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Evolution of Efficient Strategies for Enone−Alkyne and Enal−Alkyne Reductive Couplings

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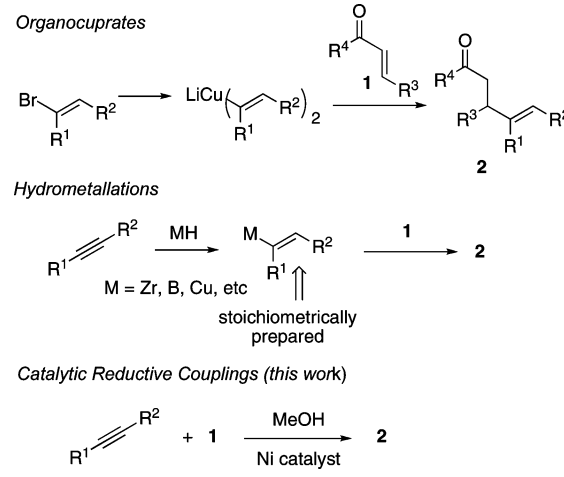
Abstract: Strategies for the reductive coupling of enones or enals with alkynes have been developed. The reducing agents employed include organozincs, organoboranes, organosilanes, and methanol. The latter of these strategies is simple, cost-effective, and tolerant of many functional groups. Isotopic labeling strategies have provided supporting evidence for the mechanistic proposals.

Introduction

Conjugate additions to enones, enoates, and their derivatives are among the most widely used reactions in the preparation of functionalized carbonyl derivatives.[1] The installation of alkene functionality by conjugate addition is well established, with many powerful variants. Traditional vinyl cuprate additions require prior synthesis of a vinyl halide, followed by lithium halogen exchange, cuprate formation, and then addition to the electrophilic alkene substrate (Scheme 1).[1] Alkyne hydrometalation strategies provide a powerful alternative to reagents derived from metal halogen exchange, but the stoichiometric generation of an alkenyl metal species is nonetheless still required.[2] Catalytic methods for the direct reductive coupling of enones and alkynes have attracted considerable recent study including work from our lab, and such methods enjoy the advantage of avoiding the stoichiometric assembly of vinyl organometallic reagents.[3] While this feature provides an important advance, the choice of reducing agent employed becomes an important defining feature of the practicality of the method.[4]

Early reports from our lab illustrated that intramolecular reductive couplings of enones and alkynes were possible by utilizing $ZnEt_2$ as the reducing agent in the presence of a Ni(0) catalyst.[5] This work built upon the important earlier studies of Ikeda, who illustrated that alkynylstannane reagents could participate in enone−alkyne alkylative coupling processes that transfer the alkynyl unit during coupling to generate a conjugated enyne product.[6] More recent advances from our laboratories illustrated conceptually similar couplings of enones and enals employing organoborane and silane reducing agents.[7] In concurrent studies, Cheng illustrated that cobalt-catalyzed processes involving zinc-mediated reductive couplings provide an effective procedure for enoate conjugate additions, which is an especially useful observation given the poor reactivity of enoates in the nickel-catalyzed processes.[8] A recent report from our laboratories then illustrated that reducing agents may be omitted

Scheme 1. Progression of Strategies for Effecting Conjugate Addition



(1) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1992; Vol. 41, pp 135−631.

(2) (a) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (b) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (c) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689. (d) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. (e) El-Batta, A.; Hage, T. R.; Plotkin, S.; Bergdahl, M. *Org. Lett.* **2004**, *6*, 107. (f) Yanagi, T.; Sasaki, H.; Suzuki, A; Miyaura, N. *Syn. Commun.* **1996**, *26*, 2503.

(3) (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (c) Montgomery, J.; Amarasinghe, K. K. D.; Chowdhury, S. K.; Oblinger, E.; Seo, J.; Savchenko, A. V. *Pure Appl. Chem.* **2002**, *7*, 129.

(4) For a recent review highlighting the progression from the use of stoichiometric metallated species to contemporary catalytic methods: Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.

(5) (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (c) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449. (d) Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839.

(6) (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. (c) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511.

(7) (a) Herath, A.; Thompson, B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712. (b) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 8132.

(8) (a) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696. (b) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032. (c) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876.

