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Unexpected Copper(II) Catalysis: Catalytic Amine Base Promoted β-Borylation of α,β-Unsaturated Carbonyl Compounds in Water

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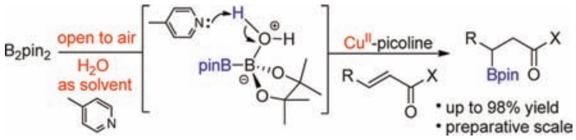
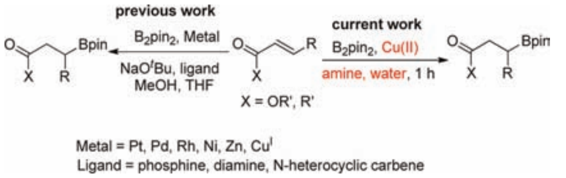
ABSTRACT



Using bis(pinacolato)diboron, catalytic amounts of Cu^{II}, and various amine bases in water under atmospheric conditions at rt, acyclic and cyclic α,β-unsaturated ketones and esters are β-borylated in up to 98% yield. Mechanistic investigations using UV−vis spectroscopy, ^{11}B NMR, and solvent kinetic isotope effect suggest that the role of the amine is not only to coordinate to Cu^{II} but also to activate a nucleophilic water molecule to form the reactive sp^2-sp^3 diboron complex.

Preparation of organoboronic acids and their derivatives remains an active area of intense research because of their functional group tolerance and remarkable versatility to be converted into a wide variety of functional groups.[1] In particular, the Suzuki−Miyaura cross-coupling (SMC) reaction provides a convenient route to construct difficult C−C bonds. Although the use of SMC has become ubiquitous, the cross-coupling of sp^3 carbon centers remains a challenge. Recent advances in this field include stereospecific cross-coupling of secondary benzylic boronates,[2] α-(acylamino)-benzylboronic esters,[3] nonbenzylic alkyl β-trifluoroboratohomoenolates,[4] and alkyl-1,1-diboron compounds.[5] Indeed, methods to prepare alkylboronic acid SMC substrates are necessary to access increasingly more complex molecules. Two approaches currently exist for α,β-unsaturated carbonyl compounds: organometallic conjugate addition to β-borylated compounds[6] and transition metal-catalyzed borylation.[7] Among the transition metal-catalyzed methods, the Cu^I-catalyzed conjugate borylation of electron deficient olefins has garnered significant attention (Scheme 1).

Scheme 1. Metal Catalyzed Conjugate Borylation Approaches



Building on the pioneering work of Hosomi[8] and Miyaura,[9] Yun expanded the scope of substrates from unsaturated

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(1) (a) Hall, D. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH GmbH & Co.: Weinheim, 2011. (b) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704–6716.

(2) Imao, D.; Glasspoole, B. W.; Laberge, V. r. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.

(3) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193.

(4) (a) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108–17110. (b) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795–1798.

(5) Lee, J. C.; McDonald, R.; Hall, D. G. *Nat. Chem* **2011**, *3*, 894–9.

(6) Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544–5545.

(7) (a) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194–1196. (b) Bonet, A.; Sole, C.; Gulyas, H.; Fernandez, E. *Curr. Org. Chem.* **2010**, *2*, 2531–2548. (c) Mantilli, L.; Mazet, C. *ChemCatChem* **2010**, *2*, 501–504.

(8) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825.

(9) (a) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 126–127. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47–53.

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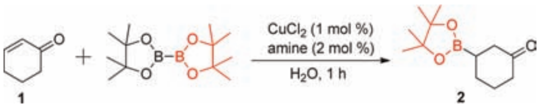
ketones and esters to include more challenging α,β-unsaturated amides.[10] Catalytic asymmetric variants as well as metal-free conditions have also been developed.[7a,11] Although other transition metals (Pt,[12] Pd,[13] Rh,[14] Ni,[15] and Zn[16]) were effective as catalysts, Cu^I-catalyzed reports dominate the literature in part because copper is an inexpensive metal and its reactivity can be tuned by altering the ligands. Bis(pinacolato)diboron (B_2pin_2) is widely used as the boron source in a majority of reports; however, other reagents such as pinacolatodiisopropanolaminatodiboron[17] and tetrahydroxydiborane[18] can be used as alternatives.

