Organic Process Research & Development

REVIEW

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Unlocking Hydrogenation for C−C Bond Formation: A Brief Overview of Enantioselective Methods

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ABSTRACT: Hydrogenation of π-unsaturated reactants in the presence of carbonyl compounds or imines promotes reductive C−C coupling, providing a byproduct-free alternative to stoichiometric organometallic reagents in an ever-increasing range of C═X (X = O, NR) additions. Under transfer hydrogenation conditions, hydrogen exchange between alcohols and π-unsaturated reactants triggers generation of electrophile−nucleophile pairs, enabling carbonyl addition directly from the alcohol oxidation level, bypassing discrete alcohol oxidation and generation of stoichiometric byproducts.

1. INTRODUCTION

A principal characteristic of a "process-relevant" method is the ability to transform abundant, renewable feedstocks to value-added products in the absence of stoichiometric byproducts.[1] This characteristic is embodied by catalytic hydrogenation,[2] which has found broad use across all segments of the chemical industry, including the manufacture of chiral pharmaceutical ingredients on scale.[3] Similarly, alkene hydroformylation,[4] which may be viewed as the prototypical C−C bond forming hydrogenation, combines basic feedstocks (synthesis gas and α-olefins) with complete atom economy to produce aldehydes.[5,6] Presently, hydroformylation ranks as the largest volume application of homogeneous metal catalysis.

Given the broad impact of hydrogenation and hydroformylation on chemical manufacture, a systematic effort to discover hydrogen-mediated C−C bond formations *beyond* hydroformylation was undertaken in our laboratory.[7−9] Remarkably, it was found that hydrogenation of π-unsaturated reactants in the presence of carbonyl compounds or imines promotes reductive C−C coupling, providing an alternative to stoichiometric organometallic reagents in a range of C═X (X = O, NR) additions. Further, under transfer hydrogenation conditions, hydrogen exchange between alcohols and π-unsaturated reactants was found to trigger generation of electrophile−nucleophile pairs, enabling carbonyl addition directly from the alcohol oxidation level, bypassing discrete alcohol oxidation[10] and generation of stoichiometric byproducts (Scheme 1).

In this account, a concise overview of enantioselective C−C bond forming hydrogenations and transfer hydrogenations is provided. This account is not exhaustive but is meant to survey functional group interconversions with attention to processes of greatest potential synthetic utility. More detailed discussions of mechanism and stereochemistry are provided in the primary literature, and individual topics encompassed in this review are presented in several recent monographs.[7]

2. C−C BOND FORMING HYDROGENATION

Despite its routine use for well over a century, alkene hydroformylation and the parent Fischer−Tropsch process remained the only examples of hydrogen-mediated reductive coupling at the onset of our studies.[4−6] Hence, it became necessary to identify a mechanistic pathway that would unlock hydrogenation for C−C bond formation. Whereas neutral rhodium complexes engage in rapid hydrogen oxidative addition,[11] hydrogen oxidative addition is turnover limiting for cationic rhodium catalysts.[12,13] Thus, using cationic complexes of rhodium, it was found that the diminished rate of hydrogen oxidative addition and the availability of an additional coordination site conspire to promote oxidative coupling to form metallacyclic intermediates, which are subject to hydrogenolysis to form products of reductive C−C bond formation in the absence of byproducts (Scheme 2).

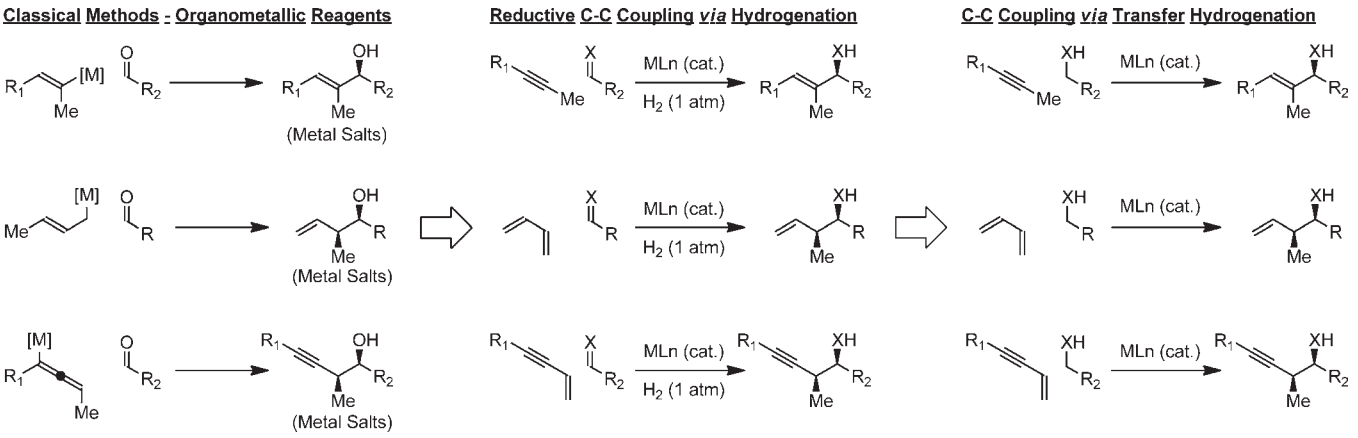
Through the implementation of oxidative coupling pathways, numerous C−C bond forming hydrogenations were developed. For example, hydrogenation of enones in the presence of aldehydes employing a cationic rhodium catalyst modified by a TADDOL-like phosphonite ligand delivers products of reductive aldol addition with high levels of relative and absolute stereocontrol.[14] Similarly, high levels of substrate directed asymmetric induction are achieved in hydrogen-mediated reductive aldol additions to *N*-Boc-α-amino aldehydes.[15] Notably, due to the configurational instability of *N*-Boc-α-amino aldehydes, corresponding additions of alkali enolates are unknown. This reactivity pattern is applicable to other activated olefins, as demonstrated by hydrogen-mediated coupling of 2-vinylpyridines and *N*-arylsulfonyl imines to furnish branched products of imine addition.[16] In each case, *syn*-diastereoselectivity is observed, as the adjacent substituents about the metallacyclic intermediate prefer a *trans*-orientation (Scheme 3).

