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Asymmetric Catalysis

# Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to α,β-Unsaturated Carbonyl Compounds in Water**

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Organic reactions are usually carried out in organic solvents in modern organic chemistry, and it is very rare to use water as the reaction medium despite water being safe, benign, environmentally friendly, and inexpensive compared with organic solvents.[1] In organic reactions in aqueous media, there are two major obstacles to be surmounted. First, many reactive substrates, reagents, and catalysts are decomposed or deactivated by water. Second, most organic substances are insoluble in water. On the other hand, we have investigated organic reactions in water from the standpoint that the most ideal reactions, enzymatic reactions in vivo, are carried out in water, and have found unique reactivity and selectivity in aqueous media, which are not observed in organic solvents where water plays key roles.[2]

α-Chiral boron derivatives are an important class of compounds, because the C−B linkage can be transferred into C−O, C−N, and C−C bonds through 1,2-migration of intermediary ate complexes with appropriate nucleophiles, with retention of stereogenic centers.[3] Enantioselective boron conjugate addition to α,β-unsaturated carbonyl and related compounds provides one of the most efficient routes to α-chiral boron compounds. Based on seminal reports of $\mathrm{Cu^I}$-catalyzed conjugate borylation,[4] Yun et al. reported an enantioselective method for $\mathrm{Cu^I}$-catalyzed conjugate borylation.[5] After that, several catalytic asymmetric borylations using $\mathrm{Cu^I}$ with chiral ligands were reported.[6] Furthermore, other metal-catalyzed[7] and metal-free[8] enantioselective boron conjugate additions to α,β-unsaturated carbonyl and related compounds have also been reported. In all of those cases, the reactions were carried out in organic solvents, and to the best of our knowledge, there has been no report of this conjugate addition in water.[9]

In previous papers, we have shown that addition reactions of allylboronates and allenylboronates to aldehydes and acylhydrazones proceeded smoothly in the presence of metal hydroxides such as $\mathrm{Zn(OH)_2}$, $\mathrm{Cu(OH)_2}$, $\mathrm{Bi(OH)_3}$, and others in aqueous media.[10] In these reactions, metal hydroxides that had not been used as catalysts in organic synthesis were shown to be suitable and stable catalysts in aqueous media, and that exchange processes from boron to the second elements were crucial to promote the reactions. Based on a hint obtained from this work, we assumed a similar exchange process from the B atom of bis(pinacolato)diboron ($\mathrm{B_2(pin)_2}$) to a second element. Herein, we report enantioselective boron conjugate additions to various α,β-unsaturated carbonyl compounds and nitrile in water catalyzed by $\mathrm{Cu(OH)_2}$ with a chiral ligand. Very rare chiral $\mathrm{Cu^{II}}$ catalysis in water is also described.[11,12]

First, we conducted the reaction of $\mathrm{B_2(pin)_2}$ with chalcone in water in the presence of several promising metal hydroxides that were expected to work well in water. It was found that some metal hydroxides worked well with ligands. For example, when $\mathrm{Cu(OH)_2}$ was combined with dibenzylamine (DBA), the desired 1,4-addition product **1a** was obtained in 88% yield (Table 1, entry 1). $\mathrm{Zn(OH)_2}$ showed inferior reactivity (entry 2). We then investigated several chiral ligands in an attempt to produce enantioselective reactions. Asymmetric catalysis in water is extremely difficult to achieve because many chiral catalysts decompose rapidly in the presence of water.[13] We have already investigated water-compatible Lewis acidic metals (cations), in which $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$ are involved.[14] We have also demonstrated that combinations of $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$ with chiral 2,2′-bipyridine ligand **L1**[15] were effective for enantioselective ring-opening reactions of *meso*-epoxides[12] and allylation reactions of aldehydes,[10b,d] respectively, in aqueous media. It was found that $\mathrm{Cu(OH)_2}$-**L1** showed very promising results; namely, the desired addition product was obtained in 83% yield with a 90.5:9.5 enantiomeric ratio (e.r.) in the presence of $\mathrm{Cu(OH)_2}$ (10 mol%) with **L1** (12 mol%) at RT in water for 12 h (entry 3). Whereas $\mathrm{Zn(OH)_2}$-**L1** showed lower yield and enantioselectivity (entry 4), combinations of $\mathrm{Cu(OH)_2}$ with chiral ligands **L2** and **L3** gave high yields with moderate enantioselectivities (entries 5 and 6). The use of water as a solvent is essential for reactivity and selectivity; the reactions did not proceed at all or proceeded very sluggishly in typical organic solvents such as THF, toluene, $\mathrm{CH_2Cl_2}$, DMF, DMSO, MeOH, and EtOH (entries 7–13). With 5 mol% catalyst loading, the enantioselectivity decreased slightly (entry 14). We then examined several reaction conditions to further improve the yield and the enantioselectivity, and found that some additives were effective for that purpose. Among them, the use of acetic acid (entry 16) or trifluoroacetic acid (entry 17) were found to be the most effective to improve both yield and enantioselectivity. Boronic acid was also effective as an additive (entry 19). Finally, the desired product was obtained in 95% yield with 99.5:0.5 e.r. when the reaction was conducted at 5 °C (entry 21). It was also confirmed that the product was isolated