Despite the great number of reports detailing the installation of boron on the β-carbon of an α,β-unsaturated carbonyl, most reaction conditions have disadvantages: some are uneconomical (employing expensive ligands and a high catalyst loading), others are harsh (strong base such as *tert*-butoxide is required), and more importantly, the reactions are air-sensitive, often requiring the use of a glovebox or Schlenck techniques. Thus, there is a need for a more efficient and convenient method for the synthesis of alkylboronic acids. Herein we report an amine base promoted β-borylation protocol of α,β-unsaturated carbonyls in water and open to air. In addition, we demonstrate the first Cu^{II}-catalyzed β-borylation reaction and provide mechanistic insight to the efficient borylation reaction.

Previous work in our laboratory[17]established that complexation of B_2pin_2 by a Lewis base is necessary for the *in situ* formation of an activated diboron.[19] Hence, we began our investigation by screening suitable additives that can affect the borylation reaction in water without any organic cosolvent.[20] Preliminary studies indicated that amine bases are inefficient in catalyzing the β-borylation reaction in organic solvents in the presence of copper. Surprisingly, we found that addition of a catalytic amount of inexpensive, commercially available amines allowed the efficient conversion of 2-cyclohexenone **1** to the corresponding boratohomoenolate **2** in the presence of $CuCl_2$ in water (Table 1).

Table 1. Screening of Additives and Reaction Conditions[a]



entry	base additive	conv %[b]
1	benzylamine	98.2
2	piperidine	96.6
3	triethylamine	95.0
4	TMEDA	98.2
5	DBU	95.6
6	pyridine	98.1
7	4-picoline	>99.9
8	3-picoline	98.4
9	2,6-lutidine	97.5
10	DMAP[c]	99.8
11	imidazole	97.8
12	quinoline	76.9
13	2,2′-bipyridine[c]	17.7
14	proton sponge	99.8
15	none	20.3
16	4-picoline	42.9 (0[d])
17	sodium acetate	86.0
18	sodium hydroxide	86.0

[a] Reaction conditions: B_2pin_2 (1.1 equiv), 2-cyclohexen-1-one (1.0 equiv), and amine (2 mol %) were added to a 1-dram, PTFE vial with a magnetic stir bar. 1.5 mL of a stock $CuCl_2$ (1.72 mM) solution in water was added and stirred vigorously for 1 h at rt. [b] Conversions determined by GC analysis. [c] Amine was dissolved in THF before addition. [d] In the absence of $CuCl_2$ using nuclease-free or Milli-Q water.

In marked contrast to Cu^I-catalyzed β-borylation in organic solvents,[9b,10,11,11f,17a,17c,18,21] the current protocol is most efficient with a Cu^{II} source (*vide infra*).[22] Cu^{II} salts are especially convenient because of their high solubility in water and resistance to oxidation upon exposure to air. Gratifyingly, we found that a variety of primary, secondary, and tertiary aliphatic amines provided excellent conversion to **2** (entries 1–4). Use of a strong base was also effective (entry 5). Heteroaromatic amines performed better on average than aliphatic amines, with 4-picoline giving the highest conversion (entries 6–11). Quinoline showed decreased activity, likely due to decreased solubility in water (entry 12). On the other hand, 2,2′-bipyridine gave a significantly lower conversion, possibly as a result of

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(10) Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889.

(11) (a) Lee, J. E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. (b) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2008**, *28*, 659–662. (c) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665. (d) Lillo, V.; Bonet, A.; Fernandez, E. *Dalton Trans.* **2009**, 2899–2908. (e) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–5. (f) Bonet, A.; Gulyas, H.; Fernandez, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130–4.

(12) (a) Lawson, Y. G.; Lesley, M. J. G.; Norman, N. C.; Rice, C. R.; Marder, T. B. *Chem. Commun.* **1997**, 2051–2052. (b) Abu Ali, H.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962–3965. (c) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Baucherel, X.; Tulloch, A. A. D.; Tooze, R. P. *Chem. Commun.* **2004**, 1854–1855.

(13) Bonet, A.; Gulyás, H.; Koshevoy, I. O.; Estevan, F.; Sanaú, M.; Úbeda, M. A.; Fernández, E. *Chem.—Eur. J.* **2010**, *16*, 6382–6390.

(14) (a) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323–2325. (b) Shiomi, T.; Adachi, T.; Toribatake, K.; Zhou, L.; Nishiyama, H. *Chem. Commun.* **2009**, 5987–5989.