Hydrogenation of alkynes in the presence of carbonyl and imine partners provides allylic alcohols and allylic amines, respectively, in the absence of stoichiometric byproducts. For example, hydrogenation of acetylenic aldehydes employing a cationic rhodium catalyst induces reductive cyclization to form enantiomerically enriched heterocycles.[17] Using cationic iridium catalysts, hydrogenation of 1,2-dialkyl substituted alkynes in the presence of *N*-arylsulfonyl imines provides trisubstituted

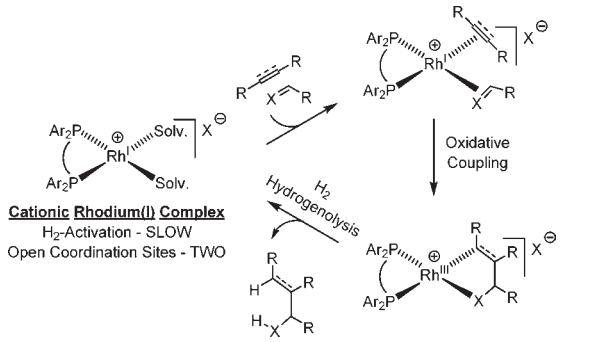
Received: July 19, 2011
Published: September 09, 2011

dx.doi.org/10.1021/op200195m | *Org. Process Res. Dev.* 2011, 15, 1236–1242

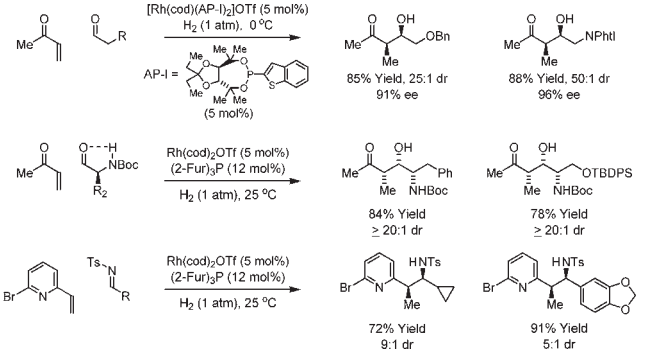
Scheme 1. Hydrogen-mediated C−C bond formations beyond hydroformylation



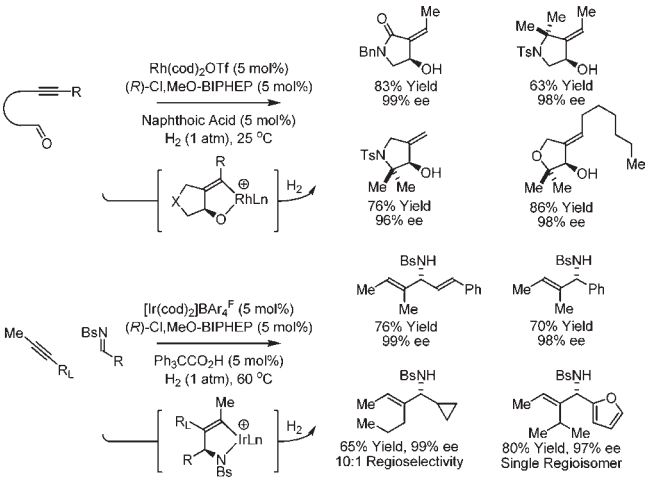
Scheme 2. Cationic rhodium complexes promote hydrogen-mediated reductive coupling via oxidative coupling pathways



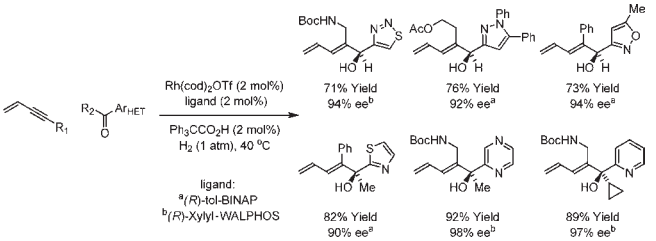
Scheme 3. Hydrogenation of activated olefins to form products of C−C bond formation



Scheme 4. Intra- and intermolecular hydrogen-mediated C−C coupling of unactivated alkynes



Scheme 5. Hydrogen-mediated couplings of 1,3-enynes with heterocyclic aromatic aldehydes or ketones



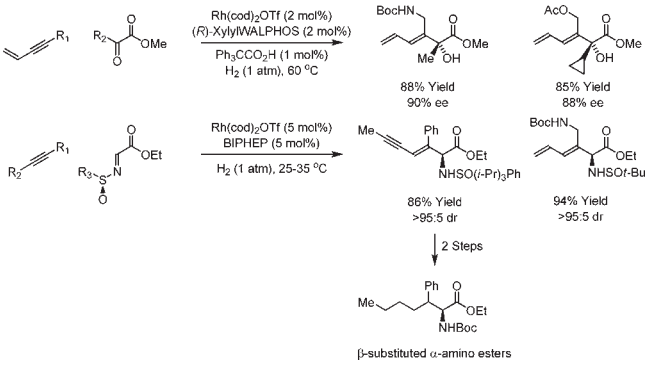
allylic amines.[18] For both processes, complete levels of *E*/*Z* selectivity (≥95:5) are observed. Such alkyne-C═X (X = O, NR) reductive couplings bypass use of preformed vinylmetal reagents (Scheme 4).