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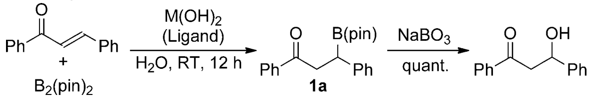
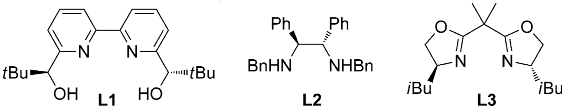
**Table 1:** Optimization of reaction conditions.[a]



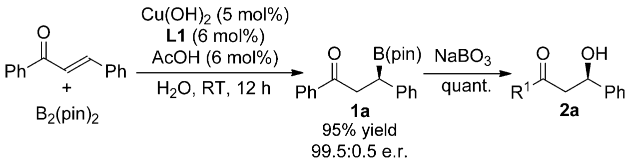
| Entry | M | Solvent | Additive | Ligand | Yield [%] | e.r. |
|---|---|---|---|---|---|---|
| 1 | Cu | $H_2O$ | – | DBA | 88 | – |
| 2 | Zn | $H_2O$ | – | DBA | 64 | – |
| 3 | Cu | $H_2O$ | – | **L1** | 83 | 90.5:9.5 |
| 4 | Zn | $H_2O$ | – | **L1** | 17 | 73:27 |
| 5 | Cu | $H_2O$ | – | **L2** | 79 | 68:32 |
| 6 | Cu | $H_2O$ | – | **L3** | 80 | 68.5:31.5 |
| 7 | Cu | THF | – | **L1** | NR | – |
| 8 | Cu | toluene | – | **L1** | NR | – |
| 9 | Cu | $CH_2Cl_2$ | – | **L1** | NR | – |
| 10 | Cu | DMF | – | **L1** | trace | – |
| 11 | Cu | DMSO | – | **L1** | NR | – |
| 12 | Cu | MeOH | – | **L1** | 17 | 64.5:35.5 |
| 13 | Cu | EtOH | – | **L1** | 1 | – |
| 14 | Cu | $H_2O$ | – | **L1** | 84 | 90:10 |
| 15 | Cu | $H_2O$ | pyridine | **L1** | 72 | 85:15 |
| 16 | Cu | $H_2O$ | AcOH | **L1** | 93 | 94.5:5.5 |
| 17 | Cu | $H_2O$ | TFA | **L1** | 93 | 93:7 |
| 18 | Cu | $H_2O$ | $PhCO_2H$ | **L1** | 86 | 90.5:9.5 |
| 19 | Cu | $H_2O$ | $H_3BO_3$ | **L1** | 94 | 93.5:6.5 |
| 20 | Cu | $H_2O$ | AcOK | **L1** | 90 | 90.5:9.5 |
| 21[b] | Cu | $H_2O$ | AcOH | **L1** | 95 | 99.5:0.5 |

[a] For entries 1–13: M(OH)$_2$ (10 mol%); for entries 14–21 M(OH)$_2$ (5 mol%). [b] The reaction was conducted at 5 °C. Ac = acetyl, DBA = dibenzylamine, DMF = dimethylformamide, DMSO = dimethylsulfoxide, NR = no reaction, Pin = pinacol, TFA = trifluoroacetic acid.



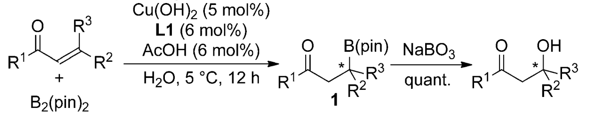
**L1** **L2** **L3**

as an α-chiral boron derivative **1a**, which was quantitatively converted to β-hydroxy ketone **2a** by treatment with NaBO$_3$ (Scheme 1). It was found to be more convenient for determining the enantioselectivity of **2a** by HPLC analysis on a chiral stationary phase.



