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# C–C Bond Formation via Copper-Catalyzed Conjugate Addition Reactions to Enones in Water at Room Temperature

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Ⓢ *Supporting Information*

**ABSTRACT:** Conjugate addition reactions to enones can now be done in water at room temperature with in situ generated organocopper reagents. Mixing an enone, zinc powder, TMEDA, and an alkyl halide in a micellar environemnt containing catalytic amounts of Cu(I), Ag(I), and Au(III) leads to 1,4-adducts in good isolated yields: no organometallic precursor need be formed.

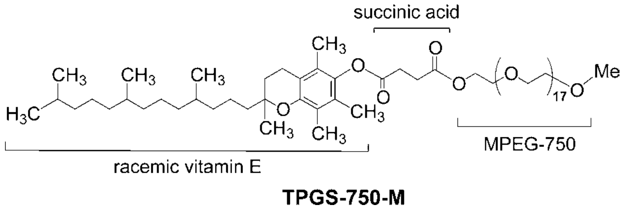


**Figure 1.** Structure for polyoxyethanyl-$\alpha$-tocopheryl succinate (TPGS-750-M).

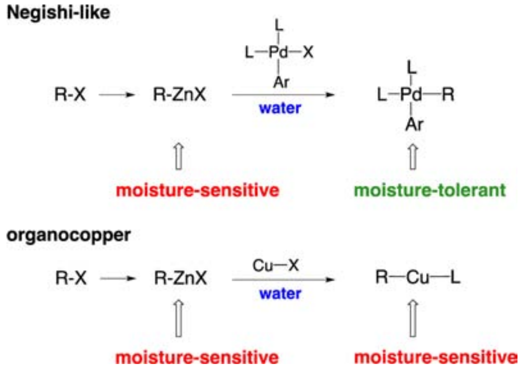
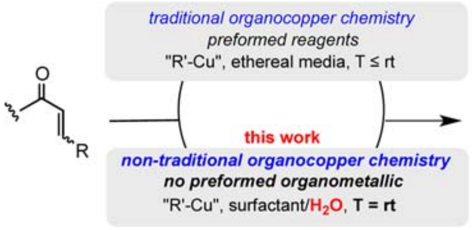


**Figure 2.** Distinctions between intermediates in Pd- vs Cu-catalyzed reactions.

The origins of organocopper chemistry in synthesis date back to the late 1940s and early 1950s when Kharasch[1] and Gilman[2] first disclosed the preparation of Grignard- and organolithium-derived organocuprates, respectively. These fundamental reagents are generally scribed as "$R_2CuMgX$" and "$R_2CuLi$", the hallmark of each being their ability to deliver both $C_{sp^3}$ and $C_{sp^2}$ residues from copper to carbon,[3] most notably in a conjugate addition sense.[4] Indeed, such species and their reactions with Michael acceptors are standard entries in textbooks on basic organic chemistry. But along with such instruction comes an appreciation for the incompatibility of organocopper reagents of almost all varieties with water; hence, practitioners must go to considerable lengths to ensure use of dry copper salt precursors, dry organic, aprotic solvents, and proper handling of organometallic precursors, whether obtained as items of commerce or freshly prepared prior to use.[5] And while alternative inroads to organocopper reagents have been devised over time (e.g., transmetalations, etc.[6]), the overall level of tolerance to moisture, in general, is essentially nil. In this report, as counterintuitive as it may seem, new technology for achieving organocopper-mediated 1,4-additions is reported that not only is tolerant of moisture but also, in fact, is performed entirely in water as the gross reaction medium (Scheme 1). Moreover, unlike most conjugate additions (e.g., to enones) that occur best at lower temperatures,[3] these proceed smoothly at ambient temperature. Hence, no investment of energy beyond that provided at room temperature need be made.

**Scheme 1. Comparison Approaches: Traditional vs Micellar Catalysis**



There is no true precedent for Cu-catalyzed conjugate additions of alkyl (or alkenyl, or aryl) groups to enones in aqueous media, with the exception of alkynyl conjugate additions by Carreira.[7a] Early work by Luche demonstrated promising results using a Zn/Cu couple in aqueous media, using copper or $NH_4Cl$ to activate zinc under ultrasonication leading to a radical pathway.[7b−d]

Related methodology developed by Fleming performed preferentially on silica applies solely to unsaturated nitriles,[8] partners that, while excellent radical acceptors,[9] are typically not ready participants toward copper-mediated 1,4-additions.[3b] As