(15) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5031–5033.

(16) Kajiwara, T.; Terabayashi, T.; Yamashita, M.; Nozaki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6606–6610.

(17) (a) Gao, M.; Thorpe, S. B.; Santos, W. L. *Org. Lett.* **2009**, *11*, 3478–3481. (b) Thorpe, S. B.; Guo, X.; Santos, W. L. *Chem. Commun.* **2011**, *47*, 424–426. (c) Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3997–4007.

(18) Molander, G. A.; McKee, S. A. *Org. Lett.* **2011**, *13*, 4684–4687.

(19) Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulyás, H.; Fernández, E. *Chem.—Eur. J.* **2012**, *18*, 1121–1126.

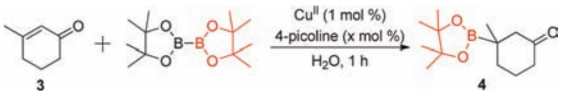
(20) Chea, H.; Sim, H. S.; Yun, J. *Bull. Korean Chem. Soc.* **2010**, *31*, 551–552.

(21) (a) Chea, H.; Sim, H. S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855–858. (b) Sim, H.-S.; Feng, X.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 1939–1943. (c) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982–983. (d) Fleming, W. J.; Muller-Bunz, H.; Lillo, V.; Fernandez, E.; Guiry, P. J. *Org. Biomol. Chem.* **2009**, *7*, 2520–4. (e) Chen, I. H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098–4101. (f) Feng, X.; Yun, J. *Chem. Commun.* **2009**, 6577–6579. (g) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008–5011.

(22) During the submission of this manuscript, $Cu(OTf)_2$ was reported as a catalyst: Ibrahem, I.; Breistein, P.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12036–12041.

rigid bidentate binding to copper (entry 13).[23] A proton sponge also provided excellent conversion (entry 14). As expected, the reaction was sluggish in the absence of amine or copper (entries 15−16). As shown in entry 16, when the reaction was run using in-house deionized water, a background conversion of 43% resulted, suggesting a possibility of transition-metal-free reaction. However, analysis of the deionized water revealed 40 ppb Cu by ICP-MS, an indication that a minute level of copper is capable of catalyzing the transformation.

Table 2. Screening of Copper Sources and Stoichiometry[a]

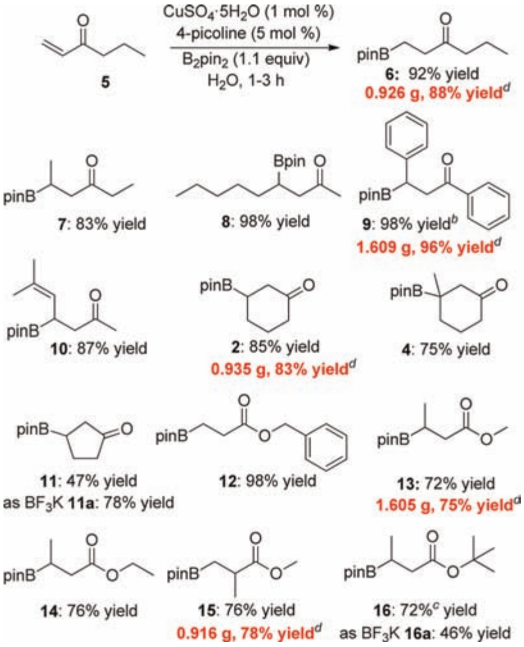


entry	Cu source	4-picoline (mol %)	conv %[b]
1	$CuCl_2$	2%	<1
2	$CuCl_2$	5%	72.8
3	$CuSO_4$	2%	39.9
4	$CuSO_4$	5%	89.5
5	$Cu(OAc)_2$	5%	84.0
6	$Cu(BF_4)_2$	5%	78.3
7	CuCl	5%	77.4
8	$CuSO_4$[c]	5%	33.5

[a] Reaction conditions identical to Table 1. [b] Conversion determined by GC analysis. [c] With 20 mol % sodium ascorbate.