10.1021/ja9083607 CCC: $40.75

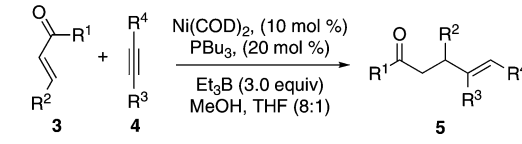
altogether from enal-alkyne couplings by engineering an internal redox pathway.[9] This strategy provides a means to access ester-containing products starting from enal via the unusual redox interchange inherent in the process. Alkenes have recently been recognized by Jamison as useful inputs for the generation of γ,δ-unsaturated carbonyls by the three-component addition of enones, alkenes, and silyl triflates, and as noted herein, the alkene addition method illustrates complementary characteristics to alkyne addition methods.[10] A variant involving alkene−enone additions from Ogoshi recently illustrated that the silyl triflate may be omitted under more forcing conditions.[11]

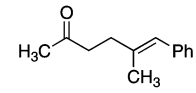
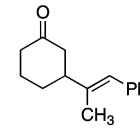
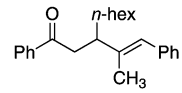
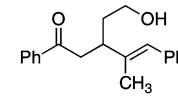
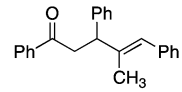
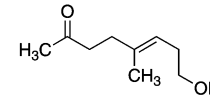
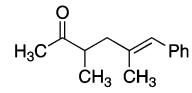
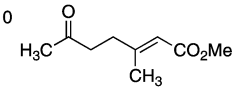
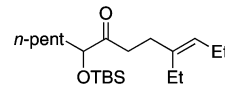
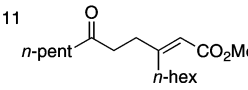
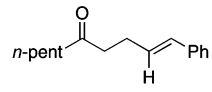
Considering the increase in practicality of conjugate additions dating back to early developments in organocuprate chemistry up to the current state of procedures described above, we were motivated to further advance methods for enone−alkyne reductive couplings to the highest possible level of practicality. Recent developments from Krische[12] and Sigman[13] in the development of C−C bond-forming reductive coupling processes that utilize alcohols as the reducing agent have had a major impact on the underlying efficiencies of aldehyde addition processes and cross-couplings, respectively. These important advances motivated us to consider this strategy as means for accessing γ,δ-unsaturated carbonyls by the reductive couplings of enones and alkynes. The ability to carry out conjugate addition reactions in simple hydroxylic solvents in the absence of any other reducing agent would provide an important advance toward avoiding the limitations and inefficiencies of alternate methods for effecting conjugate addition. In this report, we provide a full account of our recent studies on the intermolecular reductive coupling of enones or enals with alkynes and describe for the first time the use of methanol as the reducing agent in couplings of this type.[14]

Results and Discussion

Development of Triethylborane-Mediated Enone−Alkyne Reductive Couplings. Although efficient reductive cyclizations of alkynyl enones employing diethylzinc in anhydrous THF as the reducing agent were developed by our lab in the mid 1990s,[5] two critical changes in reaction setup are required to allow efficient intermolecular processes to proceed. By employing a methanol/THF cosolvent system, and employing triethylborane as reducing agent, a variety of simple enones and alkynes undergo efficient reductive coupling in the presence of $Ni(COD)_2$ (10 mol %) and PBu_3 (20 mol %). The scope of this procedure is relatively broad, and a representative sampling of effective substrate combinations are depicted below (Table 1).[7a] As shown, effective variants include couplings of α-substituted and β-substituted enones, cyclic or acyclic enones, α′-silyloxy-enones, and enones that possess free hydroxyls. Similarly, terminal alkynes, aromatic and nonaromatic internal alkynes, and ynoates were efficiently tolerated. Regioselectivities are high with aromatic and terminal alkynes, whereas regioisomeric mixtures are observed with nonaromatic internal alkynes. As the examples illustrate, several features are particularly noteworthy. First, the method tolerates unprotected hydroxyls and ester functionality, which would be problematic for many alternate methods including the use of organolithium-derived cuprates. Second, the combination of enones and ynoates is interesting from the standpoint of chemoselectivity. Both starting components are effective Michael acceptors, yet no homocoupling is observed for either component. Only a modest excess of the ynoate is required, and slow addition techniques are not required.