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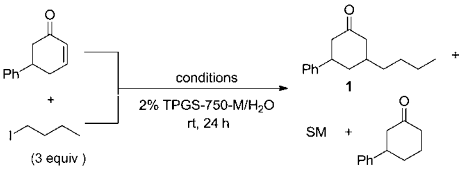
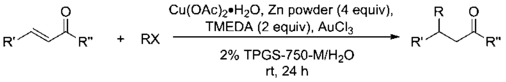
**Table 1. Optimization of Reaction Conditions**[a]

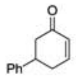
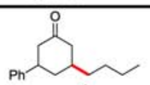
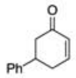
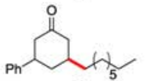
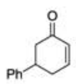
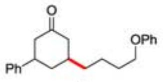
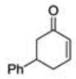
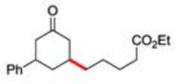
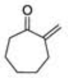
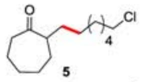
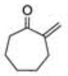
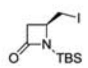
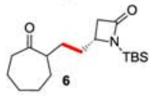
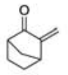
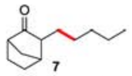
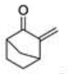
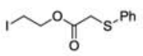
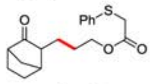
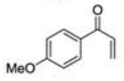
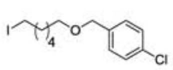
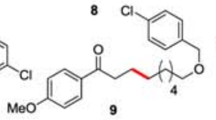
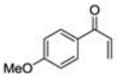
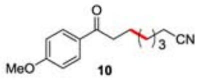
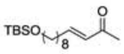
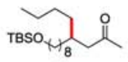
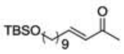
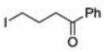
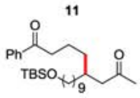
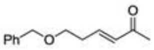
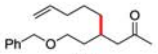


| entry | conditions | yield of **1** (%)[b] |
|---|---|---|
| 1 | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), Zn powder (4 equiv), TMEDA (5 equiv) | 54 |
| 2 | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) | 67 |
| 3 | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), $LiClO_4$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) | 78 |
| 4 | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), $AuCl_3$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) | 87 |
| **5**[c] | **$Cu(OAc)_2{\cdot}H_2O$ (5 mol%), $AuCl_3$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv)** | **93** |
| 6[d] | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), $AuCl_3$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) | 50 |
| 7 | $AuCl_3$ (5 mol%), Zn powder (4 equiv), TMEDA (2 equiv) | 2 |

[a] For details, see Supporting Information. [b] Determined by GC on crude material. [c] Iodobutane and zinc were added in two portions: $t = 0$ h, 1.5 equiv; $t = 6$ h, 1.5 equiv. [d] Water only was used as the medium (no surfactant).

**Table 2. Conjugate Additions of Alkyl Halides to Enones**[a]



| entry | enone | alkyl-X | product | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  **1** | 87 |
| 2 |  |  |  **2** | 89 |
| 3 |  |  |  **3** | 87 |
| 4 |  |  |  **4** | 80 |
| 5 |  |  |  **5** | 82 |
| $6^c$ |  |  |  **6** | 83 |
| 7 |  |  |  **7** | 86 |
| 8 |  |  |  **8** | 75 |
| 9 |  |  |  **9** | 80 |
| 10 |  |  |  **10** | 86 |
| 11 |  |  |  **11** | 86 |
| 12 |  |  |  **12** | 83 |
| 13 |  |  |  **13** | 82 |

[a] Conditions: alkyl-X (3 equiv), Zn powder (X = I) or Zn dust (X = Br) (4 equiv), TMEDA (2 equiv), 3−5 mol% [Cu], 5 mol% $AuCl_3$, 0.5 mL 2 wt% TPGS-750-M/$H_2O$, rt, 24 h. [b] Isolated, chromatographically purified. [c] Zinc dust used.

such, excessive amounts of alkyl halide (8 equiv) and Zn (6 equiv) are needed. More recently, Loh and co-workers described the use of indium/copper leading to conjugate additions of unactivated (mainly secondary) alkyl iodides (and not bromides) to $\alpha,\beta$-unsaturated compounds in water, also via a proposed radical mechanism.[10]

