JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

A Practical and Catalytic Reductive Olefin Coupling

Julian C. Lo, Yuki Yabe, and Phil S. Baran*

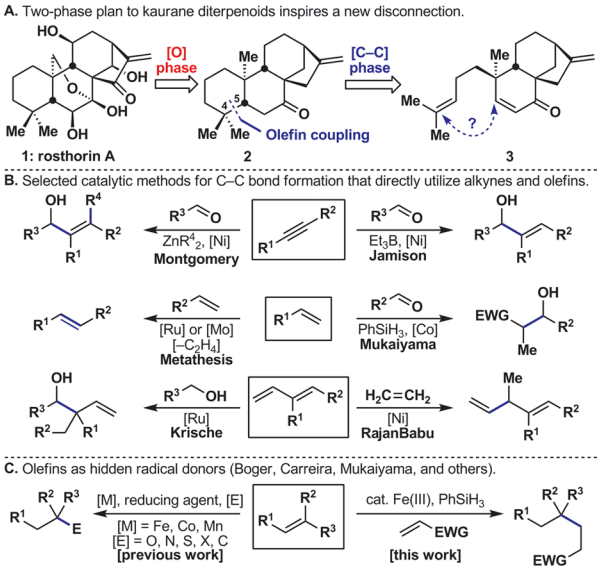
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: A redox-economic method for the direct coupling of olefins that uses an inexpensive iron catalyst and a silane reducing agent is reported. Thus, unactivated olefins can be joined directly to electron-deficient olefins in both intra- and intermolecular settings to generate hindered bicyclic systems, vicinal quaternary centers, and even cyclopropanes in good yield. The reaction is not sensitive to oxygen or moisture and has been performed on gram-scale. Most importantly, it allows access to many compounds that would be difficult or perhaps impossible to access using other methods.

Two-phase terpene total synthesis has been demonstrated to be a useful strategy to access steroids, diterpenes, and sesquiterpenes.[1] The approach consists of a cyclase phase, where a lowly oxidized terpene skeleton is rapidly constructed from inexpensive starting materials, and an oxidase phase, where a series of site-selective oxidations furnishes the desired natural product. Our laboratory is interested in pursuing such a strategy toward the *ent*-kaurane family of diterpenoids,[1d] whose members have been utilized in traditional Chinese medicine for centuries as they possess anticancer and antibacterial activities.[2] Analysis of an archetypical *ent*-kaurane, rosthorin A (**1**, Figure 1A), through the two-phase paradigm led to **2** as a proposed cyclase-phase end point. The C4−C5 motif in **2** appears in numerous terpenes and is biosynthetically derived from a polyene cyclization where C4 and C5 formally are electrophilic and nucleophilic positions, respectively.[3] Polarity reversal[4] of this disconnection led to **3** and inspired a method for directly adding an olefin, one of the most ubiquitous functionalities in organic chemistry, to an enone. Here we describe the development of a simple catalytic method for forging this type of C−C bond and demonstrate its scope in both intra- and intermolecular modes, even in highly sterically demanding contexts.

The disconnection leading **2** to **3** is desirable from the standpoint of redox economy.[5] Some inspirational and relevant examples are depicted in Figure 1B, where alkynes and olefins are used directly (i.e., without functional group interconversions) to form C−C bonds through advances in Ni catalysis,[6] metathesis,[7] reductive aldol reactions,[8] and hydrogenative C−C bond formation.[9] Of particular relevance to us are the powerful olefin functionalization methods of Boger,[10] Carreira,[11] Mukaiyama,[12] and others[13−15] which showed that unactivated olefins can be converted to putative radical species that can be intercepted by heteroatom acceptors (Figure 1C). Only three categories of C−C bond formation using these methods are reported to date: hydrocyanation with TsCN,[10b,11f] hydroaldoximation and hydrocyanooximation with phenyl sulfonyl oximes,[11i] and cyclization