Table 1. Scope of Triethylborane-Mediated Reductive Couplings[a]



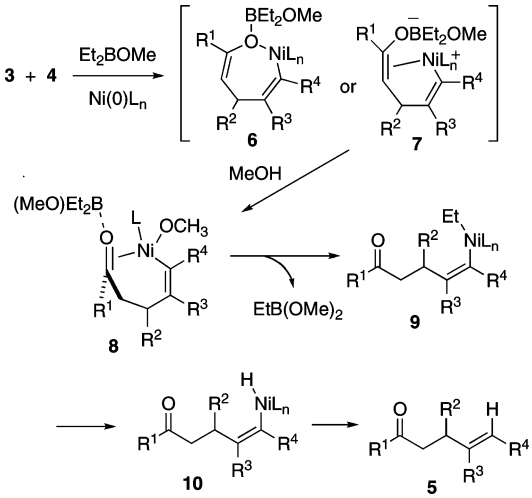
entry	product (yield, regioselectivity)	entry	product (yield, regioselectivity)
1	 85% (>95:5)	7	 80% (>95:5)
2	 65% (>95:5)	8	 84% (>95:5)
3	 90% (>95:5)	9	 50% (3:1)
4	 80% (>95:5)	10	 74% (>95:5)
5	 72%	11	 78% (>95:5)
6	 74% (>95:5)		

[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_3B, 0.1 equiv of $Ni(COD)_2$, and 0.2 equiv of PBu_3 at 50 °C. A product ratio of >95:5 indicates that no other stereo- or regioisomer was detected at a level greater than 5%.

Our studies illustrate that the methanol component in the solvent mixture is required. This effect may be attributed to the role of methanol in promoting alkyl transfer of the organoborane, as well as in promoting hydrolysis of a transiently generated nickel enolate motif. The likely mechanism for this transformation involves complexation of the enone **3** and alkyne

(9) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469.
(10) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893.
(11) Ogoshi, S.; Haba, T.; Ohashi, M. *J. Am. Chem. Soc.* **2009**, *131*, 10350.
(12) (a) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (b) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066. (c) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (d) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (e) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (f) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (g) See also Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W. J. *J. Am. Chem. Soc.* **2005**, *127*, 10836.
(13) (a) Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193. (b) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3219. (c) Gligorich, K. M.; Iwai, Y.; Cummings, S. A.; Sigman, M. S. *Tetrahedron* **2009**, *65*, 5074.
(14) For a preliminary account of portions of this work, see ref 7.

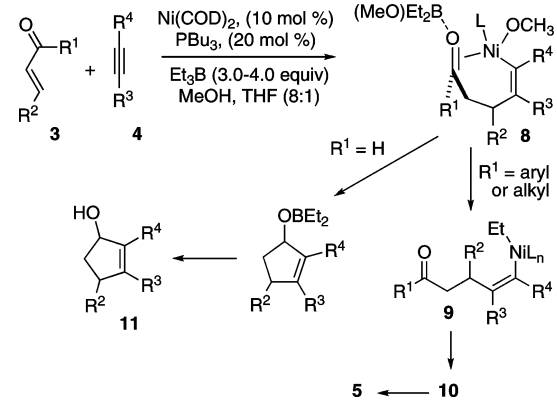
Scheme 2. Mechanism of Triethylborane-Mediated Reductive Couplings