Underscoring functional group compatibility, conjugated enynes participate in reductive couplings to diverse heterocyclic aromatic aldehydes and ketones to provide heteroaryl substituted secondary and tertiary carbinols, respectively. Using rhodium catalysts modified by (*R*)-tol-BINAP or (*R*)-xylyl-WALPHOS, uniformly high levels of enantioselectivity are observed. Manipulation of the diene moiety of the coupling products allows access to a variety of functional group arrays (Scheme 5).[19]

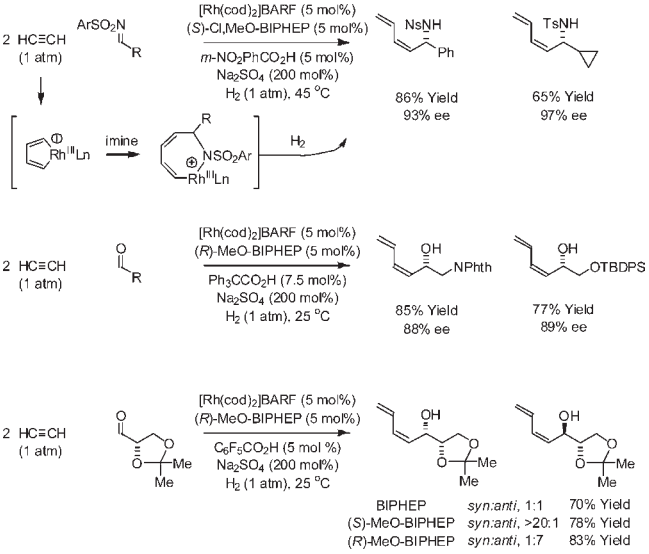
Using cationic rhodium catalysts, hydrogenation of conjugated alkynes in the presence of glyoxalates and pyruvates provides the corresponding α-hydroxy esters with high levels of enantiomeric enrichment.[20] Conjugated enynes and diynes

dx.doi.org/10.1021/op200195m |*Org. Process Res. Dev.* 2011, 15, 1236–1242

Scheme 6. Formation of α-hydroxy esters and α-amino esters via C−C bond forming hydrogenation



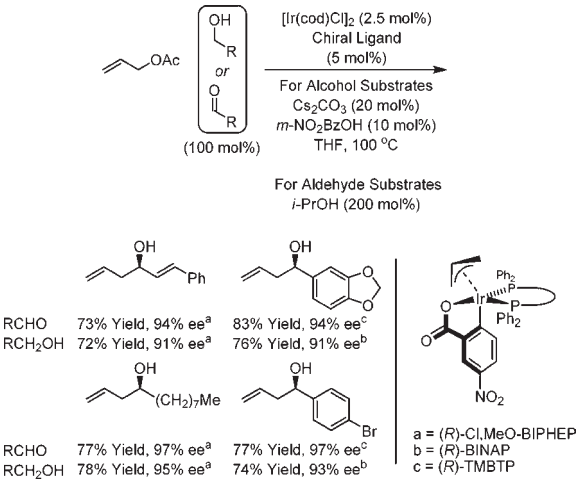
Scheme 7. Rhodium catalyzed hydrogenation of acetylene in the presence of carbonyl and imine partners



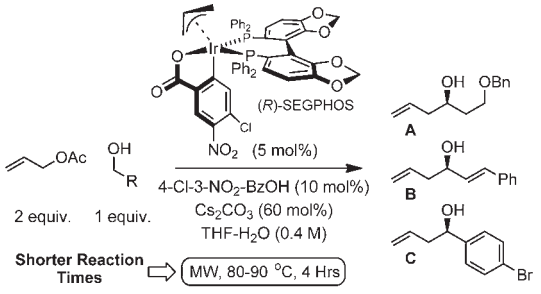
also participate in reductive couplings to (*N*-sulfinyl)iminoacetates under the conditions of rhodium catalyzed hydrogenation.[21] Using an appropriately substituted *N*-sulfinyl substituent,[22] the corresponding β,γ-unsaturated α-amino acid esters are generated as single diastereomers. Exhaustive hydrogenation of the diene or enyne side chain of the C−C coupling product provides access to β-substituted α-amino acids (Scheme 6).