**Scheme 1.** Conversion of an α,β-unsaturated ketone into a β-hydroxyl carbonyl compound.

**Table 2:** Substrate scope.



| Entry | $R^1$ | $R^2$ | $R^3$ | Yield [%] | e.r. |
|---|---|---|---|---|---|
| 1 | Ph | Ph | H | 95 | 99.5:0.5 |
| 2 | 4-$FC_6H_4$ | Ph | H | 91 | 94.5:5.5 |
| 3 | 4-$FC_6H_4$ | 2-$ClC_6H_4$ | H | 90 | 98:2 |
| 4 | 4-$MeOC_6H_4$ | Ph | H | 90 | 96:4 |
| 5 | Ph | 4-$ClC_6H_4$ | H | 90 | 94:6 |
| 6 | Ph | 4-$MeOC_6H_4$ | H | 95 | 94.5:5.5 |
| 7 | Ph | Me | H | 98 | 91:9 |
| 8 | Ph | *i*Pr | H | 91 | 94:6 |
| 9 | Ph | *t*Bu | H | 87 | 95.5:4.5 |
| 10 | Me | Ph | H | 88 | 90:10 |
| 11 |  | $-(CH_2)_3-$ |  | quant. | 91:9 |
| 12[a] | Ph | Ph | Me | 87 | 98.5:1.5 |
| 13[a] | Me | Ph | Me | 91 | 96.5:3.5 |
| 14[b] | MeO | Ph | H | 85 | 91:9 |
| 15[b] | EtO | Ph | H | 73 | 91:9 |
| 16 | EtO | Me | H | 80 | 93:7 |
| 17 | $NMe_2$ | Ph | H | 76 | 95.5:4.5 |
| 18 | $NEt_2$ | Ph | H | 80 | 94.5:5.5 |
| 19 |  | NCCH=CHPh |  | 85 | 90.5:9.5 |

[a] B$_2$(pin)$_2$ (1.6 equiv) was used. [b] Without AcOH.

The substrate scope of α,β-unsaturated carbonyl compounds was surveyed using Cu(OH)$_2$ (5 mol%) with chiral ligand **L1** (6 mol%) at 5 °C in water for 12 h (Table 2). Several acyclic α,β-unsaturated ketones reacted smoothly with B$_2$(pin)$_2$ under the conditions to afford the desired 1,4-addition products in high yields with high enantioselectivities (entries 1–10). Remarkably, a cyclic α,β-unsaturated ketone and β,β-disubstitued enones also reacted with B$_2$(pin)$_2$ smoothly with the same catalyst to afford the corresponding addition products in high yields with high enantioselectivities (entries 11–13). It should be noted that optically active tertiary alcohols were synthesized with excellent *ee* values in the latter two cases (entries 12 and 13). α,β-Unsaturated esters (entries 14–16) and amides (entries 17 and 18) are also good substrates, and the desired addition products were obtained in high yields with high enantioselectivities. Moreover, cinnamyl nitrile reacted with B$_2$(pin)$_2$ under these conditions to afford the corresponding boron product in high yield and with high enantioselectivity (entry 19). It should be noted that a single chiral Cu$^{II}$ catalyst can be applicable to a wide variety of α,β-unsaturated carbonyl compounds and nitrile in this asymmetric boron conjugate addition reaction; to the best of our knowledge, this is the first example of such a case. Furthermore, the experimental procedure is very simple: substrates are combined in the presence of inexpensive and readily available Cu(OH)$_2$ and chiral bipyridine ligand **L1** (and sometimes acetic acid) in water.

In addition to the use of water as a solvent, Cu$^{II}$ catalysis is very rare in the boron conjugate addition to α,β-unsaturated carbonyl compounds.[9,16] Indeed, 1,4-addition of diboron to α,β-unsaturated carbonyl compounds has been catalyzed by Cu$^{I}$ in organic solvents in many cases.[7,8] On the other hand, whereas Cu(OH)$_2$ was found to be very effective in water, the activity of Cu$^{I}$ is not clear, because Cu$^{I}$ species are known to be unstable in water.[17] Based on the experimental results, we propose the catalytic cycle of the chiral Cu(OH)$_2$-catalyzed asymmetric boron conjugate addition to α,β-unsaturated carbonyl compounds in water shown in Scheme 2. The Cu(OH)$_2$-**L1** complex **3** reacts with B$_2$(pin)$_2$ to form key Cu$^{II}$ intermediate **4**. We assume that **4** is sufficiently Lewis acidic to form complex **5**, in which α,β-unsaturated carbonyl compounds are activated by **4**, and boron addition might occur via six-membered cyclic transition states to afford **6**.