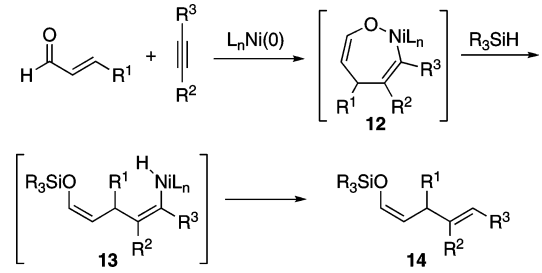
4 to a Ni(0)/PBu_3 species, followed by oxidative cyclization to nickel metallacycle **6** or **7** (Scheme 2).[15] Involvement of the organoborane may accelerate this oxidative cyclization. The role of Et_3B in promoting metallacycle formation in aldehyde−alkyne couplings was recently computationally evaluated by Houk and Jamison,[16] and proposals of this Lewis acidic role of Et_3B were depicted by Tamaru in aldehyde−diene couplings.[17] The role of organozincs in promoting metallacycle formation was studied in our collaborative work with Schlegel,[18] and experimental demonstrations of rate acceleration promoted by other Lewis acids were documented by Ogoshi for other classes of metallacycles.[19] The species generated upon stirring Et_3B in methanol has been characterized as Et_2BOMe,[20] and we assume that this species is likely generated under the mixed solvent system employed in our studies. The enolate derived from oxidative cyclization may be viewed as either a boron or nickel enolate **6** or **7**, simply depending upon whether the Ni−O interaction is maintained. After the formation of **6** or **7**, protonation of the enolate by methanol would generate species **8**, followed by ethyl transfer from boron to nickel to generate **9**, β-hydride elimination to produce **10**, and reductive elimination to produce the observed conjugate addition product **5**.

Development of Trialkylsilane-Mediated Enal−Alkyne Reductive Couplings. One class of reactions that fails using the above protocol is the reductive coupling of enals with alkynes. Whereas simple conjugate addition products are not obtained, instead, efficient conversion of the enal and alkyne to a

Scheme 3. Divergent Behavior of Enones and Enals



Scheme 4. Suppression of [3 + 2] Cycloaddition by the Use of Organosilanes

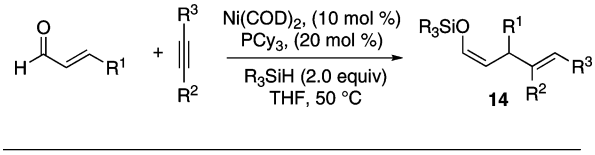


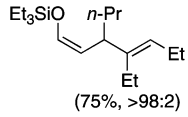
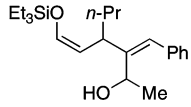
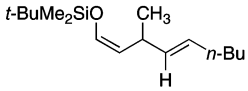
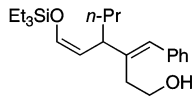
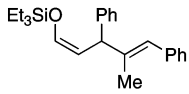
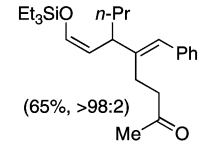
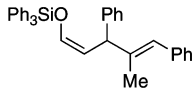
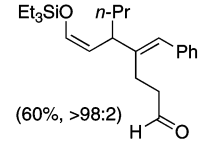
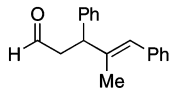
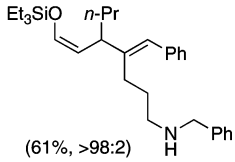
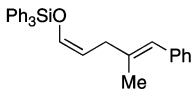
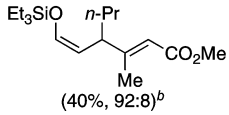
cyclopentenol product via [3 + 2] reductive *cycloaddition* is observed.[21] We envision the mechanism of enone-alkyne reductive coupling and enal alkyne [3 + 2] reductive cycloaddition as being closely related. With vinyl nickel species **8** serving as a common intermediate, (Scheme 3), reduction by Et_3B leads to formation of acyclic product **5** via intermediates **9** and **10** as depicted above (Scheme 2). However, in the enal variant, intermediate **8** (R^1 = H) now possesses an electrophilic aldehyde still complexed to the alkenyl nickel unit. Direct addition of the nickel alkenyl functionality to the aldehyde then occurs to initiate five-membered ring closure leading to the [3 + 2] cycloaddition product **11**.