The hydrogen-mediated reductive coupling of acetylene in the presence of carbonyl and imine partners provides products of (*Z*)-butadienylation.[23] As corroborated by isotopic labeling, ESI-MS, and computational studies,[24] the reaction occurs through an unusual mechanism involving formation of a rhodacyclopentadiene[25] followed by C═X (X = O, NR) insertion and hydrogenolysis of the seven-membered metallacycle. Using chirally modified cationic rhodium catalysts, allylic alcohols and allylic amines are formed in highly optically enriched form. Hydrogenative coupling of acetylene to α-chiral aldehydes using enantiomeric rhodium catalysts ligated by (*S*)-MeO-BIPHEP and (*R*)-MeO-BIPHEP provides adducts with good levels of catalyst directed diastereoselectivity. This process was used in a formal synthesis of all eight L-hexoses (Scheme 7).[23c]

Scheme 8. Enantioselective iridium catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level



Scheme 9. Chromatographic recovery and recycling of the iridium catalyst in enantioselective carbonyl allylations from the alcohol oxidation level



Chromatographic Recovery and Recycling of Catalyst

	First Run	Second Run	Third Run
A	75% Yield, 93% ee 84% Cat. Recovery	71% Yield, 94% ee 82% Cat. Recovery	70% Yield, 94% ee 85% Cat. Recovery
B	81% Yield, 97% ee 86% Cat. Recovery	78% Yield, 98% ee 84% Cat. Recovery	75% Yield, 97% ee 89% Cat. Recovery
C	81% Yield, 94% ee 92% Cat. Recovery	77% Yield, 96% ee 88% Cat. Recovery	77% Yield, 96% ee 85% Cat. Recovery

3. C−C BOND FORMING TRANSFER HYDROGENATION

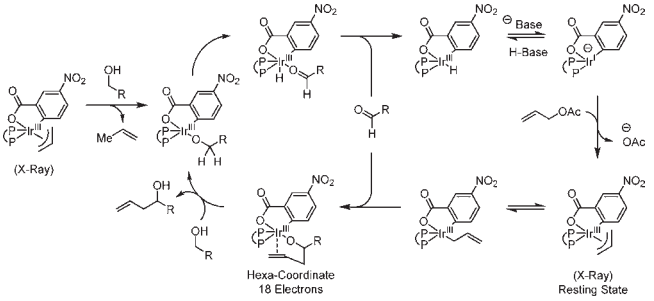
Under transfer hydrogenation conditions using *ortho*-cyclometalated iridium catalysts generated *in situ* from allyl acetate, 3-nitrobenzoic acid, and a chiral *bis*-phosphine ligand, enantioselective carbonyl allylation is achieved from the alcohol or aldehyde oxidation level using allyl acetate as the allyl donor.[26] Aliphatic, allylic, and benzylic alcohols are transformed to the corresponding homoallylic alcohols with uniformly high levels of enantioselectivity. In the presence of isopropanol, but under otherwise identical conditions, aldehydes are converted to an equivalent set of adducts. This protocol circumvents cryogenic conditions and the stoichiometric use of metallic reagents or reductants (Scheme 8).

The cyclometalated iridium π-allyl *C,O*-benzoate complexes, which have been characterized by single crystal X-ray

diffraction, are sufficiently robust that they may be purified chromatographically. Even more remarkable, these complexes may be recovered from reaction mixtures by conventional silica gel chromatography and recycled multiple times without any decline in performance. This capability is established in highly enantioselective reactions of aliphatic, allylic, and benzylic alcohols under microwave conditions in aqueous organic media.[27] While chromatographic recycling is certainly not feasible on scale, the stability displayed by the catalyst augers well for distillative product removal, as in hydroformylation, and immobilization of the catalyst (Scheme 9).

A catalytic mechanism consistent with the collective data begins with protonolysis of the iridium π-allyl complex by the reactant alcohol to furnish a pentacoordinate iridium alkoxide. β-Hydride elimination produces aldehyde and an iridium hydride, which deprotonates to generate an anionic iridium(I) intermediate. Oxidative addition of allyl acetate provides the π-allyl complex. Because the π-allyl complex is the catalyst resting state, it can be chromatographically recovered from the reaction mixture. Turnover-limiting aldehyde addition provides an iridium alkoxide. This hexacoordinate 18-electron complex is resistant to β-hydride elimination due to coordination of the homoallylic olefin. Exchange of the homoallylic iridium alkoxide with reactant alcohol releases the product and regenerates the pentacoordinate iridium alkoxide to close the catalytic cycle (Scheme 10).

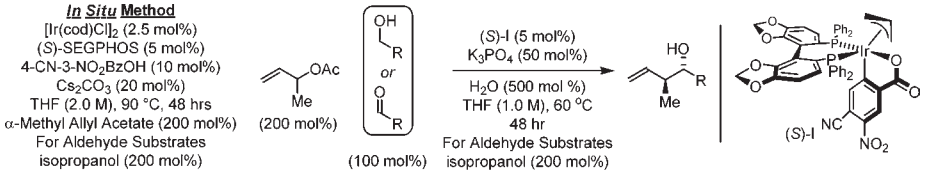
Scheme 10. Catalytic mechanism for iridium catalyzed carbonyl allylation under transfer hydrogenation conditions

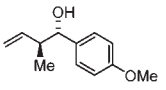
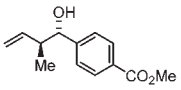
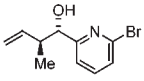
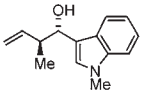
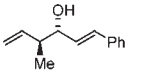
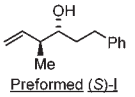
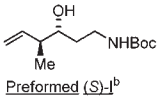
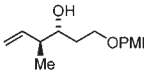


Corresponding carbonyl crotylations employing α-methyl allyl acetate can be conducted using the iridium *C,O*-benzoate complex that is assembled *in situ* from $[Ir(cod)Cl]_2$, allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chiral phosphine ligand (*S*)-SEGPHOS.[28a] However, although *in situ* assembly of the catalyst is convenient and excellent enantioselectivities typically were observed (>95% ee), only modest levels of *anti*-diastereoselectivity were evident (5:1−11:1 dr). Use of the chromatographically purified catalyst allows the reaction to be performed at lower temperature (60 °C), resulting in enhanced levels of *anti*-diastereo- and enantioselectivity (Scheme 11).[28b]

