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Mechanistic Insights into Nickel-Catalyzed Cycloisomerizations

John H. Phillips and John Montgomery*

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

jmontg@umich.edu

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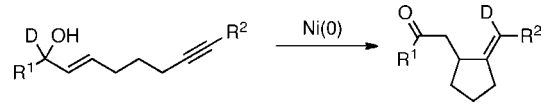
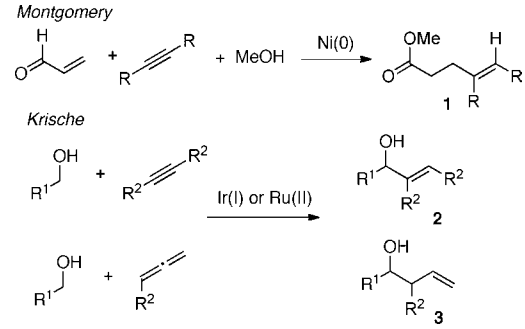
ABSTRACT



A nickel-catalyzed cycloisomerization coupling an allylic alcohol with an alkyne has been developed. Mechanistic insights gained through deuterium-labeling crossover studies and stereochemical probes illustrate that oxidation of the allylic alcohol to a metal-free enone is not involved in the cyclization pathway. The intermediacy of a metallacycle directly derived from oxidative cyclization of Ni(0) with the allylic alcohol and alkyne is consistent with the results obtained. The simple mechanistic probes employed could be useful in the study of many classes of cycloisomerization processes.

Transition metal catalyzed couplings involving the union of two different π-components have been developed in many contexts.[1] In some cases, a completely atom-economical rearrangement of starting materials leads to products.[1a,b] In other cases, reducing agents are employed, leading to a net two-electron reduction during the coupling event.[1c−i] The substrate combinations that efficiently participate in redox-neutral rearrangements often differ structurally from the combinations that participate in reductive coupling processes. Coupling reactions that normally require external reducing agents can potentially be made more atom economical and cost-effective by developing strategies where the redox partner is an integral component of the starting material. Recent work from our laboratory has illustrated that nickel-catalyzed enal−alkyne−alcohol three-component couplings possess such a feature.[2] As illustrated (Scheme 1), during the C−C bond-forming event producing compound **1**, reduction of the alkyne to an alkene simultaneously with oxidation of an aldehyde to an ester removes the need for an external reducing agent commonly utilized in processes of this type. The extensive body of work from Krische involving transfer hydrogenation-mediated couplings shares this characteristic as well.[3] As examples in the formation of **2** and **3** illustrate, during the C−C bond forming process,

Scheme 1. C−C Bond Formations Mediated by Redox Exchange



(1) (a) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (c) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (d) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. (e) Montgomery, J.; Sormunen, G. J. *Top. Curr. Chem.* **2007**, *279*, 1−23. (f) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449. (g) Ikeda, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120–5122. (h) Skukcas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394–1401. (i) Jeganmohan, M.; Cheng, C. H. *Chem.−Eur. J.* **2008**, *14*, 10876–10886.

(2) (a) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469–471. (b) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024–17029.

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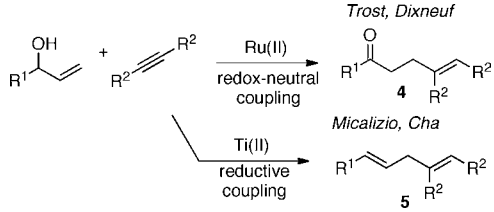
either an alkyne or an allene may be reduced to an isolated alkene simultaneously with the oxidation of the starting alcohol to a carbonyl component that is captured in the bond-forming process. Processes of this type stand to improve the efficiency of the underlying transformations that otherwise require external reductants.