The [3 + 2] reductive cycloaddition reaction is an interesting process in its own right as previously communicated,[21] and related processes have since been reported by Cheng[22] and Toste and Bergman.[23] However, the need for an efficient reductive *coupling* of enals and alkynes still remained. The mechanistic analysis described above suggested that suppression of the [3 + 2] reductive cycloaddition pathway might be difficult for any set of conditions that proceeded through intermediate **8**. For this reason, we were attracted to the use of silane reducing agents in aprotic solvents. In the absence of organoboranes, metallacycle **12** could be directly produced by oxidative cyclization (Scheme 4). σ-Bond metathesis of **12** would generate intermediate **13**, followed by generation of enol silane product **14** by C−H reductive elimination. The absence of methanol in the solvent composition would ensure that metallacyclic enolate protonation does not occur under the reaction conditions, and the formation of the enol silane functionality generated by the σ-bond metathesis event would ensure that the aldehyde is not

(15) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370.
(16) (a) McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654. For development of the synthetic procedures related to this study, see: (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.
(17) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397.
(18) Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636.
(19) (a) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802. (b) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810.
(20) (a) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923. For the use of $Ni(COD)_2/Et_3B$ in methanol, see: (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364.
(21) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030.
(22) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166.
(23) Schomaker, J. M.; Toste, F. D.; Bergman, R. G. *Org. Lett.* **2009**, *11*, 3698.

Table 2. Scope of Trialkylsilane-Mediated Reductive Couplings[a]



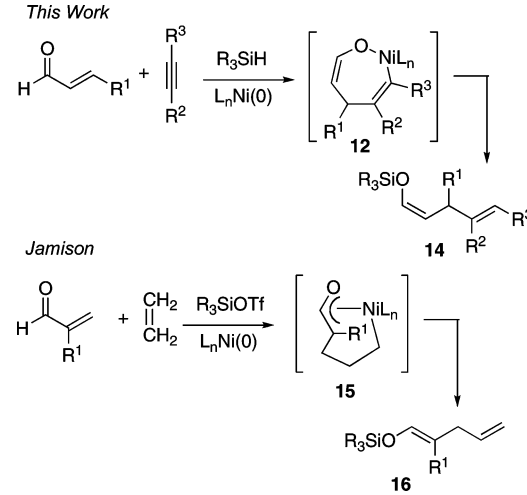
entry	product (yield, ratio)	entry	product (yield, ratio)[a]
1	 (75%, >98:2)	8	 (75%, 79:21)[d]
2	 (50%, 81:19)[b]	9	 (91%, >98:2)
3	 (87%, >98:2)	10	 (65%, >98:2)
4	 (92%, >98:2)	11	 (60%, >98:2)
5	 (86%, >98:2)[c]	12	 (61%, >98:2)
6	 (69%, >98:2)		
7	 (40%, 92:8)[b]		

[a] Reactions were carried out in THF using 1.0 equiv of enone, 1.5 equiv of alkyne, 2.0 equiv of silane, 0.1 equiv of $Ni(COD)_2$, and 0.2 equiv of PCy_3 at 50 °C. A product ratio of >98:2 indicates that no other stereo- or regioisomer was detected at a level greater than 2%. [b] Isomer ratio refers to the regiochemistry of alkyne insertion. [c] Me_2PhSiH was used as reducing agent. [d] Isomer ratio refers to relative stereochemistry of the two stereocenters.

liberated during the integral mechanistic steps. These features should suppress the competing [3 + 2] cycloaddition manifold.

As envisioned by this analysis, the silane-mediated reductive coupling of enals and alkynes employing a catalyst from $Ni(COD)_2$ (10 mol %) and PCy_3 (20 mol %) in THF provides a straightforward and versatile entry to enol silanes. Representative examples are depicted below (Table 2).[7b] The process is efficient with acrolein as well as enals that possess β-alkyl- and β-aryl substitution. In all cases, control of stereochemistry of both newly formed alkenes is highly selective, and the *Z*-enol silane stereochemistry is always observed. A variety of organosilanes efficiently participate in the process, and while most lead to isolable enol silanes, couplings with Me_2PhSiH afford products that undergo complete hydrolysis upon purification to afford the aldehyde product. Of particular note is the remarkable functional group tolerance compared with other methods for enol silane preparation. Whereas electrophilic silicon reagents are typically employed in the synthesis of enol silanes, the use of organosilanes instead allows tolerance of a variety of