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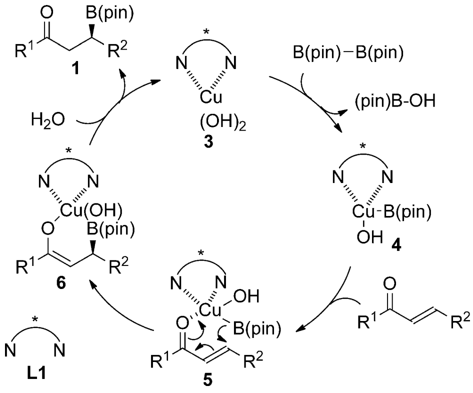
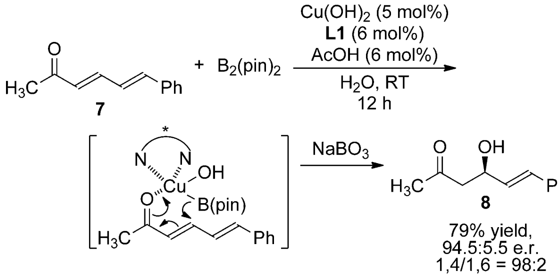


**Scheme 2.** Proposed catalytic cycle.

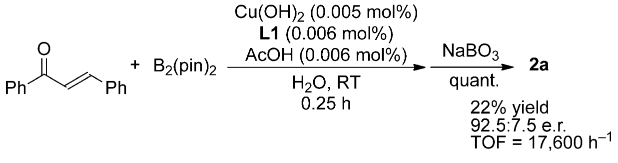
Cu$^{II}$ enolate **6** is then immediately protonated by $H_2O$ to give desired compound **1**, along with regeneration of **3**. Chiral induction might occur via the aforementioned six-membered cyclic transition states; these relatively rigid transition states would be formed with excellent chiral environments created by bipyridine ligand **L1** to realize high enantioselectivities with a wide substrate scope. As for the additive, acetic acid (AcOH) may react with $Cu(OH)_2$; however, a 1:1 mixture of $Cu(OH)_2$/AcOH gave the best results after testing ratios of $Cu(OH)_2$ and AcOH. Therefore, the exclusive formation of $Cu(OAc)_2$ is impossible under the conditions. When $Cu(OAc)_2$ (10 mol %) was used independently as the catalyst at RT for 12 h, product **2a** was obtained in 90 % yield with 92.5:7.5 e.r.

As an extension of this work, we conducted the reaction of α,β,γ,δ-unsaturated ketone **7** with $B_2(pin)_2$ under the standard conditions (Scheme 3). In this experiment, the 1,4-addition product **8** was predominantly obtained (79 % yield, 1,4-adduct/1,6-adduct = 98:2) in 94.5:5.5 e.r., which might support the cyclic transition state **5** of this asymmetric transformation.



**Scheme 3.** The reaction of α,β,γ,δ-unsaturated ketone **7** with $B_2(pin)_2$.

Finally, the turnover frequency (TOF) of the chiral Cu$^{II}$ catalyst in water was confirmed to be very high. In the presence of $Cu(OH)_2$ (0.005 mol %), **L1** (0.006 mol %), and AcOH (0.006 mol %), chalcone reacted with $B_2(pin)_2$ at RT in water for 15 min to afford **2a** in 22 % yield with 92.5:7.5 e.r. The TOF reached 17,600 $h^{-1}$, which is the highest value ever reported in an asymmetric boron conjugate addition reaction (Scheme 4).[18]



