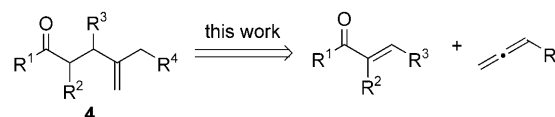# Communications

Regioselective Nickel-Catalyzed Reductive Couplings of Enones and Allenes**
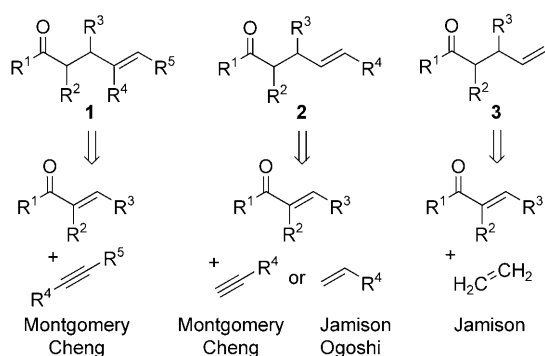
Wei Li, Nan Chen, and John Montgomery

Catalytic reductive coupling processes have been developed in numerous contexts as a strategy for the regio- and stereoselective installation of alkenes.[1] The direct coupling of a polar π system with a relatively nonpolar π system is often a successful strategy for selectively accomplishing synthetically desirable heterocouplings while avoiding undesired homocoupling of either reagent. For example, reductive couplings of aldehydes, enones, enals, or imines paired with alkynes, alkenes, or allenes have been extensively developed in recent years. Processes of this type are often highly effective in controlling both the position and stereochemistry of di-, tri-, and tetrasubstituted alkenes within polyfunctional molecules. Among these methods, the preparation of γ,δ-unsaturated carbonyl groups by nickel- and cobalt-catalyzed processes has been the subject of considerable study. The catalytic strategies developed for synthesis of γ,δ-unsaturated carbonyl groups by the coupling of two π-containing components include enone–alkyne additions in work reported by our group[2,3] and by Cheng and co-workers,[4] and enone–alkene additions in work reported by Jamison and co-workers,[5] and Ogoshi et al.[6] (Scheme 1). Processes of this type provide an important counterpart to organocuprate technology and hydrometallative processes, while having the advantage of not requiring the stoichiometric preparation of an alkenyl metal species.

Stereodefined trisubstituted alkenes **1**, *trans*-disubstituted alkenes **2**, and monosubstituted alkenes **3** may be readily prepared by the above-mentioned enone–alkyne and enone–alkene coupling processes. However, a general strategy for the preparation of 1,1-disubstituted alkenes **4** by these methods has not been developed.[7,8] Since terminal alkyne reductive coupling strategies and hydrometallative processes typically favor formation of the conjugate addition product **2** with a 1,2-disubstituted alkene, the 1,1-disubstituted alkene **4** is considerably more difficult to prepare.[9,10] As depicted below (Scheme 2), regiocontrolled reductive coupling of an

Scheme 2. New entry into γ,δ-unsaturated ketones with a 1,1-disubstituted alkene.

enone and allene could potentially provide efficient access to product **4**, although issues of regioselectivity and chemoselectivity often render intermolecular processes involving allenes difficult to optimize into efficient processes.[11] Catalytic couplings of enones with allenes have been developed as efficient entries into 1,3-dienes,[12] cyclopentanols,[13] and δ,ε-unsaturated carbonyl compounds;[14] however, the direct catalytic reductive coupling of enones and allenes has not been previously described. Herein, we describe that highly regioselective catalytic reductive coupling of enones and terminal allenes provides an effective and general solution to the preparation of γ,δ-unsaturated carbonyls that possess the 1,1-disubstituted alkene substructure (**4**).

Our efforts to develop the desired reductive coupling of enones and allenes began with a broad screen of ligands and reducing agents in the coupling of the enone **5a** and allene **6a**, using [Ni(cod)$_2$] (10 mol%) as the precatalyst. The use of Et$_3$B as a reducing agent with monodentate phosphines led to inefficient couplings in THF (Table 1, entry 1), but the use of a methanol/THF mixed solvent system afforded efficient couplings to provide a 41:59 mixture of regioisomers **4a** and **1a** (Table 1, entry 2). Notably, since regioisomer **1** may be obtained by reductive couplings of internal alkynes with enones (Scheme 1), we quickly focused on efforts to optimize the formation of isomer **4** given the lack of efficient methods for preparing this structural motif. In addition to PPh$_3$, other monodentate phosphines such as PCy$_3$ and P(*o*-tol)$_3$ were

Scheme 1. Previously reported entries into γ,δ-unsaturated ketones.