Scheme 5. Complementarity of Enal−Alkyne and Enal−Alkene Couplings



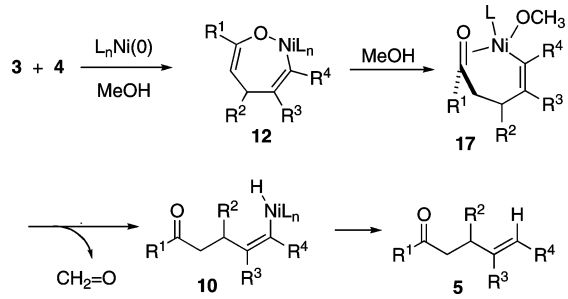
functional groups including alcohols, esters, ketones, aldehydes and secondary amines. The only alternate procedure for enol silane synthesis that has demonstrated this range of functional group tolerance is the Trost Ru-catalyzed alkene−alkyne coupling procedure that selectively generates *E*-enol silanes,[24] thus making the Ni- and Ru-catalyzed processes entirely complementary.

The consistently observed *Z*-enol silane stereochemistry provides evidence that the η^1 *O*-bound nickel metallacyclic enolate **12** is involved as a productive intermediate (Scheme 5). The seven-membered metallacycle with an η^1 enolate requires formation of the *Z*-enolate that is maintained in subsequent mechanistic steps to ultimately produce *Z*-enol silane **14**. This outcome can be contrasted with the recent studies of Jamison on enone-alkene couplings using silyl triflate promoters.[10] That method provides similar products, but with the *E*-enol silane **16** being selectively produced. The mechanism proposed by Jamison for his method involves formation of η^3 nickel enolate species **15**, and indeed, it is likely the differing hapticity of the metallacyclic enolates derived from otherwise similar couplings of alkenes and alkynes that leads to this profound change in enol silane stereochemistry, thus establishing the two methods as complementary. In addition, the positions where functionality may be installed is different between the two methods. Notably, an enone-alkyne-derived nickel metallacycle was previously characterized by our lab as the η^1 *O*-enolate species, as evidenced by both crystallographic and NMR characterization.[15,18] In contrast, a cyclic nickel enolate derived from enone-cyclopropyl ketone coupling was characterized by Ogoshi as the η^3 nickel enolate.[25] Based on these precedents, it appears likely that the hybridization of atoms within the metallacycle framework, the ring size, and the resulting ring strain differences result in the key hapticity change that ultimately reverses the observed enol silane geometry.[26]

Development of Methanol-Mediated Enone−Alkyne Reductive Couplings. With efficient methods in hand for the reductive couplings of enones and alkynes using trialkylboranes and of enals and alkynes using trialkylsilanes, we next considered the

(24) (a) Trost, B. M.; Surivet, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2001**, *123*, 2897. For an overview of related methods, see: (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.
(25) Tamaki, T.; Nagata, M.; Ohashi, M.; Ogoshi, S. *Chem.—Eur. J.* **2009**, *15*, 10083.

Scheme 6. Reductive Couplings Using Methanol as Reducing Agent

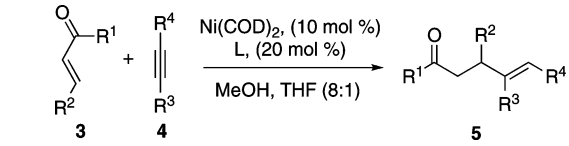


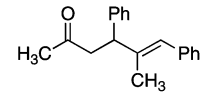
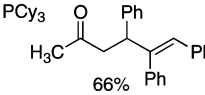
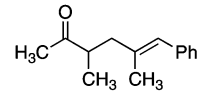
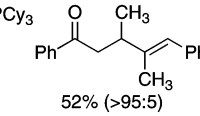
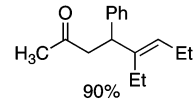
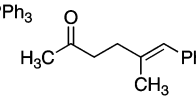
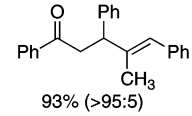
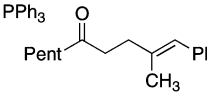
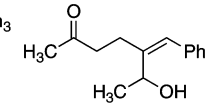
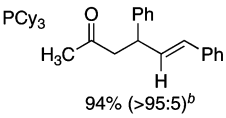
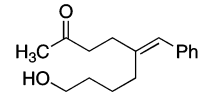
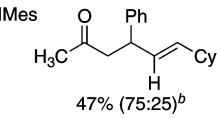
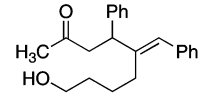
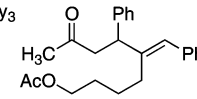
possibility of increasing the practicality and cost of the enone-alkyne coupling procedure by directly using methanol as the reducing agent, thereby avoiding the use of a pyrophoric reducing agent. The analysis leading to this possibility comes from considering the mechanism proposed for Et_3B-based reductive couplings. As noted above, Et_3B-based reductive couplings required the use of a methanol-THF cosolvent system, to allow the production of intermediate **8** by protonation of the metallacyclic enolate motif (Scheme 2). We reasoned that species **17**, generated in the absence of Et_3B, could potentially be coaxed to undergo β-hydride elimination directly to form nickel hydride species **10**, ultimately leading to product **5** (Scheme 6). For the Et_3B-free pathway to succeed, not only must intermediate **17** undergo β-hydride elimination, but the oxidative cyclization to generate metallacycle **12** must proceed in the absence of the borane Lewis acidity.