Entry	Fe(III) Salt	Reductant	Solvent	T (°C)	4[a]	5[a]	6[a]	7[a]
1	$Fe_2(ox)_3$•$6H_2O$ (2.0 equiv)	$NaBH_4$	$EtOH/H_2O$	0	20	5	0	75
2	$Fe_2(ox)_3$•$6H_2O$ (2.0 equiv)	$NaBH(OAc)_3$	THF/H_2O	0 to rt	89	0	5	6
3	$Fe_2(ox)_3$•$6H_2O$ (2.0 equiv)	$(TMS)_3SiH$	THF/H_2O	0 to 60	23	0	77	0
4	$Fe_2(ox)_3$•$6H_2O$ (2.0 equiv)	Et_3SiH	THF/H_2O	0 to 60	0	0	100	0
5	$Fe_2(ox)_3$•$6H_2O$ (2.0 equiv)	$PhSiH_3$	$EtOH/H_2O$	0 to rt	15	0	11	74
6	$Fe(acac)_3$ (1.0 equiv)	Et_3SiH	EtOH	60	100	0	0	0
7	**$Fe(acac)_3$ (1.0 equiv)**	**$PhSiH_3$**	**EtOH**	**60**	**0**	**0**	**0**	**100**
8	$Fe(acac)_3$ (30 mol%)	$PhSiH_3$	$EtOH/(CH_2OH)_2$	60	0	0	0	100

Figure 1. (A) Retrosynthesis of rosthorin A. (B) Examples of C−C bond formation that directly utilize alkynes and olefins. (C) Recent hydrofunctionalizations of unactivated olefins inspire reductive olefin coupling. (D) Optimization of reaction conditions. [a]Ratios by GC/MS.

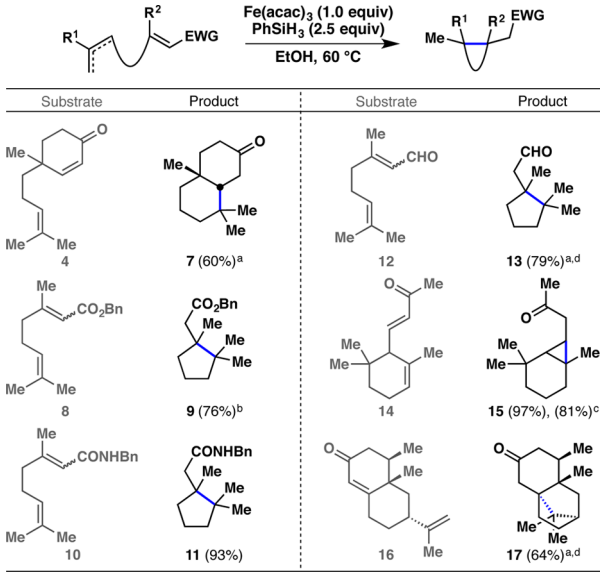
of 1,6-dienes.[10b,15] With these promising precedents, initial studies toward a reductive cyclization[16] were carried out.

When a simplified variant of proposed intermediate **3**, enone **4**, was subjected to Boger's $Fe_2(ox)_3$·$6H_2O$ and $NaBH_4$ conditions,[10] the *cis*-fused decalin **7** was obtained along with both unreacted starting material and a small amount of allylic alcohol **5** (Figure 1D, entry 1). Although the *trans*-decalin was

Received: November 19, 2013
Published: January 15, 2014

   dx.doi.org/10.1021/ja4117632 | J. Am. Chem. Soc. 2014, 136, 1304−1307

Table 1. Scope of the Intramolecular Reductive Coupling



[a]Used 30 mol% $Fe(acac)_3$ in $EtOH/(CH_2OH)_2$ (5:1). [b]Used 20 mol% $Fe(acac)_3$ in $DCE/(CH_2OH)_2$ (5:1). [c]Run on gram-scale with 2.0 equiv $PhSiH_3$. [d]Used 1.5 equiv $PhSiH_3$.

originally desired, the *cis*-decalin still provided an opportunity to develop a general C−C bond-forming reaction. Thus, optimization of the formation of *cis*-decalin **7** was pursued.

Since $NaBH_4$ would limit the functional group tolerance of the reaction, milder reducing agents were explored. $NaBH(OAc)_3$ eliminated the formation of **5** but resulted in the undesired formation of **6**, presumably from a competitive vinylogous Prins cyclization where $Fe_2(ox)_3{\cdot}6H_2O$ simply acts as a Lewis acid[17] (entry 2). This byproduct was exclusively formed when $(TMS)_3SiH$ and Et_3SiH were used as the reducing agent (entries 3 and 4), whereas $PhSiH_3$ produced *cis*-decalin **7** as the major product along with a small amount of **6** (entry 5).