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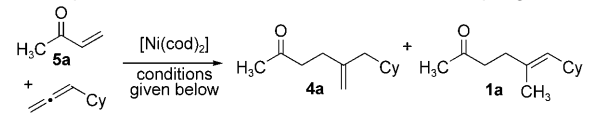Fax: (+1) 734-763-1106
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Table 1: Optimization of the enone–allene reductive couplings.

Entry	Ligand	Solvent	Reductant	Yield [%] (4a/1a)[a]
1	PPh$_3$	THF	Et$_3$B	39 (43:57)
2	PPh$_3$	THF/MeOH (1:8)	Et$_3$B	73 (41:59)
3	PCy$_3$	THF/MeOH (1:8)	Et$_3$B	71 (31:69)
4	P(o-tol)$_3$	THF/MeOH (1:8)	Et$_3$B	63 (31:69)
5	PPh$_3$	THF	Et$_3$SiH	77 (93:7)
6	PPh$_3$	toluene	Et$_3$SiH	84 (93:7)
7	PPh$_3$	THF/MeOH (1:8)	Et$_3$SiH	58 (62:38)
8	PCy$_3$	toluene	Et$_3$SiH	27 (81:19)[b]
9	IMes	THF	Et$_3$SiH	<10
10	IPr	THF	Et$_3$SiH	<10

[a] Product ratios were determined for crude reaction mixtures by using GC and NMR analyses. Yield refers to combined yield of all product isomers recovered after chromatographic purification. Unless otherwise noted, compound **1a** was obtained as the *E* isomer. [b] Compound **1a** was obtained as a 59:41 ratio of *E* and *Z* isomers. IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, IPr = *N*,*N*′-bis(2,6-(diisopropyl)phenyl)imidazol-2-ylidene.

effective with Et$_3$B in methanol/THF to obtain similar mixtures of products **4a** and **1a** (Table 1, entries 3 and 4). We then examined the use of Et$_3$SiH as a reducing agent, and couplings with PPh$_3$ as a ligand in THF were effective and highly selective for the desired product **4a** (Table 1, entry 5). Results were comparable with Et$_3$SiH and PPh$_3$ in toluene (Table 1, entry 6). However this reducing agent/ligand combination in MeOH/THF afforded a 2:1 mixture of **4a** and **1a** in moderate yield (Table 1, entry 7). Couplings with Et$_3$SiH and PCy$_3$ in toluene were low yielding (Table 1, entry 8). Additionally, couplings with Et$_3$SiH and either of the N-heterocyclic carbenes IMes and IPr in THF provided low yields of **4a**.

On the basis of the above experiments, we opted to additionally explore the formation of 1,1-disubstituted alkene products of general structure **4** using the optimized reaction conditions (Et$_3$SiH and [Ni(cod)$_2$] (10 mol%), PPh$_3$ (20 mol%), toluene, 50°C; Table 1, entry 6). Under these reaction conditions, reductive couplings of methyl vinyl ketone were efficient with a range of monosubstituted allenes (Table 2), including aliphatic (Table 2, entry 1) and aromatic (Table 2, entry 2) allenes, those possessing silyloxy (Table 2, entry 3), acetoxy (Table 2, entry 4), or hydroxy functionality (Table 2, entry 5) in a remote position, or an alkoxy functional group directly attached to the allene (Table 2, entry 6). All cases were selective for the desired 1,1-disubstituted alkene product, with the exception of a hydroxy-containing allene, which predominantly formed a regioisomeric product (Table 2, entry 5). The interesting mechanistic basis for differing regioselectivity in the presence of hydroxy functionality (either in the substrate or solvent) is discussed below. Variation in the enone substrate is also tolerated, as evidenced by the efficient participation of α-alkyl-substituted and β-alkyl- or β-aryl-substituted enones (Table 2, entries 7–12). Additionally, although monosubstituted allenes were our

primary focus for gaining access to the 1,1-disubstituted alkene products, 1,3-disubstituted cyclic and acyclic allenes were also effective participants in preparing mixtures of stereoisomeric trisubstituted alkene products in which the *Z* alkene stereochemistry is favored (Table 2, entries 13 and 14).