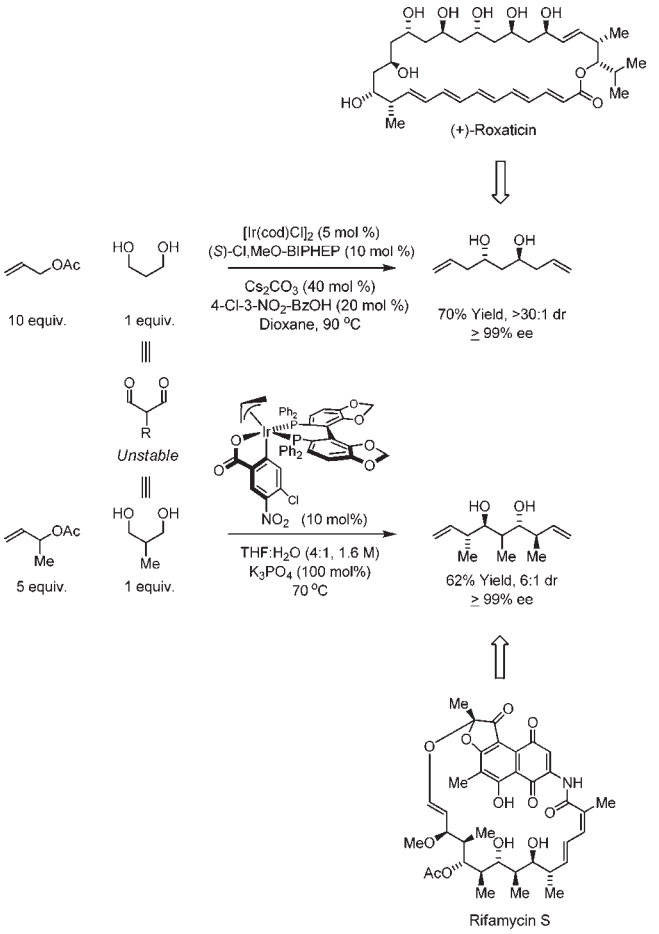
Enantioselective carbonyl allylation and crotylation from the alcohol oxidation level enables carbonyl allylation processes that are not possible using conventional allylmetal and crotylmetal reagents. For example, although 1,3-dialdehydes are intractable and cannot be used in enantioselective double allylation,[29] 1,3-propanediols are stable and engage in efficient two-directional allylation to provide C_2-symmetric adducts.[30] In these processes, the minor enantiomer of the *mono*-allylated intermediate is

Scheme 11. Enantioselective iridium catalyzed carbonyl crotylation from the alcohol or aldehyde oxidation level



Oxidation Level			
			
Alcohol	Preformed (*S*)-I 78% Yield, 16:1 dr, 97% ee	Preformed (*S*)-I 91% Yield, 10:1 dr, 95% ee	Preformed (*S*)-I 78% Yield, 11:1 dr, 98% ee
Aldehyde	82% Yield, 17:1 dr, 98% ee	89% Yield, 12:1 dr, 98% ee	81% Yield, 13:1 dr, 98% ee
Alcohol	*In Situ* (*S*)-I 73% Yield, 8:1 dr, 95% ee	*In Situ* (*S*)-I 67% Yield, 5:1 dr, 90% ee	*In Situ* (*S*)-I 70% Yield, 7:1 dr, 95% ee
Aldehyde	78% Yield, 11:1 dr, 97% ee	75% Yield, 7:1 dr, 97% ee	80% Yield, 11:1 dr, 96% ee
			
Alcohol	Preformed (*S*)-I 50% Yield, 14:1 dr, 98% ee	Preformed (*S*)-I 75% Yield, 7:1 dr, 98% ee	Preformed (*S*)-I 72% Yield, 10:1 dr, 93% ee
Aldehyde	75% Yield, >20:1 dr, 97% ee	74% Yield, 10:1 dr, 98% ee	77% Yield, 10:1 dr,98% ee
Alcohol	*In Situ* (*S*)-I no product observed	*In Situ* (*S*)-I 73% Yield, 5:1 dr, 95% ee	*In Situ* (*S*)-I 61% Yield, 7:1 dr, 86% ee
Aldehyde		78% Yield, 6:1 dr, 98% ee	66% Yield, 8:1 dr, 98% ee
			
Alcohol	Preformed (*S*)-I 71% Yield, >20:1 dr, 99% ee	Preformed (*S*)-I[b] 71% Yield, >20:1 dr, 96% ee	Preformed (*S*)-I 76% Yield, 15:1 dr, 97% ee
Aldehyde	71% Yield, >20:1 dr, 98% ee	66% Yield, >20:1 dr, 99% ee	76% Yield, >20:1 dr, 99% ee
Alcohol	*In Situ* (*S*)-I 69% Yield, 7:1 dr, 98% ee	*In Situ* (*S*)-I no product observed	*In Situ* (*S*)-I 73% Yield, 7:1 dr, 95% ee
Aldehyde	71% Yield, 11:1 dr, 98% ee		88% Yield, 7:1 dr, 95% ee

Scheme 12. Enantioselective double allylation and double crotylation of 1,3-propanediols to form polyacetate and polypropionate building blocks