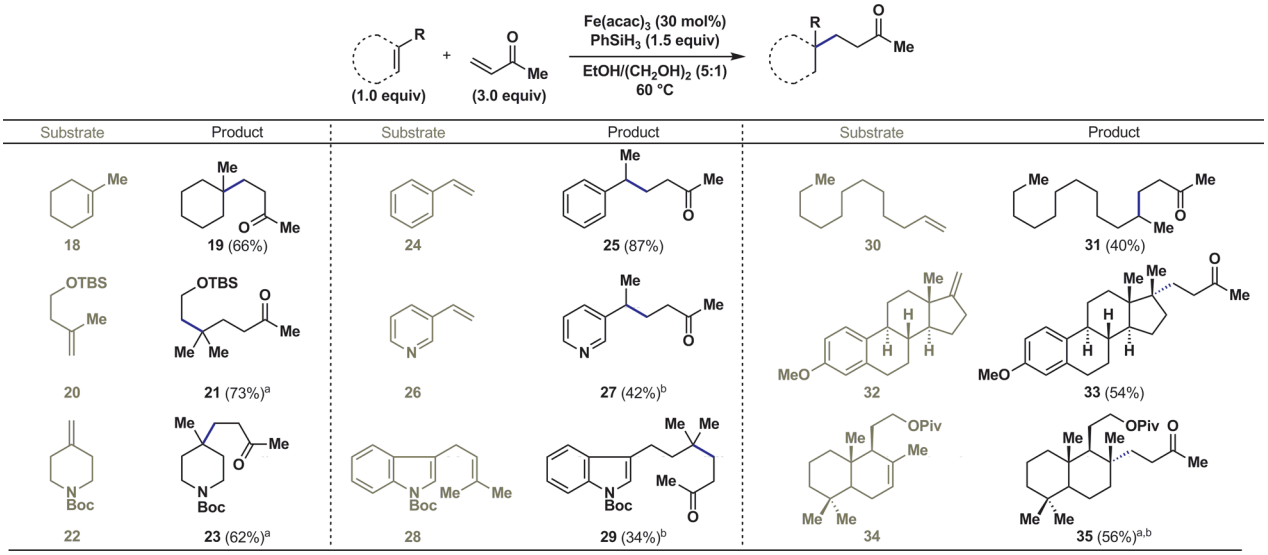
Switching the Fe(III) salt to $Fe(acac)_3$ gave a monophasic reaction medium.[10a] Under these conditions, use of Et_3SiH as the reductant led to the recovery of starting material (entry 6), whereas $PhSiH_3$ led to full conversion to the desired **7** (entry 7). When the amount of $Fe(acac)_3$ was decreased to 30 mol%, **7** was still formed exclusively (entry 8) with 60% isolated yield (Table 1), demonstrating that this reductive olefin coupling could be run in a catalytic fashion. Although not essential, the use of ethylene glycol as a cosolvent in entry 8 prevented the formation of $PhSi(OEt)_3$, a byproduct of the reaction that complicated purification.

Other substrates were also found to be amenable to intramolecular coupling (Table 1), with the reaction succeeding in more sterically demanding contexts, such as the formation of vicinal all-carbon quaternary centers.[18] Thus, cyclizing benzyl geranate (**8**), *N*-benzylgeranamide (**10**), and citral (**12**) to cyclopentanes **9**, **11**, and **13** proceeded smoothly in 76, 93, and 79% yield, respectively. As the formation of **9** demonstrates, decreasing the amount of $Fe(acac)_3$ to 20 mol% and using DCE as cosolvent instead of EtOH still resulted in cyclization. The cyclizations were found to be insensitive to oxygen and moisture and were generally complete in <1 h.

Highly strained ring systems could also be formed, as evidenced by the cyclization of the skipped diene α-ionone (**14**) to generate cyclopropane **15** in 97% yield. This cyclization could also be conducted easily on gram-scale, albeit with a small reduction in yield (81%). Although cyclopropanes have been previously formed by irradiating skipped dienes in specialized cases,[19] to our knowledge, this represents the first general method for such a transformation. To our surprise, even (+)-nootkatone (**16**) was cyclized in 64% yield to give highly congested bicyclo[2.2.1]heptane **17**, in which one of the newly formed adjacent quaternary centers is neopentyl. Such ring systems would be difficult to construct otherwise.