The high levels of regioselectivity and stereoselectivity observed in this report are noteworthy, given the complexities with these issues that are often seen with allene addition processes. Presuming that the processes involve an initial oxidative cyclization to a metallacyclic intermediate,[15] six different metallacycles (**7—12**) could potentially be formed with different regiochemical arrangements or with different stereochemistry of the exocyclic alkene (Scheme 3). Additionally, metallacycles **9** and **12** could each be formed as a mixture of diastereomers. Of these possibilities, **7–9** are derived from C−C bond formation at the allene central carbon atom, as required for formation of the observed products. Metallacycles **10–12** would be derived from C−C bond formation at an allene terminal carbon atom, and are therefore inconsistent with the products obtained.

The regioselectivity of the initial C−C bond-forming step in other classes of reductive couplings of allenes has been shown to strongly depend upon the nature and Lewis acidity of the reducing agent.[16–19] Processes selective for addition to the internal or the terminal carbon atoms of allenes have both been demonstrated in various nickel-catalyzed coupling processes. For example, the extensive developments from Ng and Jamison involving allene–aldehyde reductive coupling reactions,[16] as well as the related allene–CO$_2$ coupling processes developed by Mori and co-workers,[17] both involve C−C bond formation at the allene central carbon atom. In contrast, the inter- and intramolecular nickel-catalyzed aldehyde–allene coupling reactions involving organozinc reagents reported independently by Kang and Yoon, and by our group, exclusively involved addition to the terminal carbon atom of the allene.[18] Extensive work from Krische and co-workers has demonstrated couplings at an allene terminal carbon atom through transfer hydrogenative couplings of allenes with alcohols.[19] Alkylative cyclizations of allenes with electron-deficient alkenes were reported in our synthetic approach to kainic acid, where intramolecular additions were observed exclusively at the proximal terminal carbon atom of the allene.[14] As seen with the allene–aldehyde reductive couplings involving silane or borane reducing agents noted above, the coupling reactions developed in this work exclusively involve addition at the allene central carbon atom, which is consistent with the involvement of metallacycles **7–9**.

The observed regioselectivity of enone–allene reductive couplings using silane reagents in THF or toluene is most readily rationalized by the involvement of metallacycle **9**. Cases where metallacycle **7** would be destabilized by allylic[1,3] strain derived from substitution of R^3 and R^4 (i.e. Table 2, entries 8–11) are highly selective for the desired terminal methylene isomer **4**. Selective formation of metallacycle **9** and subsequent σ-bond metathesis of the Ni–O and Si–H bonds would afford the intermediate **13** (Scheme 4). Direct reductive elimination of this intermediate without allylic rearrangement would afford the observed product **4** after hydrolysis of the enol silane **14**. In contrast, we propose that reactions

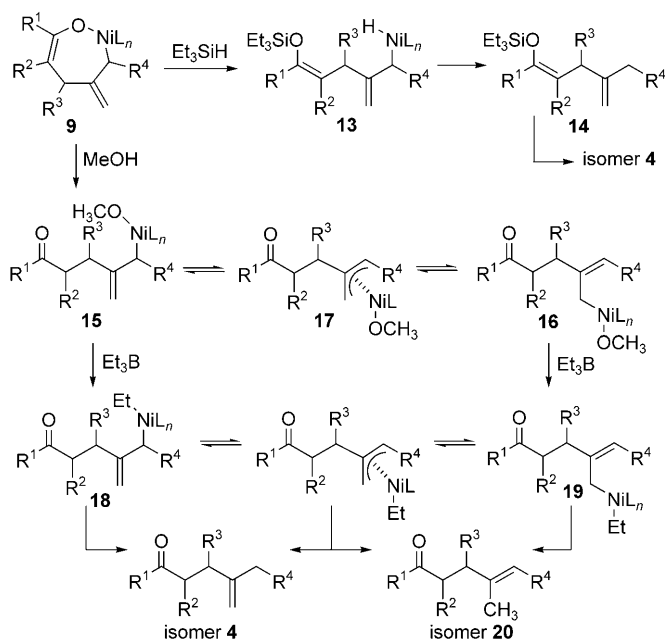**Table 2:** Scope of the enone–allene reductive couplings.