The union of allylic alcohols with alkynes is one of the few substrate combinations that undergo efficient couplings in both reductive and nonreductive manifolds. Developments from Trost and Dixneuf illustrated that atom-economical couplings of allylic alcohols with alkynes employing ruthenium catalysis proceed to afford substituted ketone products **4**,[4,5] whereas Micalizio[6] and Cha[7] independently reported that titanium-mediated couplings of similar substrates proceed with net reduction and elimination to provide 1,4-diene products **5** (Scheme 2).[8] To better

Scheme 2. Couplings of Allylic Alcohols and Alkynes



understand the potential for developing new classes of metal-catalyzed coupling events that proceed by redox-mediated pathways without the use of an external reductant, we have investigated couplings of allylic alcohols with alkynes and employed crossover studies and stereochemical probes to better define how the redox-neutral pathways proceed. The insights gained from this study illustrate mechanistic features that may guide further reaction discovery efforts.

Our mechanistically focused efforts have primarily examined intramolecular variants of allylic alcohol−alkyne couplings. Initial explorations of the cycloisomerization of substrate **6** illustrated that ligand choice and base additive were both essential elements for promoting efficient cyclizations to produce **7** (Table 1). All cycliza-

Table 1. Optimization of Allylic Alcohol−Alkyne Coupling

entry	ligand	base	solvent	temp (°C)	addition time[a]	yield
1	none	none	$PhCH_3$	90	3 h	4
2	none	*t*-BuOK	$PhCH_3$	90	3 h	20
3	IPr[b]	*t*-BuOK	$PhCH_3$	90	3 h	18
4	PBu_3	*t*-BuOK	$PhCH_3$	90	3 h	7
5	PCy_3	*t*-BuOK	$PhCH_3$	90	3 h	35
6	PCy_3	none	$PhCH_3$	60	3 h	17
7	PCy_3	*t*-BuOK	$PhCH_3$	90	30 min	58
8	PCy_3	*t*-BuOK	$PhCH_3$	60	30 min	71
9	PCy_3	*t*-BuOK	$PhCH_3$	rt	30 min	45
10	PCy_3	*t*-BuOK	$PhCH_3$	60	none	17

[a] Addition time refers to the ynal addition time by syringe drive. [b] 10 mol % ligand was used.

tions were conducted with 10 mol % $Ni(COD)_2$ as the precatalyst. Cyclizations in the absence of added ligands were inefficient (entries 1 and 2). The use of the N-heterocyclic carbene 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene (IPr) was inefficient, as was PBu_3 (entries 3 and 4). Modestly improved yields were seen with PCy_3 in the presence of KO-*t*-Bu, and yields with PCy_3 in the absence of this base additive were lower (entries 5 and 6). Using the combination of PCy_3 and KO-*t*-Bu with 30 min syringe drive addition of the ynal, comparisons of reactions conducted at various temperatures illustrated that reactions conducted at 60 °C provided an optimized yield of 71% (entries 7−9). Yields without syringe drive addition of the ynal were markedly lower since competing pathways such as alkyne trimerization were minimized with slow addition (entry 10). On the basis of these experiments, the optimized conditions from entry 8 were examined with different substrates.

Using the optimized protocol, cyclizations bearing either aromatic or silyl functionality on the alkyne were found to proceed efficiently (Table 2, entries 1−3). However, terminal alkynes were poor substrates for the cyclization (entry 4). The allylic alcohol functionality tolerated either aromatic (entries 1−3) or aliphatic (entry 5) substitution on the secondary hydroxyl. Primary allylic alcohols, however, failed to participate in the cycloisomerizations (entry 6). A six-membered ring cyclization also proceeded in moderate yield with a phenyl-substituted alkyne (entry 7). In addition to the above examples involving cyclization, a

(3) For a review, see: (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46. (b) For alkynes: Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066–2067. (c) For allenes: Bower, J.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134–15135.

(4) (a) Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 10402–10403. (b) Trost, B. M.; Indolese, A. F.; Muller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615–623. (c) Trost, B. M.; Surivet, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2001**, *123*, 2897–2898. (d) Dérien, S.; Jan, D.; Dixneuf, P. H. *Tetrahedron* **1996**, *52*, 5511–5524.

