

Cite this: *Chem. Sci.*, 2022, **13**, 12625

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 10th October 2022
Accepted 20th October 2022

DOI: 10.1039/d2sc05621f
rsc.li/chemical-science

I. Historical perspective

Catalytic hydrogenation and transfer hydrogenation account for roughly 14% of reactions used to prepare small-molecule clinical candidates (GMP reactions),¹ and it is estimated that hydrogenation catalysis will continue to expand.² Beyond hydrogenation, a survey of >9 million patents demonstrate that carbonyl additions (alongside Suzuki couplings) are among the most widely utilized methods for C–C bond formation in the pharmaceutical industry.³ These data have inspired our laboratory to develop a family of metal-catalyzed hydrogen auto-transfer reactions⁴ that merge the characteristics of catalytic hydrogenation and carbonyl addition by exploiting the native reducing power of alcohols for the concomitant generation of organometallic nucleophiles (from π -unsaturated pronucleophiles) and carbonyl electrophiles. In this way, carbonyl addition is achieved from the alcohol oxidation level in the absence of stoichiometric organometallic reagents. Processes of this type convert lower alcohols to higher alcohols, and are distinct from so-called “borrowing hydrogen” reactions,⁵ which affect formal hydroxyl substitution (Fig. 1).

Ruthenium(II) complexes are octahedral d^6 metal ions with unoccupied $d_{x^2-y^2}$ orbitals, making them well-suited for alkoxide β -hydride elimination (Fig. 2). Indeed, beyond borrowing hydrogen processes,⁵ diverse transformations based on ruthenium(II)-catalyzed alcohol dehydrogenation have been developed.⁶ Important milestones in ruthenium-catalyzed hydrogen transfer include the very first examples of alkene homogenous hydrogenation developed by Halpern (1961),⁷ ruthenium-catalyzed transfer hydrogenations reported by Blum (1971),⁸ so-called “acceptorless” alcohol dehydrogenations

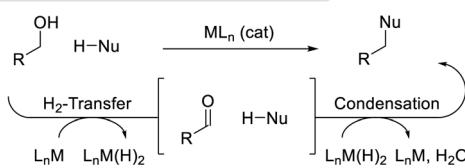
Historical perspective on ruthenium-catalyzed hydrogen transfer and survey of enantioselective hydrogen auto-transfer processes for the conversion of lower alcohols to higher alcohols

Eliezer Ortiz, Jonathan Z. Shezaf, Weijia Shen and Michael J. Krische *

Ruthenium-catalyzed hydrogen auto-transfer reactions for the direct enantioselective conversion of lower alcohols to higher alcohols are surveyed. These processes enable completely atom-efficient carbonyl addition from alcohol proelectrophiles in the absence of premetalated reagents or metallic reductants. Applications in target-oriented synthesis are highlighted, and a brief historical perspective on ruthenium-catalyzed hydrogen transfer processes is given.

described by Robinson (1977),⁹ oxidative esterifications devised by Shvo and Murahashi (1981)^{10a,b} and related oxidative aminations (Murahashi 1991),^{10c} respectively, as well as borrowing hydrogen alcohol aminations described by Watanabe (1981).¹¹ In a major advance, Noyori developed highly enantioselective ruthenium-catalyzed hydrogenations and transfer hydrogenations (1986 and 1995, respectively).¹² Finally, ruthenium-catalyzed hydrogen auto-transfer reactions that transform lower alcohols to higher alcohols were developed in the present authors' laboratory (2008).^{13,14} Corresponding enantioselective ruthenium-catalyzed processes soon followed (2011) and, in recent years, have expanded to encompass diverse reaction types. In this monograph, enantioselective methods for conversion of lower alcohols to higher alcohols *via* ruthenium-catalyzed hydrogen auto-transfer are catalogued.¹⁵ For surveys on the broader topic of metal-catalyzed carbonyl reductive couplings, the reader is referred to the review literature.¹⁶

Hydroxyl Substitution via “Borrowing H₂”



Lower Alcohols to Higher Alcohols via H₂ Auto-Transfer

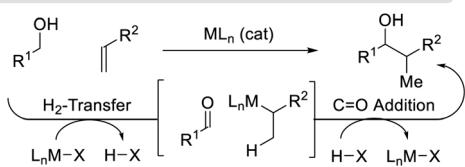


Fig. 1 Two major classes of hydrogen auto-transfer processes.