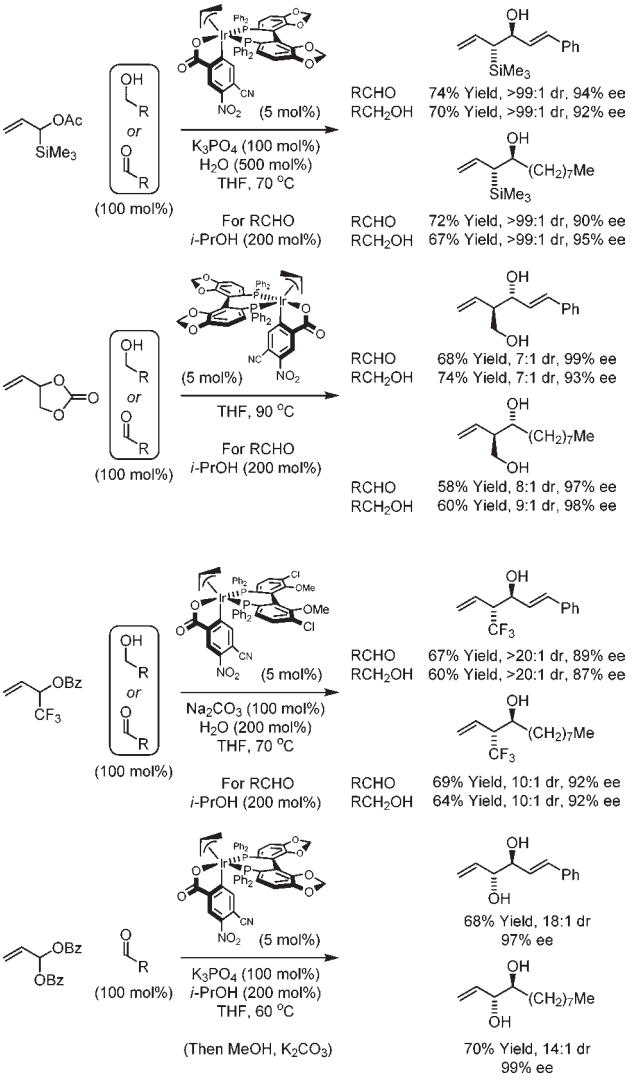


transformed to the *meso*-diastereoisomer, thereby amplifying levels of enantioselectivity.[31] Through iterative two-directional chain elongation of 1,3-propanediol, a total synthesis of the oxo-polyene macrolide (+)-roxaticin was achieved in 20 steps.[32] Corresponding double crotylations of 2-methyl-1,3-propanediol result in the generation of *pseudo*-C_2-symmetric polypropionate stereoquintets, which appear as substructures in diverse polyketide natural products. Using the chromatographically isolated iridium catalyst modified by (*R*)-SEGPHOS, 1 of 16 possible stereoisomers is formed predominantly.[33] This methodology was used to form the C19−C27 *ansa* chain of rifamycin S in 8 steps (originally prepared in 26 steps), constituting a formal synthesis of the natural product (Scheme 12).[34]

Beyond carbonyl allylation and crotylation, other types of enantioselective allylations are promoted by *ortho*-cyclometalated iridium catalysts, including α-(trimethylsilyl)allylation,[35a] α-(hydroxymethyl)allylation,[35b] α-(trifluoromethyl)allylation,[35c] and α-(hydroxy)allylation.[35d] In each case, enantioselective carbonyl addition is achieved in the absence of stoichiometric metallic reagents (Scheme 13).

The products of allylation are readily transformed to enantiomerically enriched heterocycles that would otherwise be difficult to prepare. For example, diastereo- and enantioselective α-(trifluoromethyl)allylation of *N*-Boc-aminopropanol enables

Scheme 13. Various diastereo- and enantioselective allylations via iridium catalyzed transfer hydrogenation

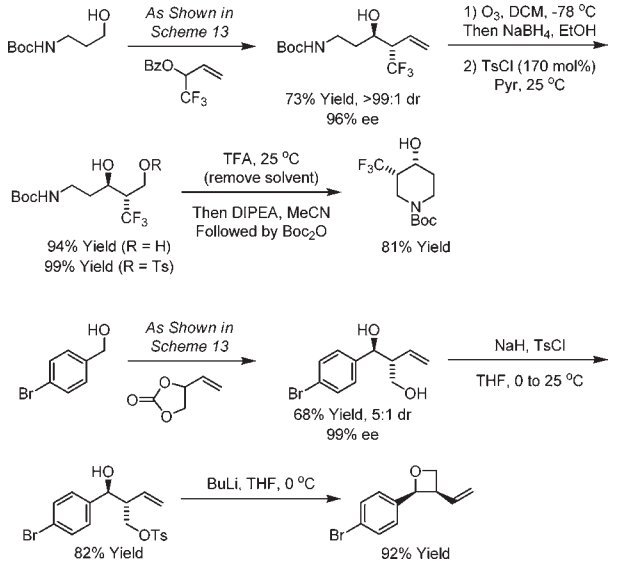


a four-step synthesis of the indicated piperidine.[35c] A three-step synthesis of *cis*-2,3-disubstituted oxetanes is achieved through carbonyl α-(hydroxy)allylation from the alcohol oxidation level (Scheme 14).[35d]