The applicability of this method to intermolecular settings was next examined by evaluating the reaction of a series of "donor" olefins with 3 equiv of methyl vinyl ketone (MVK) as an "acceptor" (Table 2). Upon exposure to the standard conditions, 1-methylcyclohexene (**18**) proved to be a competent donor, with the corresponding adduct **19** isolated in 66% yield. Although homocoupling of the participating olefins was anticipated, such

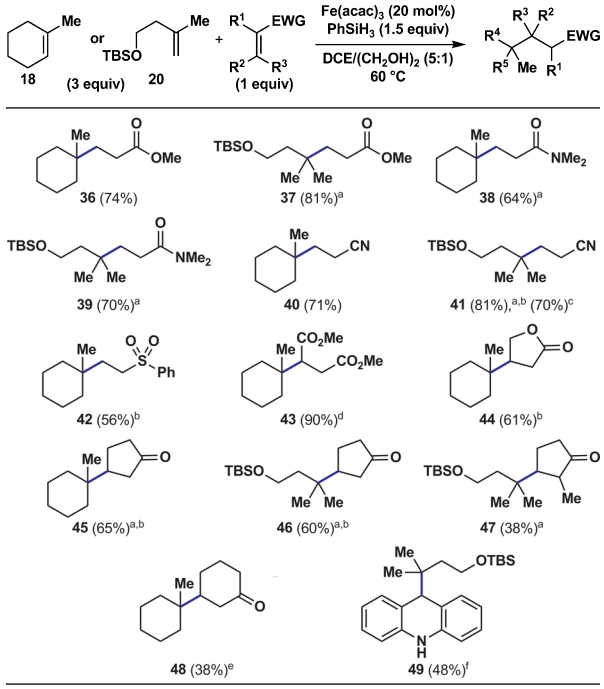
Table 2. Donor Scope of the Intermolecular Reductive Coupling



[a]Used 2.5 equiv $PhSiH_3$. [b]Used 100 mol% $Fe(acac)_3$.

dx.doi.org/10.1021/ja4117632 | J. Am. Chem. Soc. 2014, 136, 1304−1307

Table 3. Acceptor Scope of the Intermolecular Reductive Coupling



[a]Used 1.0 equiv donor and 3.0 equiv acceptor. [b]Used 40 mol% $Fe(acac)_3$. [c]Run on gram-scale. [d]Used DCE/$(CH_2OH)_2$ (1:1). [e]Used 100 mol% $Fe(acac)_3$. [f]Used 1.0 equiv donor and 1.1 equiv acceptor.

products were not observed. Furthermore, the newly forged bond was formed at the more substituted side of the donor olefin, in a fashion complementary to the hydroboration/radical conjugate addition developed by Renaud[20] and the hydrozirconation/conjugate addition sequence developed by Wipf.[21] Both of those methods result in the opposite regioselectivity, where bond formation occurs at the least substituted side of the donor olefin.

Tolerated functional groups include TBS ethers and *tert*-butyl carbamates, as demonstrated by the formation of **21** and **23** in 73 and 62% yield, respectively. The use of styrene (**24**) as a donor led to ketone **25** as the major product in 87% yield. Additionally, the methodology tolerated heteroaromatic functionalities, although in modest yields, with 3-vinylpyridine (**26**) and *N*-Boc-3-prenylindole (**28**) giving **27** and **29** in 42 and 34% yield, respectively.

A competitive process that was occasionally observed was the reduction of the donor olefin to its saturated counterpart. Thus, coupling 1-dodecene (**30**) to MVK resulted in the isolation of dodecane (not shown) in 30% yield along with the desired ketone **31** in 40% yield. The sterically encumbered estrone 3-methyl ether derivative **33**, which bears two vicinal all-carbon quaternary centers, was isolated in 54% yield as a single diastereomer, with the reduced derivative of **32** (not shown) also isolated in 17% yield. However, MVK could be added to (+)-sclareolide derivative **34** from its least hindered face to produce **35** in 56% yield without reduction of the starting material.

The scope of the acceptor olefins was next probed, using 1-methylcyclohexene (**18**) or TBS ether **20** as the donor (Table 3). In addition to MVK, methyl acrylate, *N*,*N*-dimethylacrylamide, and acrylonitrile all served as efficient acceptors, providing **36**–**41** in yields of 64–81%. Notably, TBS ether **20** can be coupled with acrylonitrile on gram-scale to provide nitrile **41** with only a minor reduction in yield. Phenyl vinyl sulfone also participated in the reaction, although it required a catalyst loading of 40 mol% and gave moderate yields of **42**. The reaction proceeded more smoothly using doubly activated acceptors, with dimethyl fumarate providing diester **43** in 90% yield.