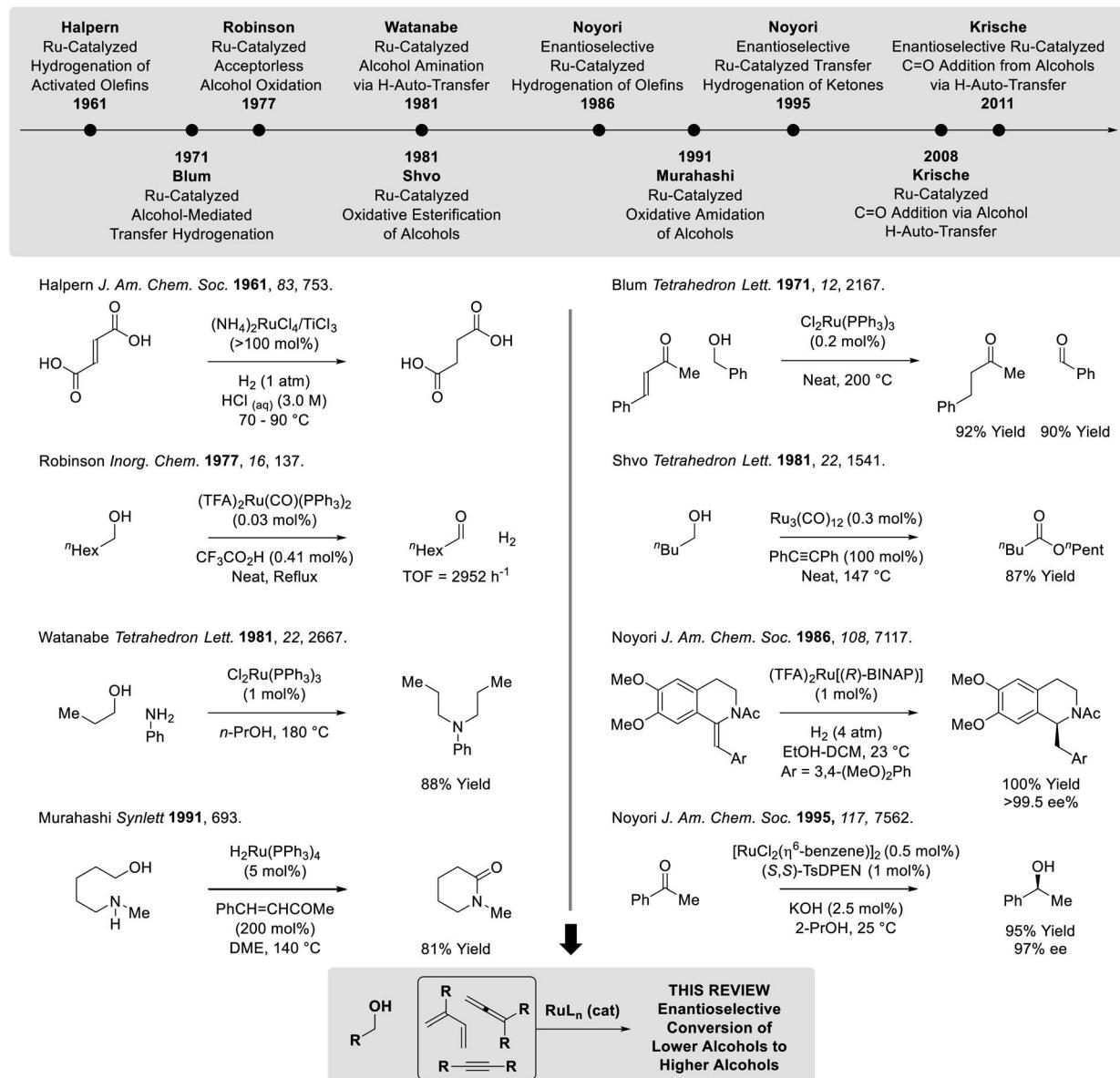


Fig. 2 Selected milestones in homogeneous ruthenium-catalyzed hydrogen transfer.