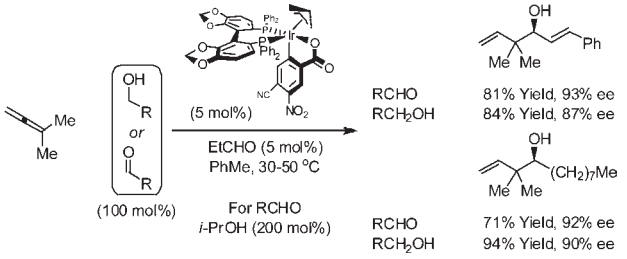
The appearance of iridium hydrides in the catalytic mechanism (Scheme 10) suggests the feasibility of recruiting allenes and dienes as allyl donors *via* hydrometalation. Indeed, cyclometalated iridium *C,O*-benzoates modified by (*S*)-SEGPHOS promote enantioselective carbonyl *tert*-prenylation from the alcohol or aldehyde oxidation level under exceptionally mild conditions (30−50 °C).[36] For reactions conducted from the alcohol oxidation level, stoichiometric byproducts are completely absent. Interestingly, the absolute stereochemistry of *tert*-prenylation is opposite to that observed in the aforementioned allylations (Scheme 15).

Finally, transfer hydrogenation catalysts based on ruthenium also promote carbonyl addition from the alcohol or aldehyde oxidation level. For example, using chiral ruthenium catalysts modified by (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS, the indicated silyl-substituted butadiene, which is prepared in a single manipulation from chloroprene, engages in *syn*-diastereo- and

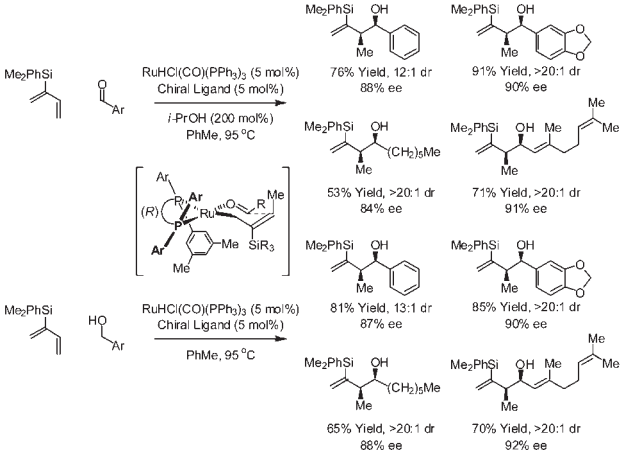
Scheme 14. Synthesis of enantiomerically enriched heterocycles using transfer hydrogenative allylation



Scheme 15. Enantioselective carbonyl *tert*-prenylation from the alcohol or aldehyde oxidation level



Scheme 16. Enantioselective *syn*-diastereo- and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level *via* ruthenium catalyzed transfer hydrogenation



enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level.[37] Here, to address the issue of relative stereocontrol, the silyl substituent directs formation of geometrically defined σ-allylruthenium intermediates, which react stereospecifically through closed, chairlike transition structures (Scheme 16).

4. CONCLUSION

While numerous first-generation methods for chemical synthesis exist, very little of this methodology is amenable to large volume application. Inspired by the process relevance of hydrogenation and hydroformylation, we have developed a broad, new family of enantioselective C−C bond forming hydrogenation and transfer hydrogenations. The atom economy exhibited by these transformations, particularly the exclusion of stoichiometric metallic byproducts, suggests these methods would be viable candidates for use at the process level upon minimization of the catalyst loading. The reactivity embodied by these processes evokes numerous possibilities in terms of related transformations, including imine addition from the amine oxidation and the direct C−C coupling of α-olefins. These topics are currently under investigation in our laboratory.

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ACKNOWLEDGMENT

Acknowledgment is made to the Robert A. Welch Foundation (F-0038), the NIH-NIGMS (RO1-GM069445), Eli Lilly and Company, Merck, Johnson and Johnson, Firmenich, Umicore, Takasago, and the ACS-GCI, for partial support of the research described in this account.

REFERENCES

(1) For selected reviews, see: (a) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002. (b) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273. (c) Beller, M. *Eur. J. Lipid Sci. Technol.* **2008**, *110*, 789.

(2) (a) Sabatier, P.; Senderens, J. B. *C. R. Hebd. Seances Acad. Sci.* **1897**, *124*, 1358. (b) Sabatier, P.; Senderens, J. B. *C. R. Hebd. Seances Acad. Sci.* **1899**, *128*, 1173. (c) Sabatier, P.; Senderens, J. B. *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 210. For a biographical sketch of Paul Sabatier, see: (d) Lattes, A. *C. R. Acad. Sci. Ser. IIc: Chem.* **2000**, *3*, 705.

(3) For selected reviews, see: (a) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224. (b) Thommen, M. *Spec. Chem. Mag.* **2005**, *25*, 26. (c) Thayer, A. M. *Chem. Eng. News* **2005**, *83*, 40. (d) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912. (e) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734. (f) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (g) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411. (h) Blaser, H.-U.; Pugin, B.; Spindler, F.; Thommen, M. *Acc. Chem. Res.* **2007**, *40*, 1240.

(4) Roelen, O. Chemische Verwertungsgesellschaft mbH, Oberhausen. German Patent DE 849,548. 1938. *Chem. Abstr.* **1944**, *38*, 5501.