Although many amines participate as good additives, we chose 4-picoline for further optimization since it gave the highest conversion. When a more sterically demanding substrate, 3-methylcyclohexenone (**3**), was used (Table 2), the desired product **4** was only observed in good conversion with 1:5 Cu/amine stoichiometry (compare entry 1 vs 2). A further survey of copper sources revealed that a more water-soluble $CuSO_4$ resulted in excellent conversion and that other copper(II) sources were also effective (entries 3−6). We were surprised to discover that Cu^{II} was an effective borylation catalyst since, to the best of our knowledge, only Cu^{I} catalyst systems have been reported. To investigate the Cu^{II} catalysis, the reaction was run with CuCl with good conversion (entry 7); however, this result is misleading because Cu^{I} disproportionates (to Cu^{0} and Cu^{II}) in water and provides a Cu^{II} source.[24] To further confirm that Cu^{I} is not the active catalyst, $CuSO_4$ was reduced in situ to Cu^{I} in the presence of excess sodium ascorbate.[25] As expected, the conversion decreased; however trace Cu^{II} is likely still present that is capable of catalyzing the reaction (*vide supra*) because of the fast oxidation of Cu^{I} by molecular oxygen (entry 8).[26] Taken together, these studies suggest that Cu^{II} is the active catalyst under aqueous conditions and that Cu^{II} may be the active catalyst for reactions run under organic solvents.

Scheme 2. Cu^{II}-Catalyzed Boryl Conjugate Addition with Acyclic and Cyclic α,*β*-Unsaturated Ketones and Esters[a]



[a] Reaction conditions: B_2pin_2 (1.1 equiv), **1** (1.0 equiv), and 4-picoline (0.05 equiv) were added to a 5 mL round-bottomed flask with a magnetic stir bar. $CuSO_4$ (1 mol %) dissolved in 3 mL of deionized water was added, and the reaction was stirred vigorously for 1−3 h at rt. [b] Chalcone was dissolved in minimal THF before addition. [c] NMR yield. [d] Preparative scale.

With the optimized conditions in hand (Table 2, entry 4), we explored the scope and limitations of this reaction with a variety of α,*β*-unsaturated carbonyl compounds (Scheme 2). For example, borylated acyclic ketones **6**−**9** were synthesized in good to excellent yield (up to 98% isolated yield). Furthermore, a conjugated dienone was regiospecifically borylated on the *β*-position to afford **10**. Cyclic enones (**2**, **4**, and **11**) were also readily transformed in good yields; cyclopentenone resulted in a moderate yield as the pinacol ester **11**, but conversion to the trifluoroborate salt **11a** significantly improved the isolated product yield. To our delight, α,*β*-unsaturated esters also generated borylated products in good to excellent yields (**12**−**15**). A limitation of the reaction is evident with *tert*-butyl crotonate (**16**), which afforded the product in only 46% yield as the potassium trifluoroborate salt **16a**. To demonstrate the practical utility of the developed protocol, we performed reactions on a preparative scale. Indeed, the borylated products (**2**, **6**, **9**, **13**, and **15**) were efficiently formed in yields within experimental error of the small scale version. Moreover, the products in Scheme 1 were isolated by

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(23) Ozutsumi, K.; Kawashima, T. *Inorg. Chim. Acta* **1991**, *180*, 231–238.

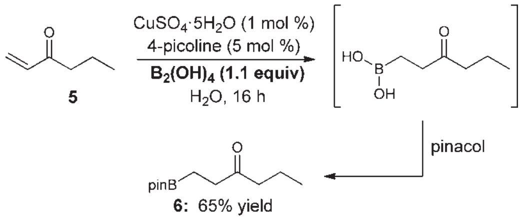
(24) A distinct difference in the physical appearance of the copper sources was observed. For example, a gray/black precipitate appeared with CuCl while $CuSO_4$ was a homogeneous pale blue solution.

(25) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–9. (b) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193.

(26) Martell Arthur, E. Chelates of Ascorbic Acid. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; American Chemical Society: 1982; Vol. 200, pp 153−178.

simple extraction (except for water-soluble **11**) because the alkene starting materials were consumed and any excess B_2pin_2 decomposed into water-soluble pinB-OH. Although the current conditions cannot yet be extended to α,*β*-unsaturated amides, tetrahydroxydiborane as the boron source provided a moderate yield of **6** upon treatment with pinacol (Scheme 3).