**Scheme 4.** Turnover frequency test.

In summary, we have developed enantioselective 1,4-additions of diboron to α,β-unsaturated carbonyl compounds and a nitrile catalyzed by $Cu(OH)_2$ and a chiral bipyridine ligand in water. The desired products were obtained in high yields and with high enantioselectivities. Previously, similar types of reactions have been carried out predominantly by using Cu$^{I}$ with a chiral ligand in organic solvents. In contrast, this report has shown the first example of a chiral Cu$^{II}$-catalyzed asymmetric 1,4-addition of diboron in water. Under our conditions, a wide substrate scope of α,β-unsaturated carbonyl compounds, including acyclic, cyclic, and β,β-disubstituted enones, α,β-unsaturated esters, α,β-unsaturated amides, and an α,β-unsaturated nitrile, has been shown. This is also the first case where a single catalyst reacts with all of these substrates to give products with high yields and high enantioselectivities. Furthermore, several synthetic advantages of this method have been demonstrated in this reaction: 1) The reactions proceeded smoothly using inexpensive and readily available $Cu(OH)_2$ in water; no dry solvents or anhydrous conditions are needed. 2) The experimental procedure is very simple; the substrates, $Cu(OH)_2$, and chiral bipyridine ligand **L1** (and sometimes AcOH) are mixed in water. 3) A high TOF value was attained. Further investigations to elucidate the reaction mechanism, especially the detailed roles of Cu$^{II}$ and water, are now in progress.

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[1] a) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095; b) *Organic Reactions in Water* (Ed.: U. M. Lindstroem), Wiley-Blackwell, Oxford, **2007**; c) *Water in Organic Synthesis (Science of Synthesis)* (Ed.: S. Kobayashi), Thieme, Stuttgart, **2012**.

[2] a) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816; b) H. Yorimitsu, T. Nakamura, H. Shinokubo, K. Oshima, K. Omoto, H. Fujimoto, *J. Am. Chem. Soc.* **2000**, *122*, 11041; c) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275; d) U. Schneider, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13824; e) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153; f) T. Kitanosono, M. Sakai, M. Ueno, S. Kobayashi, *Org. Biomol. Chem.* **2012**, *10*, 7134.

[3] a) M. Tortosa, *Angew. Chem.* **2011**, *123*, 4036; *Angew. Chem. Int. Ed.* **2011**, *50*, 3950; b) S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 17096; c) J. Chang, H. Lee, D. G. Hall, *J. Am. Chem. Soc.* **2010**, *132*, 5544; d) D. Imao, B. W. Glasspoole, V. S. Laberge, C. M. Crudden, *J. Am. Chem. Soc.* **2009**, *131*, 5024; e) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778; f) D. G. Hall, *Boronic Acids. Preparation, Applications in Organic Synthesis*

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*and Medicine*, Wiley-VCH, Weinheim, **2005**; g) E. Hupe, P. Marek, I. Knochel, *Org. Lett.* **2002**, *4*, 2861; h) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207.

[4] a) T. Ishiyama, N. Miyaura, K. Takahashi, *J. Organomet. Chem.* **2001**, *625*, 47; b) T. Ishiyama, N. Miyaura, K. Takahashi, *Chem. Lett.* **2000**, 982; c) A. Hosomi, H. Ito, J. Tateiwa, H. Yamanaka, *Tetrahedron Lett.* **2000**, *41*, 6821.

[5] a) X. Feng, J. Yun, *Chem. Eur. J.* **2010**, *16*, 13609; b) H. Chea, H. S. Sim, J. Yun, *Adv. Synth. Catal.* **2009**, *351*, 855; c) H. S. Sim, X. Feng, J. Yun, *Chem. Eur. J.* **2009**, *15*, 1939; d) J. E. Lee, J. Yun, *Angew. Chem.* **2008**, *120*, 151; *Angew. Chem. Int. Ed.* **2008**, *47*, 145; e) S. Mun, J. E. Lee, J. Yun, *Org. Lett.* **2006**, *8*, 4887.

[6] a) J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894; b) A. L. Moure, R. G. Arrayás, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6701; c) G. A. Molander, S. A. McKee, *Org. Lett.* **2011**, *13*, 4684; d) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk, D. T. McQuade, *Org. Lett.* **2010**, *12*, 5008; e) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491; f) J. A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566.

[7] For rhodium, see: T. Shiomi, T. Adachi, K. Toribatake, L. Zhou, H. Nishiyama, *Chem. Commun.* **2009**, 5987; for nickel and palladium, see: E. Fernández, M. J. Geier, V. Lillo, S. A. Westcott, *Org. Biomol. Chem.* **2009**, *7*, 4674.

[8] a) H. Wu, S. Radomkit, J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 8277; b) J. M. O'Brien, K. S. Lee, A. M. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630; c) A. Bonet, E. Fernández, H. Gulyás, *Angew. Chem.* **2010**, *122*, 5256; *Angew. Chem. Int. Ed.* **2010**, *49*, 5130; d) J. A. Schiffner, K. Müther, M. Oestreich, *Angew. Chem.* **2010**, *122*, 1214; *Angew. Chem. Int. Ed.* **2010**, *49*, 1194; e) K. S. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253.