Cyclic acceptors generally gave slightly lower yields, with 2-furanone providing adduct **44** in 61% yield. Cyclic enones could also be used, with 2-cyclopentenone furnishing **45** and **46** in 65% and 60% yield, respectively. Substitution at the α-position of the acceptor olefin was also tolerated, although the α-methylated cyclopentanone **47** was obtained in a diminished 38% yield as a 2:1 mixture of diastereomers. Interestingly, the use of 2-cyclohexenone as an acceptor led to a significantly lower yield of **48** as compared to **45**, even when a stoichiometric amount of $Fe(acac)_3$ was used. Finally, a heteroaromatic acceptor, acridine, could be employed to generate **49** as a proof of principle for applying this chemistry in reductive Minisci-type functionalization.[22]

The mechanism of this reductive olefin coupling was probed through a variety of experiments (Figure 2). $Fe(acac)_3$ was found to be necessary for the coupling, as its omission resulted in only recovery of starting material (Figure 2A). Interestingly, running the reaction under oxygen-free conditions in a Schlenk tube fully cyclized α-ionone (**14**) to cyclopropane **15**, indicating that oxygen was not responsible for reoxidizing the iron catalyst.

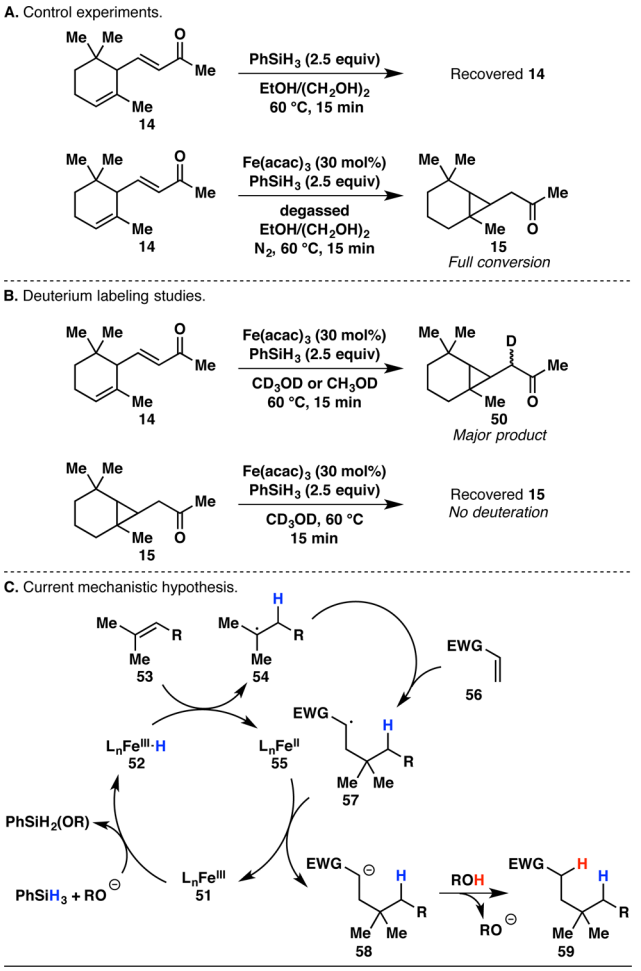


Figure 2. (A) Control experiments. (B) Deuterium labeling studies. (C) Proposed mechanism of the reductive olefin coupling.

dx.doi.org/10.1021/ja4117632 | J. Am. Chem. Soc. 2014, 136, 1304–1307

Furthermore, subjecting **14** to the reaction conditions using either CD_3OD or CH_3OD as the solvent led to the isolation of cyclopropane **50**, bearing a sole deuterium atom adjacent to the ketone (Figure 2B). The lack of deuterium incorporation on the cyclohexane ring in both instances suggests that the H that adds across the unactivated olefin originates from $PhSiH_3$. Additionally, exposing non-deuterated **15** to identical reaction conditions did not lead to any deuterium incorporation, showing that deuterium incorporation takes place during the course of the reaction and is not an artifact of hydrogen-deuterium exchange with the solvent.