Scheme 3. Two-Step Borylation–Protection with Tetrahydroxydiborane



To gain insight into the effect of an amine base on the Cu^{II}-catalyzed reaction in water, we performed ^{11}B NMR experiments at 4 °C (Figure 1). Investigation in neat 4-picoline suggests that the amine does not participate in Lewis acid–base coordination because a single boron chemical shift is observed at 31 ppm, indicative of uncomplexed B_2pin_2 (Figure 1A). This result is not surprising since B_2pin_2 is sterically hindered, and 4-picoline has only been observed to coordinate with more Lewis acidic bis(catecholato)diboron.[27] Furthermore, when water[28] was used as the NMR solvent, only B_2pin_2 and its decomposition product, pinBOH (confirmed by independent synthesis), were detected (Figure 1B and 1C). To ensure that pinBOH was not a reactive intermediate, the procedure was performed using pinBOH as the boron source, and no product was detected (Scheme 4). UV–vis measurements with increasing stoichiometry of 4-picoline/Cu^{II} revealed the expected coordination of amine to copper; i.e., successive coordination of 4-picoline to copper results in a blue shift in the spectrum (see Supporting Information (SI)).[29] We also determined that the reaction was efficient when the amine was exchanged with NaOAc, NaOH, and the noncoordinating proton sponge (Table 1, entries 14, 17–18). Furthermore a solvent kinetic isotope effect (H_2O vs D_2O) of 1.9 was determined, suggesting a possible deprotonation in the rate determining step (see SI).[30] On the basis of these observations, it is plausible to suggest that the role of the amine is twofold: (1) to form a stable 4-picoline-Cu^{II} complex and/or (2) to act as a Bronsted base to activate a nucleophilic water molecule and generate, *in situ*, an sp^2–sp^3 diboron that is capable of transmetalation with copper (Figure 2). The resulting 'borylcopper' species then undergoes boryl conjugate addition.

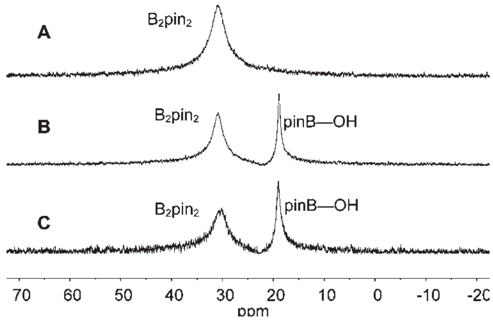
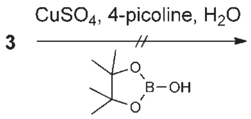


Figure 1. ^{11}B NMR spectra of B_2pin_2 in (A) 4-picoline, (B) water, and (C) water with 4-picoline (1.0 equiv) at 4 °C.

Scheme 4. Pinacol Boronic Acid: Not the Boron Source



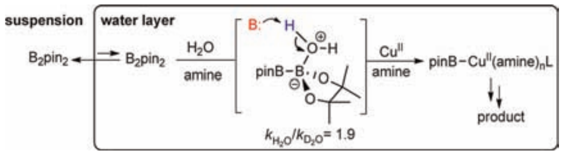


Figure 2. Proposed mechanism.

In conclusion, we have developed an efficient and practical catalytic method for the preparation of alkylboronates in good to excellent yields (up to 98%). To the best of our knowledge, this is the first report of a Cu^{II}-catalyzed method for this reaction using water as the solvent and open to air. We also provided evidence for the role of catalytic amine in the mechanism of the reaction. Further extension and application of this method is currently underway.

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Supporting Information Available. Experimental details and spectral data of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(27) (a) Clegg, W.; Dai, C. Y.; Lawlor, F. J.; Marder, T. B.; Nguyen, P.; Norman, N. C.; Pickett, N. L.; Power, W. P.; Scott, A. J. *Dalton Trans.* **1997**, 839–846. (b) Clegg, W.; Elsegood, M. R. J.; Lawlor, F. J.; Norman, N. C.; Pickett, N. L.; Robins, E. G.; Scott, A. J.; Nguyen, P.; Taylor, N. J.; Marder, T. B. *Inorg. Chem.* **1998**, *37*, 5289–5293.

(28) Water has been used as a reaction medium with B_2pin_2: Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842–7848.

(29) Leussing, D. L.; Hansen, R. C. *J. Am. Chem. Soc.* **1957**, *79*, 4270–4273.

(30) We could not exclude a rate determining protonation step of Cu-enolate when performed in organic solvent (see ref 10), which has been supported by theoretical calculation: Dang, L.; Lin, Z. Y.; Marder, T. B. *Organometallics* **2008**, *27*, 4443–4454.