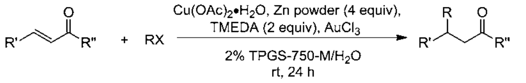
We recently disclosed highly moisture-sensitive Negishi-like cross-couplings that could be carried out in water using either alkyliodides[11a] or bromides.[11b] This methodology is enabled by small amounts of commercially available amphiphiles (e.g., 2 wt % TPGS-750-M; Figure 1)[12] that form nanomicelles in water within which the coupling occurs, where the precursor halides are used directly in the presence of Zn metal; i.e., no prior formation of RZnX is required.[11a,13]

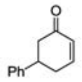
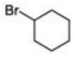
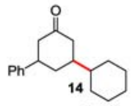
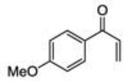
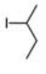
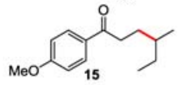
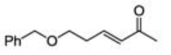
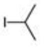
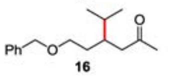
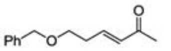
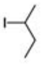
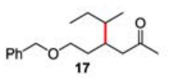
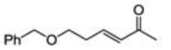
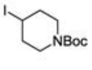
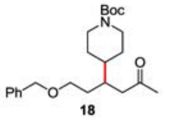
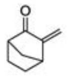
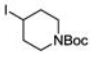
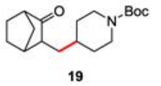
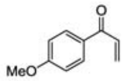
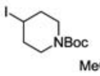
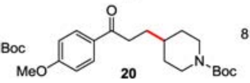
If conditions could be found such that transmetalation to copper, rather than palladium, takes place, in this case, in the presence of a Michael acceptor, 1,4-addition might ensue. However, there is a key distinguishing feature between these two types of reactions, one that suggests that a process involving organocopper species is potentially far more demanding. That is, transmetalation from Zn to Pd would provide a moisture-tolerant intermediate, while in situ generated organozinc and organocopper reagents are both highly moisture-sensitive (Figure 2).

Initially, the combination of 5-phenylcyclohexenone and 1-iodobutane was studied in aqueous TPGS-750-M as a representative substrate pair, in the presence of $Cu(OAc)_2{\cdot}H_2O$ (5 mol%) and excess zinc powder and TMEDA (Table 1). Only moderate yields of the desired product **1** (as a mixture of *cis*/*trans* isomers) were obtained due to a significant amount of unreacted starting material (>40%), along with lesser quantities (ca. 5%) of reduced enone (entry 1). A drop in the level of TMEDA led to a rise in conversion, with two equivalents being optimal (entry 2).

Addition of a catalytic amount of a Lewis acid (e.g., $LiClO_4$; entry 3) further increased the level of conversion, presumably by complexation of lithium with the enone.[14] Other salts (e.g., Li halides, $NiCl_2$, $Sc(OTf)_3$) were screened, but ultimately $AuCl_3$ was found to be the most effective (entry 4). By adding the alkyl halide and zinc in two portions, the yield could be further increased to 93% (entry 5). A control reaction carried out "on water"[15] (i.e., in the absence of TPGS-750-M) confirmed the importance of micellar catalysis in facilitating conjugate additions in aqueous media (entry 6). Attempts to vary the surfactant, including trials with Brij 30 and 35, Triton X-100, cremophor EL, and solutol HS (see Supporting

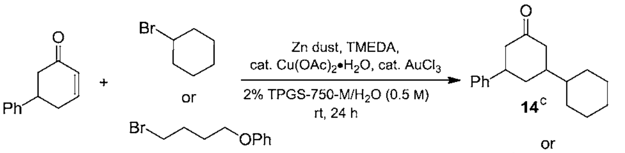
**Table 3. Conjugate Addition Reactions of Secondary Alkyl Halides to Enones**[a]

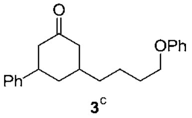


| entry | enone | alkyl-X | product | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  **14** | 85 |
| 2[c] |  |  |  **15** | 83 |
| 3 |  |  |  **16** | 90 |
| 4 |  |  |  **17** | 85 |
| 5 |  |  |  **18** | 88 |
| 6 |  |  |  **19** | 85 |
| 7 |  |  |  **20** | 81 |

[a]Conditions: alkyl-X (3 equiv), Zn powder (X = I) or Zn dust (X = Br) (4 equiv), TMEDA (2 equiv), 3 mol% [Cu], 5 mol% $AuCl_3$, 0.5 mL 2 wt% TPGS-750-M/$H_2O$, rt, 24 h. [b]Isolated, chromatographically purified. [c]Tetraethyl analogue of TMEDA used.