A mechanistic scenario consistent with these results is outlined in Figure 2C. Donor olefin **53** would abstract a hydrogen radical from Fe hydride[23] **52**—derived from Fe(III) species **51** and $PhSiH_3$[24]—to generate reduced Fe species **55** and tertiary radical **54**. Alternatively, **54** could be generated by hydrometalation of **53**, followed by homolysis of the Fe−C bond (not shown).[11e] Conjugate addition of **54** into Michael acceptor **56**,[25] followed by single-electron transfer with **55**, would provide intermediate **58** and regenerate **51**, which would re-enter the catalytic cycle. Protonation of **58** would give the coupled product **59**.

In conclusion, a practical method for the reductive coupling of olefins that utilizes a readily available and inexpensive Fe source as a catalyst has been developed. This reaction is operationally simple and has been run on gram-scale. Furthermore, it builds molecular complexity rapidly, with most reactions reaching completion in <1 h. The coupling works in both intra- and intermolecular settings and can generate highly hindered bicyclic systems, cyclopropanes, and vicinal quaternary centers.[26] The ability of this transformation to directly employ olefins in C−C bond-forming events bodes well for future applications in a variety of contexts, including the cyclase phase of two-phase terpene synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

pbaran@scripps.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by NIH/NIGMS (GM-097444), NSF (predoctoral fellowship to J.C.L.), and JSPS (postdoctoral fellowship to Y.Y.).

■ REFERENCES

(1) Overview of two-phase terpene total synthesis: (a) Ishihara, Y.; Baran, P. S. *Synlett* **2010**, *12*, 1733. Recent syntheses using the two-phase approach: (b) Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59. (c) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21. (d) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019. (e) Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878. (f) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (g) Foo, K.; Usui, I.; Götz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11491.

(2) Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.

(3) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; Wiley: West Sussex, 2009; pp 187−310.

(4) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(5) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(6) Review on Ni-catalyzed reductive couplings: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. An account on Montgomery's work: (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. An account on Jamison's work with alkynes: (b) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441. An account on Jamison's work with olefins: (d) Ho, C.-Y.; Schleicher, K. D.; Chan, C.-W.; Jamison, T. F. *Synlett* **2009**, 2565. An account on RajanBabu's work: (e) RajanBabu, T. V. *Synlett* **2009**, 853. A similar transformation using iron: (f) Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337.

(7) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(8) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 2005. Review on reductive aldol, Michael, and Mannich reactions: (b) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105.

(9) (a) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (b) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *43*, 107.

(10) (a) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904. (b) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428. (c) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588.

(11) (a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676. (b) Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099. (c) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (d) Waser, J.; González-Gómez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249. (e) Waser, J.; Gaspar, B.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (f) Gaspar, B.; Carreria, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519. (g) Gaspar, B.; Waser, J.; Carreira, E. M. *Synlett* **2007**, *24*, 3839. (h) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758. (i) Gaspar, B.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 13214.

(12) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 1071.

(13) (a) Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K. *J. Am. Chem. Soc.* **2013**, *135*, 10306. (b) Shigehisa, H.; Nishi, E.; Fujisawa, M.; Hiroya, K. *Org. Lett.* **2013**, *15*, 5158.

(14) Girijavallabhan, V.; Alvarez, C.; Njoroge, F. G. *J. Org. Chem.* **2011**, *76*, 6442.

(15) Taniguchi, T.; Goto, N.; Nishibata, A.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 112.

(16) Reviews on reductive cyclizations: (a) Krische, M. J.; Jang, H.-Y. In *Comprehensive Organometallic Chemistry III*; Mingos, M., Crabtree, R., Eds.; Elsevier: Oxford, 2006; Vol. *10*, pp 493−536. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (c) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.

(17) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

(18) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley: Weinheim, 2005.

(19) (a) Hammond, G. S.; Turro, N. J.; Fischer, A. *J. Am. Chem. Soc.* **1961**, *83*, 4674. (b) Guella, G.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1539.

(20) (a) Ollivier, C.; Renaud, P. *Chem.—Eur. J.* **1999**, *5*, 1468. (b) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925. (c) Renaud, P.; Ollivier, C.; Weber, V. *J. Org. Chem.* **2003**, *68*, 5769.

(21) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494.

(22) Duncton, M. A. J. *Med. Chem. Commun.* **2011**, *2*, 1135.

(23) Nakazawa, H.; Itazaki, M. *Top. Organomet. Chem.* **2011**, *33*, 27.

(24) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448.

(25) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377.

(26) While this work was in progress, an elegant and complementary method was reported to convert tertiary alcohols to radical species (via *tert*-alkyl *N*-phthalimidoyl oxalates) capable of intermolecularly trapping Michael acceptors: Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342.