Entry	Enone	Allene	Product yield [%] (isomer ratio)[a]	Entry	Enone	Allene	Product yield [%] (isomer ratio)[a]
1	5a	6b	73 (78:15:7)	8	5c	6a	51 (>95:5)
2	5a	6c	50 (91:9)	9	5d	6a	90 (>95:5)
3	5a	6d	85 (>95:5)	10	5e	6b	72 (93:5:2)
4	5a	6e	68 (79:21)	11	5e	6e	70 (90:5:5)
5	5a	6f	85 (78:13:9)[b]	12	5f	6a	78 (>95:5)
6	5a	6g	63 (79:21)[c]	13	5a	6h	59 (78:22)
7	5b	6a	71 (>95:5)	14	5a	6i	78 (87:13)

[a] Major product is depicted in the table. Minor isomers are *E* and *Z* isomers of structures analogous to compound **1a** unless otherwise noted. Product ratios were determined for the crude reaction mixtures by using GC and NMR analyses. Yield refers to combined yield of all product isomers recovered after chromatographic purification. [b] Major isomer is depicted. Minor isomers are the *Z* isomer of the product shown (9%) and the terminal methylene isomer (9%). [c] Yield refers to the major isomer in this example. The minor isomer detected by GCMS analysis was not isolated. Cy = cyclohexyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl.
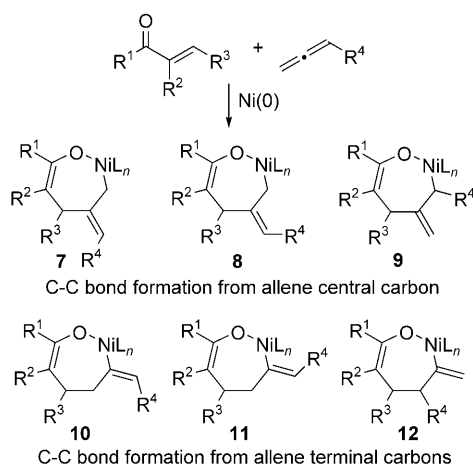
Scheme 3. Possible metallacycles in enone–allene couplings.

conducted in a methanol/THF mixed solvent system proceed by protonation of the metallacyclic intermediate before hydride (from Et₃SiH) or ethyl (from Et₃B) transfer occurs.[2e,h] In this event, the species **15** would be produced by methanol addition to metallacycle **9**. Unlike species **13**, which can undergo reductive elimination faster than allylic isomerization occurs, the species **15** and **16** are likely longer lived and can interconvert via π-allyl complex **17**. Species **18** and **19** may similarly undergo interconversion faster than β-hydride elimination occurs. Thus, pathways that involve either protic solvents, protic reagents, or triethylborane likely proceed through pathways that present opportunities for regiochemical erosion that are not available to the optimized procedure using triethylsilane in aprotic media. The formation of mixtures of **4** and **20** for reactions conducted in methanol (Table 1, entries 2–4 and 7), with unprotected hydroxy functionality (Table 2, entry 5), or with triethylborane in

Scheme 4. Proposed mechanisms for enone–allene reductive couplings.

aprotic media (Table 1, entry 1) are consistent with this rationale.

In conclusion, an efficient and highly regioselective catalytic reductive coupling of enones and allenes has been developed. With terminal allenes, this process selectively produces γ,δ-unsaturated carbonyl products with a 1,1-disubstituted alkene, which are not generally available by other reductive coupling procedures. The process provides an alternative to the stoichiometric generation of alkenyl cuprate reagents, which are somewhat cumbersome to generate for the alkene 1,1-disubstitution pattern targeted by this approach.

Experimental Section

General procedure for enone–allene reductive coupling: Toluene (1 mL) was added to a mixture of [Ni(cod)$_2$] (0.03 mmol) and triphenylphosphine (PPh$_3$; 0.06 mmol) at RT. After stirring for 5–10 min at RT, triethylsilane (0.6 mmol) and enone (0.3 mmol) were sequentially added by syringe to the dark red mixture. The allene (0.45 mmol) in toluene (4 mL) was then added using a syringe pump (1 mL h^{-1}) while the reaction mixture was heated at 50°C. The reaction mixture was stirred at 50°C until TLC analysis indicated the disappearance of the enone. The reaction mixture was concentrated, and then diluted with ethyl acetate. A solution of tetrabutylammonium fluoride (nBu$_4$NF; 0.6 mmol) in THF was added to the reaction mixture and stirred until TLC analysis indicated the disappearance of the enol silane product. The reaction mixture was washed with brine, dried over magnesium sulfate, filtered, concentrated, and then the residue was purified by column chromatography on silica gel.

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