of a pure oxygen environment.

Table 2. Atmosphere and 3-Hexyne Impact on C–N Couplings

Reaction scheme for Table 2: 2 equiv phenylboronic acid reacts with 1 equiv benzimidazole, 1.5 equiv Cu(OAc)₂, 4 equiv Et₃N, and molecular sieves in CH₂Cl₂ at room temperature to form **8** (N-phenylbenzimidazole).

	yield (%)	
	without 3-hexyne	with 4 equiv of 3-hexyne
argon	17	35
ambient	28	42
oxygen	90	87

Both alkyne ligand and reaction atmosphere impacted copper-promoted couplings of **1** and **5** with 2-chloroethanol (Table 3). In contrast to the results in Table 2, ambient atmosphere was optimal where again 3-hexyne was critical for the highest yields. Similar couplings of **1** and **5** with 2-bromoethanol showed drastically reduced yields, and no coupling occurred with 2-iodoethanol. These results suggest that a copper species is reacting with alkyl halides and the possibility that one of the functions of 3-hexyne is to moderate copper's reactivity toward alkyl chlorides.

One aspect of the alkyne ligand effect may involve complexing copper(I)⁹ byproducts resulting from both disproportionation and reductive elimination steps in the

(7) For a review on alkene and alkyne ligand effects on transition-metal-catalyzed cross-coupling reactions, see: Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

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(10) There is a primary report of alkynes promoting a copper-catalyzed coupling of Grignard reagents and alkyl halides: Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086. See also: Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545.

Table 3. Atmosphere and 3-Hexyne Impact on C–O Couplings

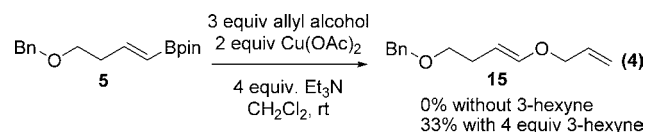
atmosphere	without 3-hexyne	with 4 equiv 3-hexyne
ambient	53%	93%
oxygen	56%	54%

atmosphere	without 3-hexyne	with 4 equiv 3-hexyne
ambient	35%	80%
oxygen	46%	28%

postulated mechanism.^{4,11} Calculations indicate copper(I) to be a better π -Lewis acid than copper(II),¹² and very recently a monomeric Cu(I) 3-hexyne complex was isolated and characterized.¹³ This might address the haloethanol results but may not be the only function of 3-hexyne. In analogy to calculations for gold(I) and gold(III) π -Lewis acidity,¹² copper(III), a key postulated intermediate resulting from disproportionation,¹¹ may also coordinate alkynes facilitating its formation and subsequent reductive elimination to copper(I).

With the reaction conditions optimized for copper-promoted coupling of pinacol vinyl boronates and functionalized alcohols, seven different alkoxydienes and two alkoxytrienes were prepared (Table 4). The 3-hexyne ligand was beneficial in every instance, although the magnitude of change was not always the same.

Further refinements in the coupling are necessary for an ideal process as alcohol partners are utilized as solvent and 2 equiv of Cu(OAc)₂ are used. Attempts to couple **5** with only 3 equiv of allyl alcohol in CH₂Cl₂ failed, but adding 3-hexyne ligand promoted the reaction, albeit in only 33% yield (eq 4).

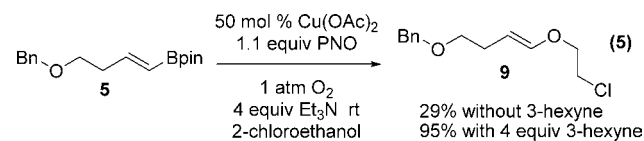


An even more dramatic 3-hexyne effect was seen in a test catalytic reaction. Coupling of **5** with 2-chloroethanol using 50 mol % of Cu(OAc)₂ and pyridine *N*-oxide under an oxygen atmosphere resulted in only a 29% yield of vinyl ether **9** (eq 5). In the presence of 4 equiv of 3-hexyne, the

Table 4. Synthesis of Alkoxydienes

yield (%)			yield (%)		
product	without 3-hexyne	with 4 equiv 3-hexyne	product	without 3-hexyne	with 4 equiv 3-hexyne
2a	35	80	2b	57	80
10a	43	69	10b	0	57
11a	46	56	11b	61	81
13	60	68	12	46	54
			14	34	37

yield jumped to 95%, thus providing significant promise for development of a catalytic process. These catalytic reaction conditions did not uniformly produce yields superior to the stoichiometric conditions, thus the latter were employed for the current studies delineating the ligand effects.



In conclusion, we found that simple alkenes and alkynes, with 3-hexyne in particular, can be important π ligands for oxidative copper-based coupling reactions. These results enabled syntheses of various alkoxydienes with removable protecting groups that are valuable substrates for Diels–Alder reactions. We also found that the 3-hexyne ligand was critical for improved modifications, such as catalytic reactions, of the copper-promoted coupling of alcohols and vinyl boronate esters. Finally, even in the presence of excess Cu(OAc)₂, the reaction atmosphere plays a critical role.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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