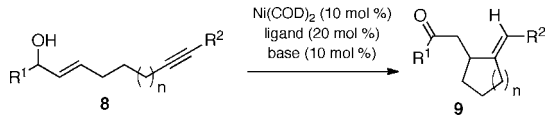
(5) For a recent synthetic application, see: Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293–6295.

(6) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112–15113.

(7) Lysendo, I. L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997–16002.

(8) For related reductive cyclizations of simple enynes, see: (a) Chen, M.; Weng, Y.; Guo, M.; Zhang, H.; Lei, A. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 2279–2282. (b) Chai, Z.; Wang, H. F.; Zhao, G. *Synlett* **2009**, 1785–1790. (c) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163. (d) Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7875–7880. (e) Jang, H. Y.; Hughes, F. W.; Gong, H. G.; Zhang, J. M.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174–6175.

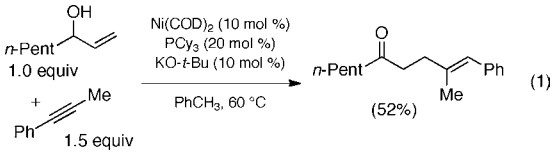
Table 2. Scope of Allylic Alcohol−Alkyne Couplings[a]



entry	R^1	R^2	n	yield %[a]
1	Ph	Ph	1	71
2	Ph	*p*-anisole	1	75
3	Ph	TMS	1	82
4	Ph	H	1	7
5	*n*-butyl	Ph	1	55
6	H	Ph	1	0
7	Ph	Ph	2	46

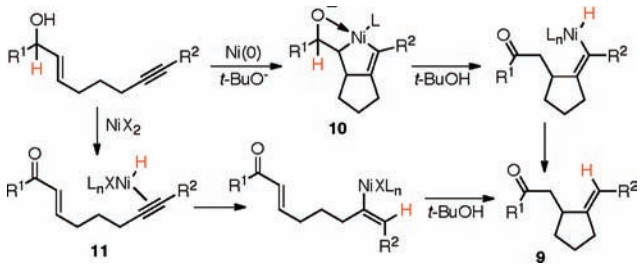
[a] Reaction conditions: allylic alcohol (1.0 equiv), $Ni(COD)_2$ (0.1 equiv), PCy_3 (0.2 equiv), *t*BuOK (0.1 equiv), toluene (0.1 M), 60 °C. The allylic alcohol was added via syringe drive over a 30 min period.

single example of an intermolecular coupling proceeded in modest yield (eq 1).



With the above preliminary data in hand, we were interested in evaluating mechanistic features of the process to elucidate the features that would allow the rational development of new processes that involve redox interchange of reactive components during a C−C bond-forming event. A number of possible mechanistic pathways may be envisioned for the above catalytic transformations. One possibility involves initial alkoxide-assisted formation of metallacycle **10** from oxidative cyclization of Ni(0) with the allylic alcohol−alkyne substrate (Scheme 3). A second possibility

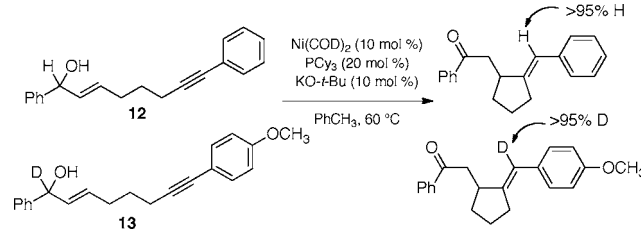
Scheme 3. Mechanistic Pathways for Coupling



involves oxidation of the allylic alcohol to an enone, followed by rapid cyclization by a process such as that depicted for **11** to **9**. This latter sequence could most likely be initiated by an adventitiously generated Ni(II) species.[9] These pathways are analogous to pathways proposed by Trost in the development of ruthenium(II)-catalyzed processes.[4] An enone intermediate could not be detected during the nickel-catalyzed processes, and injection of an enone to the reaction mixture inhibits product formation. Although these observations illustrate that appreciable buildup of enone was not occurring, the possibility remained that enones were rapidly formed and consumed during the reaction pathway.