(5) For selected reviews on alkene hydroformylation, see: (a) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17. (b) Frohning, C. D.; Kohlpaintner, C. W.; Bohnen, H.-W. Carbon Monoxide and Synthesis Gas Chemistry. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1996; Vol. 1, pp 29−104. (c) *Rhodium*

Catalyzed Hydroformylation; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Norwell, MA, 2000. (d) Breit, B.; Seiche, W. *Synthesis* **2001**, 1–36. (e) Weissermel, K.; Arpe, H.-J. Synthesis involving Carbon Monoxide. *Industrial Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2003; pp 127−144. (f) van Leeuwen, P. W. N. M. *Homogeneous Catalysis: Understanding the Art*; Kluwer: Dordrecht, 2004.

(6) Hydroformylation is an outgrowth of the Fischer−Tropsch process, which represents another key hydrogen-mediated C−C bond formation: (a) Fischer, F.; Tropsch, H. *Brennstoff-Chem.* **1923**, *4*, 276. (b) Fischer, F.; Tropsch, H. *Chem. Ber.* **1923**, *56B*, 2428.

(7) For recent reviews on C−C bond forming hydrogenation and transfer hydrogenation, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (c) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77. (d) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (e) Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, 2669. (f) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (g) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278. (h) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *43*, 107.

(8) Prior to our systematic studies, two isolated reports of hydrogenative C−C coupling were reported in the literature: (a) Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123. (b) Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1995**, *14*, 4521.

(9) Side products of reductive C−C bond formation have been observed in catalytic hydrogenation on rare occasions: (a) Moyes, R. B.; Walker, D. W.; Wells, P. B.; Whan, D. A.; Irvine, E. A. Mechanism of Ethyne Hydrogenation in the Region of the Kinetic Discontinuity: Comparison of C_4 Products. In *Catalysis and Surface Characterisation* (Special Publication); Dines, T. J., Rochester, C. H., Thomson, J., Eds.; Royal Society of Chemistry: Cambridge, 1992; Vol. 114, pp 207−212. (b) Bianchini, C.; Meli, A.; Peruzzini, M.; Vizza, F.; Zanobini, F.; Frediani, P. *Organometallics* **1989**, *8*, 2080.

(10) Alcohol oxidation on scale is considered problematic. For reviews, see: (a) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (c) Caron, S.; Dugger, R. W.; Gut Ruggeri, S.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943.

(11) For mechanistic studies on alkene hydrogenation catalyzed by neutral Rh(I) complexes, see: (a) Tolman, C. A.; Meakin, P. Z.; Lindner, D. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 2762. (b) Halpern, J.; Wong, C. S. *Chem. Commun.* **1973**, 629. (c) Halpern, J.; Okamoto, T.; Zakhariev, A. *J. Mol. Catal.* **1976**, *2*, 65.

(12) For mechanistic studies on the hydrogenation of dehydroamino acids catalyzed by cationic Rh(I) complexes, see: (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (b) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (c) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055. (d) Halpern, J. *Science* **1982**, *217*, 401.

(13) For reviews encompassing the mechanism of asymmetric hydrogenation catalyzed by cationic rhodium complexes, see: (a) Halpern, J. *Asymm. Synth.* **1985**, *5*, 41. (b) Landis, C. R.; Brauch, T. W. *Inorg. Chim. Acta* **1998**, *270*, 285.

(14) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

(15) Jung, C. K.; Krische, M, J. *J. Am. Chem. Soc.* **2006**, *128*, 17051.

(16) Komanduri, V.; Grant, C. D.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 12592.

(17) Rhee, J.-U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674.

(18) (a) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. (b) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644.

(19) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448.

(20) (a) Kong, J.-R.; Ngai, M.-Y; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (b) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873. (c) Hong, Y.-T.; Cho, C.-W.; Skucas, E.; Krische, M. J. *Org. Lett.* **2007**, *9*, 3745.

(21) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269.

(22) For reviews on the use of *N-tert*-butanesulfinyl imines in asymmetric synthesis, see: (a) Davis, F.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (c) Zhou, P.; Chen, B.-C.; Davis, F. *Tetrahedron* **2004**, *60*, 8003.

(23) (a) Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16040. (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Han, S. B.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2008**, *10*, 4133.

(24) Williams, V. M.; Kong, J.-R.; Ko, B.-J.; Mantri, Y.; Brodbelt, J. S.; Baik, M.-H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 16054.

(25) Bianchini, C.; Caulton, K. G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T. J.; Meli, A.; Peruzzini, M.; Rauscher, D. J.; Streib, W. E.; Vizza, F. *J. Am. Chem. Soc.* **1991**, *113*, 5127 and references cited therein.

(26) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

(27) Gao, X.; Krische, M. J. *Manuscript in Preparation*.

(28) (a) Kim, I. S.; Han, S.-B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350.

(29) For a review on two-directional chain synthesis, see: Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

(30) Lu, Y.; Kim, I.-S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018.

(31) This mechanism for enantiomeric enrichment is documented by Eliel and Midland: (a) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (b) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143.

(32) Han, S. B.; Hassan, A.; Kim, I.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559.

(33) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, DOI: 10.1021/ja204570w.

(34) Rifamycin S: (a) Isolation: Sensi, P.; Margalith, P.; Timbal, M. T. *Farmaco, Ed. Sci.* **1959**, *14*, 146. (b) Sensi, P.; Greco, A. M.; Ballotta, R. *Antibiot. Annual* **1959/1960**, 262. (c) Total Synthesis: Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (d) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965. (e) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (f) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(35) (a) Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 9153. (b) Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 4562. (c) Gao, X.; Zhang, Y. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4173. (d) Han, S. B.; Han, H. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760.

(36) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916.

(37) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582.