Upon initiating studies to explore the possibility of reductive couplings employing methanol as the reducing agent, our initial experiments using the precise protocol used in Et_3B-based couplings, but in the absence of Et_3B, led to inefficient couplings. While the Et_3B-based procedure used a Ni(0)/PBu_3 catalyst, we quickly found that PCy_3 and PPh_3 complexes of Ni(0) in THF/methanol do efficiently catalyze enone-alkyne reductive couplings of internal alkynes in the absence of Et_3B (Table 3). The scope of this procedure is somewhat analogous to the related Et_3B-based procedure described above, with the notable exceptions that cyclic enones participated efficiently only when Et_3B was employed. Otherwise, examples employing methyl vinyl ketone, α-substituted, or β-substituted enones were generally efficient in the Et_3B-free variant, as were couplings with a range of internal alkynes bearing various functional groups. Although PCy_3 and PPh_3 may be used interchangably in some cases, PCy_3 was generally preferred with α- or β-substituted enones, whereas PPh_3 was generally preferred with enones that lack α- and β-substitution.

Terminal alkynes are an important class of substrates that are often problematic in reductive couplings due to rapid trimerization of the terminal alkyne under the reaction conditions. In a coupling of phenylacetylene, the standard conditions with PCy_3 afforded the desired product in 59% isolated yield. However, syringe-drive addition of the alkyne improved the yield to 94%. In our prior studies of aldehyde-alkyne reductive couplings, *N*-heterocyclic carbene (NHC) ligands were relatively inefficient in the trimerization of alkynes compared with the desired reductive coupling pathway.[27] This observation proved useful here as well in the reductive coupling of enones and terminal alkynes. For example, a coupling of cyclohexyl acetylene proceeded in only 24% isolated yield even when employing slow addition of the alkyne. However, the use of the NHC IMes as ligand improved the yield to 47%. When using internal alkynes, NHC's were generally less satisfactory than PCy_3 or PPh_3. In summary, three complementary ligands are identified for the methanol-based procedure: PCy_3 for α- or β-substituted enones with internal alkynes, PPh_3 for unsubstituted enones with internal alkynes, and NHC's for couplings of terminal alkynes. Examples provided in Table 3 illustrate the optimum conditions for each example shown.

Table 3. Scope of Methanol-Mediated Reductive Couplings



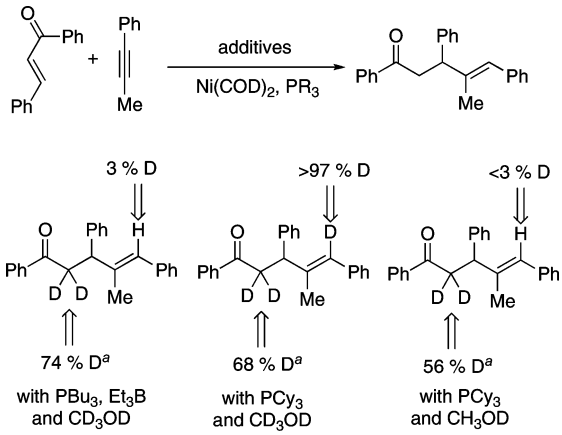
entry	L	product (yield, regioselectivity)	entry	L	product (yield, regioselectivity)
1	PCy_3	 86% (>95:5)	8	PCy_3	 66%
2	PCy_3	 63% (94:6)	9	PCy_3	 52% (>95:5)
3	PCy_3	 90%	10	PPh_3	 83% (93:7)
4	PCy_3	 93% (>95:5)	11	PPh_3	 81% (>92:8)
5	PPh_3	 70% (>95:5)	12	PCy_3	 94% (>95:5)[b]
6	PPh_3	 76% (>95:5)	13	IMes	 47% (75:25)[b]
7	PCy_3	 58% (>95:5)	14	PCy_3	 47% (>95:5)[c]

