Communication

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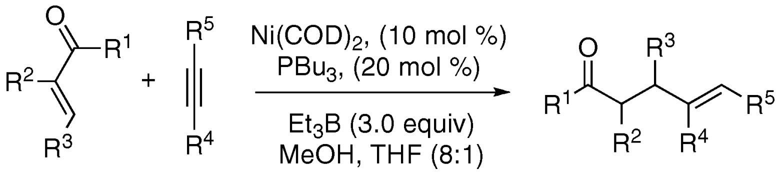

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Catalytic Intermolecular Reductive Coupling of Enones and Alkynes

Ananda Herath, Benjamin B. Thompson, and John Montgomery*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055

E-mail: jmontg@umich.edu

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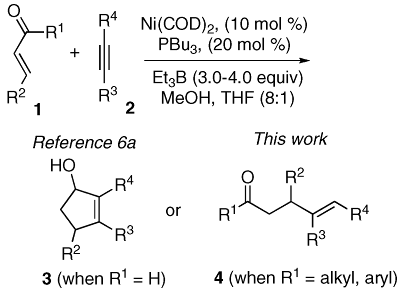
Conjugate addition reactions have long been recognized as a powerful tool for assembly of functionalized ketones, and a variety of copper-promoted processes involving enone alkenylation have been widely used to prepare γ,δ-unsaturated carbonyls.[1] Typical strategies involve either stoichiometric preparation of alkenyl copper reagents that directly add to enones, or alternatively, stoichiometric formation of a vinyl metal species (zirconium in the most prominent cases) that undergoes addition to enones in the presence of a copper or nickel catalyst.[2] Earlier studies from our laboratory illustrated that alkynyl enones undergo nickel-catalyzed reductive cyclization processes using diethylzinc as reducing agent.[3] Unfortunately, the scope of this process was limited to five-membered ring cyclizations on very simple substrates, and the use of triethylborane under aprotic conditions was also ineffective. Attempts with intermolecular versions, sterically hindered cyclizations, or larger ring cyclizations were entirely unsatisfactory. More recent studies from Cheng involving cobalt catalysis provided an efficient method for the reductive coupling of enoates and alkynes,[4] and Micalizio reported titanium-promoted alkene/alkyne reductive couplings involving nonactivated alkenes.[5] However, although powerful copper-based methods for conjugate addition of terminal alkyne-derived vinyl organometallics are known,[2] the highly desirable direct catalytic intermolecular reductive coupling of enones and alkynes without requiring vinyl organometallic preparation has not been reported.

In the course of studying catalytic [3 + 2] reductive cycloadditions of enals and alkynes recently developed in our lab,[6] we observed that simply utilizing an enone rather than an enal allowed catalytic intermolecular reductive couplings to instead proceed (Scheme 1). Recognizing the potential impact of this transformation as a complement to organocuprate technology, we set out to examine the scope of this new reductive coupling process, and the results are described herein.

A series of examples were examined to illustrate the scope of enone/alkyne reductive couplings, and an attractive range of enones and alkynes were found to participate efficiently. A variety of enones were first examined in couplings of 1-phenyl propyne (Table 1). With this representative alkyne, efficient couplings were demonstrated with a range of enones including methyl vinyl ketone (entry 1), a longer chain simple vinyl ketone (entry 2), aromatic vinyl ketones with β-alkyl or β-aryl substitution (entries 3 and 4), an α-alkyl enone (entry 5), an α′-silyloxy(vinyl)ketone (entry 6), a β-substituted enone bearing a free hydroxyl (entry 7), and a cyclic enone (entry 8). To examine the range of alkynes that efficiently participate, additional examples were then carried out. Couplings were observed with diaryl alkynes (entry 9), terminal alkynes (entry 10), nonaromatic internal alkynes (entry 11), and a hydroxyl-bearing alkyne (entries 12 and 13). Couplings with aromatic or terminal alkynes proceeded with excellent regioselection (entries 1−8, 10), whereas nonaromatic internal alkynes afforded mixtures of regioisomers (entries 12 and 13).

Scheme 1. Divergent Pathways for Reductive Couplings of Alkynes with Enals or Enones



A number of features of the above examples, particularly the range of alkyne substitution patterns and the tolerance of free hydroxyls, illustrate complementarity to alternative copper-based procedures. However, the unique characteristics of this new process are perhaps best illustrated by the chemoselective coupling of ynoates and enones (Table 2). Whereas both ynoates and enones are potential Michael acceptors, they undergo highly regio-, stereo- and chemoselective heterocouplings at room temperature without requiring a large excess of either reagent or careful control of reagent addition (entries 1−4). Failure to observe products derived from homocoupling of either starting material is perhaps surprising given the potentially similar reactivity of both components. Additionally, with ynoates being excellent Michael acceptors, hydrometallation strategies have potential to exhibit lack of chemoselectivity or reversed regioselectivity.[7] Finally, strategies for organocuprate formation via traditional lithiation sequences are typically difficult in the presence of electrophilic functional groups such as esters.[8] Avoiding each of these potential complications in a simple, catalytic protocol renders the ynoate/enone reductive coupling particularly valuable.[9]