[9] a) During this research, achiral copper(II) catalysis in water was reported; see: S. B. Thorpe, J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**, *14*, 1918.

[10] a) S. Kobayashi, M. Ueno, T. Kitanosono, *Top. Curr. Chem.* **2012**, *311*, 1; b) S. Kobayashi, T. Endo, M. Ueno, *Angew. Chem.* **2011**, *123*, 12470; *Angew. Chem. Int. Ed.* **2011**, *50*, 12262; c) S. Kobayashi, T. Kitanosono, M. Ueno, *Synlett* **2010**, 2033; d) S. Kobayashi, T. Endo, U. Schneider, M. Ueno, *Chem. Commun.* **2010**, *46*, 1260; e) M. Fujita, T. Nagano, U. Schneider, T. Hamada, C. Ogawa, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2914.

[11] a) S. Kobayashi, S. Nagayama, T. Busujima, *Chem. Lett.* **1999**, 71; b) S. Kobayashi, S. Nagayama, T. Busujima, *Tetrahedron* **1999**, *55*, 8739; c) S. Kobayashi, Y. Mori, S. Nagayama, K. Manabe, *Green Chem.* **1999**, *1*, 175; d) S. Otto, J. B. F. N. Engberts, J. C. T. Kwak, *J. Am. Chem. Soc.* **1998**, *120*, 9517; e) B. Y. Yang, X. M. Chen, G. J. Deng, Y. L. Zhang, Q. H. Fan, *Tetrahedron Lett.* **2003**, *44*, 3535.

[12] a) M. Kokubo, T. Naito, S. Kobayashi, *Tetrahedron* **2010**, *66*, 1111; b) C. Ogawa, M. Kokubo, S. Kobayashi, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 718; c) M. Kokubo, T. Naito, S. Kobayashi, *Chem. Lett.* **2009**, *38*, 904.

[13] a) S. Kobayashi, K. Manabe, *Pure. Appl. Chem.* **2000**, *72*, 1373; b) D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221; c) K. Manabe, S. Kobayashi, *Chem. Eur. J.* **2002**, *8*, 4094; d) K. Manabe, S. Kobayashi, *Acc. Chem. Res.* **2002**, *35*, 209; e) S. Kobayashi, C. Ogawa in *Asymmetric Synthesis-The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, Weinheim, **2007**, p. 110; f) "Acid Catalysis in Water": C. Ogawa, S. Kobayashi in *Organic Reactions in Water* (Ed.: U. M. Lindstroem), Wiley-Blackwell, Oxford, **2007**, p. 60; g) S. Kobayashi, *Pure. Appl. Chem.* **2007**, *79*, 235; h) "Toward Truly Efficient Organic Reactions in Water": C. Ogawa, S. Kobayashi in *Process Chemistry in the Pharmaceutical Industry, Vol. 2* (Eds.: K. Gadamasetti, T. Braish), CRC, Boca Raton, **2008**, pp. 249–265; i) C. Pan, Z. Wang, *Coord. Chem. Rev.* **2008**, *252*, 736.

[14] a) S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287; b) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954.

[15] a) C. Bolm, M. Zehnder, D. Bur, *Angew. Chem.* **1990**, *102*, 206; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 205; b) C. Bolm, M. Ewald, M. Felder, G. Schlingloff, *Chem. Ber.* **1992**, *125*, 1169; c) S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *Synthesis* **2005**, 2176.

[16] I. Ibrahem, P. Breistein, A. Córdova, *Angew. Chem.* **2011**, *123*, 12242; *Angew. Chem. Int. Ed.* **2011**, *50*, 12036.

[17] The immediate disproportionation of $Cu^{I}$ to form $Cu^{0}$ and $Cu^{II}$ is well known; see: a) P. A. Korzhavyi, I. L. Soroka, E. I. Isaev, C. Lilja, B. Johansson, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 686; b) M. Plavšić, D. Krznarić, B. Ćosović, *Electroanalysis* **1994**, *6*, 469; c) J. L. Proust, *Ann. Chim.* **1799**, *1*, 32.

[18] In previous reports,[5–8,16] the TOF was less than 50 $h^{-1}$, except for one case where a 5580 $h^{-1}$ TOF was attained using a chiral carbene $Cu^{I}$ complex in toluene, see Ref. [6d].

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