[a] Reactions were carried out in MeOH:THF (8:1) using 1.0 equiv of enone, 1.5 equiv of alkyne, 0.1 equiv of $Ni(COD)_2$, and either 0.2 equiv of PPh_3 or PCy_3, or 0.1 equiv of IMes [from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and *t*-BuOK] at 50 °C. A product ratio of >95:5 indicates that no other stereo- or regioisomer was detected at a level greater than 5%. [b] Alkyne was added by syringe drive. [c] Additionally, 13% yield of the alcohol derived from deprotection of the product acetate was obtained, giving an overall 60% yield for the desired coupling.

(26) For interconversion of *C*- and *O*-enolates of nickel, see: Campora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutiérrez-Puebla, E.; Ruiz, C. *J. Am. Chem. Soc.* **2003**, *125*, 1482.

(27) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698.

Scheme 7. Deuterium-Labeling Studies



[a] Percent D incorporation of the CH_2 moiety α to the ketone is given relative to 2 hydrogen atom units.

The failure of cyclic enones to participate when using methanol as the reducing agent may originate from the beneficial interaction of oxygen and nickel during metallacycle formation with acyclic enones, leading to the *O*-enolate **12**, which is postulated to be a key intermediate in the reactions. Cyclic enones, which are locked in the *S*-trans orientation, cannot adopt an orientation that allows the *O*-enolate to form. Instead formation of a five-membered *C*-enolate would be required for cyclic enones. The Lewis acidity of Et_3B may therefore become especially important with cyclic enones since the Ni−O interaction is not allowed to develop during metallacycle formation.

The similar scope and relative rates of couplings in the presence and absence of Et_3B raise the question of whether the borane is actually functioning as reducing agent at all in the Et_3B variant, or whether it is simply functioning as a Lewis acidic promoter. This question can be addressed by isotopic labeling studies, and a series of experiments were carried out to clarify this question. Using trans-chalcone as a test case, three experiments were performed to elucidate the nature of the reducing agent. In the variant employing $Ni(COD)_2$, PBu_3, and Et_3B, a reaction in CD_3OD/THF afforded product with 3% incorporation of deuterium at the alkenyl position (Scheme 7). An experiment with $Ni(COD)_2$ and PCy_3 performed in CD_3OD/THF, in contrast, afforded >97% deuteration at the alkenyl position. A third experiment with $Ni(COD)_2$ and PCy_3 performed in CH_3OD/THF afforded no measurable deuteration at the alkenyl position. Deuteration at the methylene position α to the phenyl ketone was observed at levels exceeding 1 unit of deuterium due to the combination of initial enolate kinetic protonation in addition to H/D exchange occurring in this acidic position. The above experiments clearly indicate that the variant using Et_3B employs the borane, not methanol, as the reducing agent. In contrast, the Et_3B-free procedure clearly employs methanol as the reducing agent by transferring a hydrogen atom from the CH_3 group to the product.

Conclusions

In summary, a group of protocols has been developed for the reductive couplings of enones or enals with alkynes. The procedures provide simple and environmentally friendly alternatives to the use of vinyl cuprate reagents in conjugate addition processes. The developments described present a progression of practicality, wherein the reducing agent required may include organozincs, organoboranes, silanes, or methanol. The latter of these developments, namely the procedure that utilizes methanol as a cosolvent and reducing agent, provides an especially attractive procedure that avoids the stoichiometric generation of metalated species and reactive or flammable reducing agents that classical alternatives require.

Acknowledgment. We acknowledge receipt of NSF grant CHE-0718250 in support of this work. Ben Thompson is thanked for preliminary contributions described in ref 7a.

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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