**Scheme 2. In-Flask Recycling of TPGS-750-M and $AuCl_3$**





**recycle study 1**

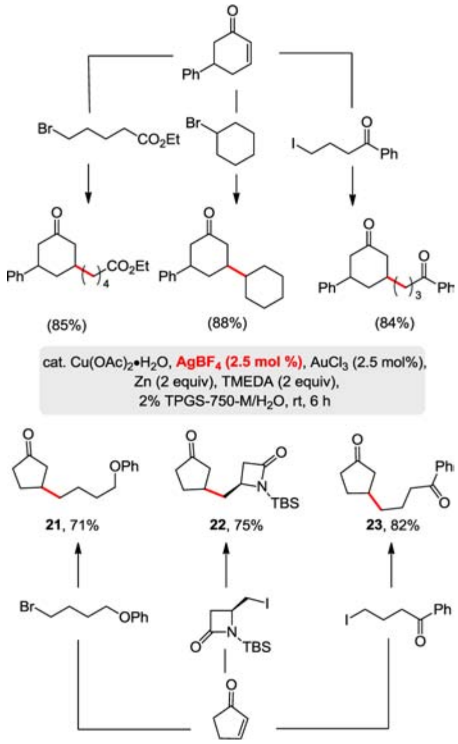
| cycle | conv.(%) | yield (%) |
|---|---|---|
| 1 | >99 | **14**, 89 |
| 2 | >99 (2)[a] | **14**, 86 |
| 3 | 97 (3)[a] | **14**, 83 |
| 4 | 95[b] (1.5)[a] | **14**, 84 |

**recycle study 2**

| cycle | yield (%) |
|---|---|
| 1 | **14**, 88 |
| 2 | **3**, 84 |
| 3 | **14**, 85 |

[a]Reduced enone. [b]Reaction time 32 h. [c]Isolated as a mix of cis/trans isomers.

**Scheme 3. The Coinage Metal Triad as Catalysts**



Information), led in all cases to significantly lower yields of the 1,4-adduct. The absence of a copper salt results in almost no formation of the product, suggesting that both $Cu(OAc)_2 \cdot H_2O$ and $AuCl_3$, along with the proper choice of amphiphile, are essential for realization of a synthetically useful process based on organocopper chemistry (entry 7).

Several enones and alkyl halides bearing functional groups can be utilized, given the mildness of the reaction conditions and the functional group tolerance for which organozinc reagents are well-known (Table 2).[16]

Secondary iodides and bromides also work well under these standard conditions (Table 3). Remarkably, no rearrangement of secondary centers was observed, unlike those known to occur in related reactions, presumably due to β-hydride elimination.[17]

Studies on the potential for recycling of *both* the aqueous medium containing the surfactant and the gold catalyst show considerable potential. In-flask recycling was achieved using minimum amounts of hexanes as the extraction solvent (Scheme 2, study 1). Each recycle, without the addition of fresh surfactant or $AuCl_3$, showed a minimal decrease in reaction rate, as well as minimal competitive enone reduction (see Supporting Information for details). Moreover, different substrate combinations can be used in each recycle, further broadening the utility of TPGS-750-M/$H_2O$ as a reaction medium (Scheme 2, study 2).

In an effort to further enhance the rate of these copper-catalyzed conjugate addition reactions, the Lewis acidity of $AuCl_3$ was modified by introduction of an equimolar (catalytic) amount of $AgBF_4$, a ploy oftentimes used in gold catalyzed reactions.[18] *Remarkably, in the presence of this additive, the amounts of alkyl halide, Zn, and* $AuCl_3$ *needed were reduced dramatically, as were reaction times.* As the examples in Scheme 3 illustrate, the overall efficiency remains high.

In summary, the first green methodology for effecting water-sensitive copper-catalyzed 1,4-additions in a totally aqueous environment has been developed. It takes advantage of micellar catalysis leveraged by use of a "designer" surfactant that forms nanoreactors of a favored size and within which organozinc reagents are formed in situ at the metal surface. The resulting organozinc species then undergo transmetalation to copper and, ultimately, conjugate addition to unsaturated ketones, giving good yields of the desired 1,4-adducts. A broad substrate scope has been demonstrated indicative of considerable generality, including tolerance to a wide range of functionality. Neither organic solvents nor energy in the form of applied heat or cooling need be invested. Further work on developing an enantioselective version of this process, as well as other coupling reactions involving organocopper complexes in water, is currently underway.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Detailed experimental procedures, analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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