The divergent reactivity of enals compared with enones (Scheme 1) can be explained within the same mechanistic framework of catalytic [3 + 2] reductive cycloadditions (Scheme 2). Oxidative cyclization of enone **1** and alkyne **2** with Ni(0) would afford metallacycle **7** or related borane adduct **8**.[10] Details of how the reducing agent (Et_3B in this report) may accelerate the oxidative cyclization was described in a computational study of organozinc-mediated alkylative couplings of alkynyl enones.[11] Once structure **7** or **8** is formed, enolate protonation would afford structure **9**. From this intermediate, using an enal starting material ($R^1 = H$), vinyl nickel addition to the tethered aldehyde would afford boron alkoxide **10** en route to [3 + 2] reductive cycloaddition product **3**. Alternatively, if carbonyl addition is sterically impeded in ketone derivatives when an enone is used (R^1 = aryl or alkyl), then ethyl transfer from boron to nickel to produce **11**, followed by β-hydride elimination to **12** and reductive elimination would generate acyclic reductive coupling product **4**. An experiment using CD_3OD afforded product **4** with no deuterium incorporation at the alkenyl position, consistent with this proposed pathway (eq 1).

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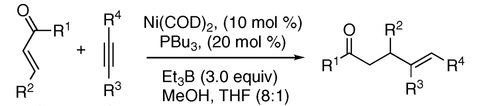
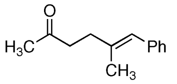
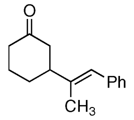
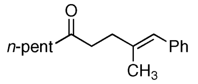
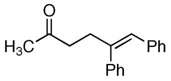
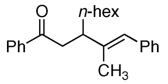
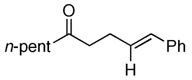
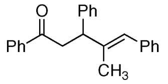
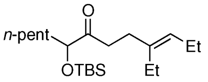
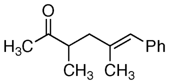
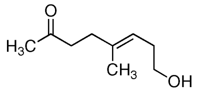
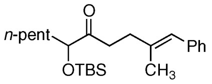
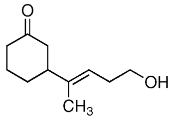
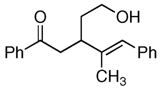
Table 1. Reaction Scope[a]

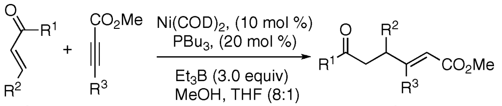


1 **2** **4**

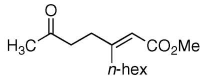
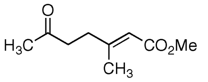
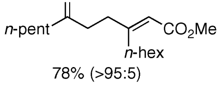
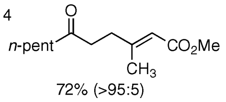
entry	product (yield, regioselectivity)	entry	product (yield, regioselectivity)
1	 85% (>95:5)	8	 80% (>95:5)
2	 78% (>95:5)	9	 63%
3	 65% (>95:5)	10	 74% (>95:5)
4	 90% (>95:5)	11	 72%
5	 80% (>95:5)	12	 50% (3:1)
6	 72% (>95:5)	13	 62% (1:1)
7	 84% (>95:5)		

[a] Reactions were carried out in MeOH/THF (8:1) using 1.0 equiv of enone, 1.5 equiv of alkyne, 3.0 equiv of Et$_3$B, 0.1 equiv of Ni(COD)$_2$, and 0.2 equiv of PBu$_3$ at 50 °C.

Table 2. Couplings Involving Ynoates[a]

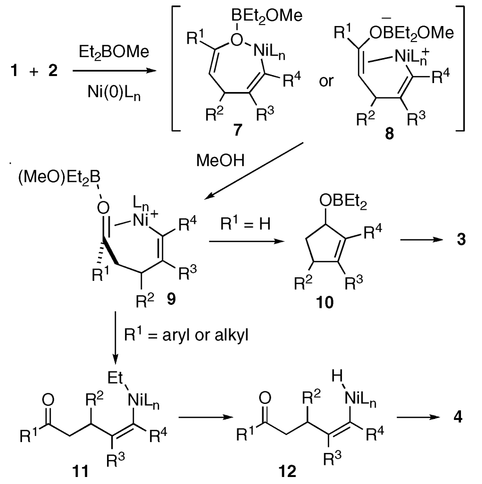


1 **5** **6**

entry	product (yield, regioselectivity)	entry	product (yield, regioselectivity)
1	 80% (>95:5)	3	 74% (>95:5)
2	 78% (>95:5)	4	 72% (>95:5)

[a] Reactions were carried out in MeOH/THF (8:1) using 1.0 equiv of enone, 1.5 equiv of alkyne, 3.0 equiv of Et$_3$B, 0.1 equiv of Ni(COD)$_2$, and 0.2 equiv of PBu$_3$ at room temperature.

Scheme 2. Proposed Mechanism



It is noteworthy that cyclic enones, which preclude formation of *O*-enolate tautomers in metallacycle **7**, are nonetheless effective participants (Table 1, entries 8 and 13). *S*-Trans enones may proceed via an intermediate analogous to **8** or the corresponding five-membered *C*-enolate metallacycle. Notably, α-substituted cyclic enones are unreactive in the process, potentially due to increased crowding of the *C*-enolate intermediate, whereas acyclic α-substituted enones are excellent participants (Table 1, entry 5).

In summary, a practical, catalytic, intermolecular, reductive coupling of enones and alkynes has been developed. Further improvements in scope, asymmetric variants, and complex synthetic applications will be reported in due course.

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Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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