To more completely examine the potential involvement of an enone intermediate, a crossover experiment utilizing substrates **12** and **13** was examined (Scheme 4). The

Scheme 4. Crossover Experiments



metallacycle mechanism involves a unimolecular hydrogen atom transfer process (via β-hydride elimination and reductive elimination), and therefore no crossover would be anticipated for this pathway. In contrast, any pathway that involves an enone intermediate may be subject to crossover in this experiment if dissociation of the enone from the catalyst during the sequence occurs (i.e., at the stage of intermediate **11**). Additionally, nickel hydride-mediated pathways such as those involved in hydrovinylation processes with electrophilic Ni(II) species would also lead to crossover in experiments of this type.[10,11] In the reaction involving **12** and **13**, no crossover was observed, which is consistent with either involvement of metallacycle **10** or with a mechanism involving enone formation where enone dissociation from the catalyst does not occur.

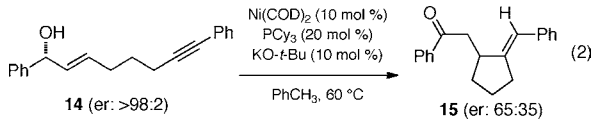
Another mechanistic probe in evaluating the potential involvement of enones is the transfer of chirality from starting materials to products (eq 2). Using enantiopure substrate **14**, if enone formation occurs, then racemic product **15** would be anticipated unless both the enone and alkyne remain coordinated to nickel without dissociation of the enone unit. Alternatively, achiral intermediates are not involved in the mechanism involving metallacycle **10**, and some level of chirality transfer would be expected. Upon conducting this experiment, enantiopure substrate **14** was

(9) Cuperly, D.; Petrignet, J.; Crevisy, C.; Gree, R. *Chem.—Eur. J.* **2006**, *12*, 3261–3274.

(10) For leading references to hydrovinylation processes: (a) RajanBabu, T. V. *Synlett* **2009**, *85*, 3–885. (b) RajanBabu, T. V.; Nomura, N.; Jin, J.; Radetich, B.; Park, H. S.; Nandi, M. *Chem.—Eur. J.* **1999**, *5*, 1963–1968.

(11) A recent report from Louie illustrates that nickel hydride-mediated cycloisomerizations may involve *ortho*-metallation of an NHC ligand. As our work involves phosphine complexes, nickel hydride generation by this mechanism is unlikely in the present manuscript. Tekavec, T. N.; Louie, J. *Tetrahedron* **2008**, *64*, 6870–6875.

converted to product **15** with 30% ee,[12] and recovered starting material in an experiment run to partial completion was recovered in enantiopure form. Therefore, while the degree of chirality transfer is insufficient for synthetic utility, the involvement of a mechanism involving free enone or enone solely bound to nickel through the alkyne may be ruled out.



(2)

On the basis of these experiments, the formation of metallacycle **10** as the operative mechanistic pathway seems most likely for the nickel-catalyzed process. Notably, the methyl ether or silyl ether of the starting allylic alcohol fails to undergo cyclization under the reaction conditions developed, lending support to the notion that alkoxide coordination as depicted in structure **10** may be important for catalysis to occur. In addition to crossover and chirality transfer experiments that support the metallacycle-based pathway, use of a Ni(0) precatalyst is most consistent with metallacycle-based pathways in comparison to related Ni(0)-catalyzed transformations previously reported.[1c−g] The mechanism of coupling of allylic alcohols and alkynes may differ according to the catalyst employed.

In summary, a base-promoted, nickel-catalyzed cycloisomerization of allylic alcohol−alkyne substrates has been developed. On the basis of crossover experiments and stereochemical probes, a mechanism involving metallacycle formation seems most likely. Further examination of other processes that take advantage of the unique mechanistic features of the nickel-catalyzed system is in progress.

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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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(12) The absolute configuration of the enantioenriched ketone was not determined.