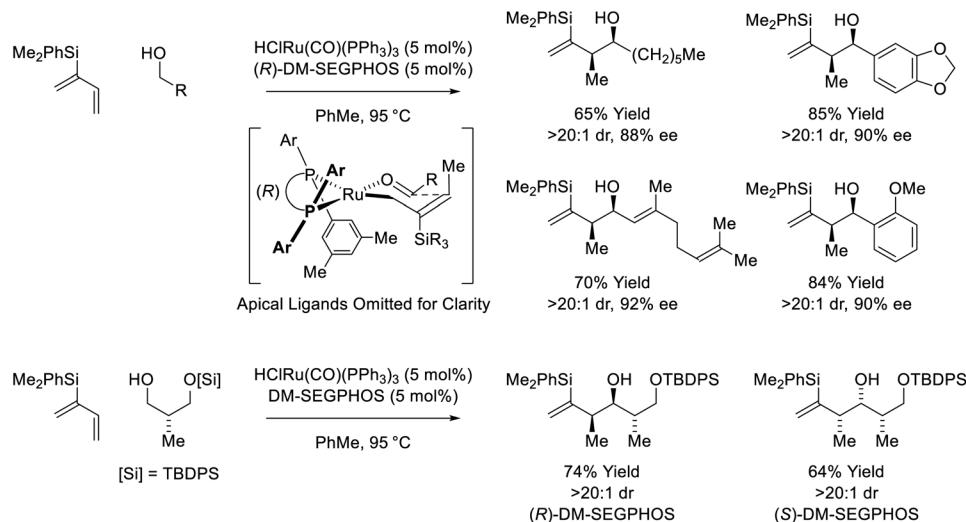
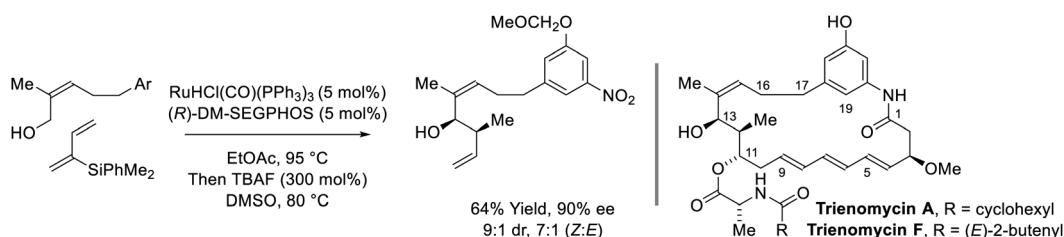
II. Enantioselective reactions of alcohols with diene and allene pronucleophiles

Following reports of racemic diene-alcohol C–C couplings *via* hydrogen auto-transfer,^{13,17} the first enantioselective ruthenium-catalyzed transformations of this type were developed (Scheme 1).^{18a} Using a chiral ruthenium catalyst modified by (R)-DM-SEGPHOS, hydrogen transfer from primary alcohols to 2-trialkylsilyl-butadienes (“silaprenes”) generates crotylruthenium–aldehyde pairs that combine to form branched secondary homoallylic alcohols with high levels of enantiomeric enrichment. Allylic 1,2-strain imposed by the trialkylsilyl moiety defines alkene geometry of the transient σ -crotylruthenium nucleophile, which participates in stereospecific aldehyde

addition through a closed transition structure to deliver the *syn*-diastereomers. Brimble exploited enantiomeric ruthenium catalysts in couplings of silaprene with the indicated chiral α -stereogenic alcohol derived from the Roche ester, enabling access to the *syn,anti*- or *syn,syn*-diketide stereotriads with good levels of catalyst-directed diastereocontrol.¹⁹ The silaprene-mediated conversion of lower alcohols to higher branched alcohols was utilized in total syntheses of trienomycins A and F (Scheme 2)^{21a} and soraphen A (not shown).^{21b}

In C–C couplings of primary alcohols with the parent diene, butadiene (an abundant petrochemical feedstock), high levels of stereoselectivity are more difficult to achieve due to the challenge of controlling the geometry of the intervening σ -crotylruthenium nucleophile. Eventually, it was found that good levels of *anti*-diastereoselectivity and enantioselectivity could be

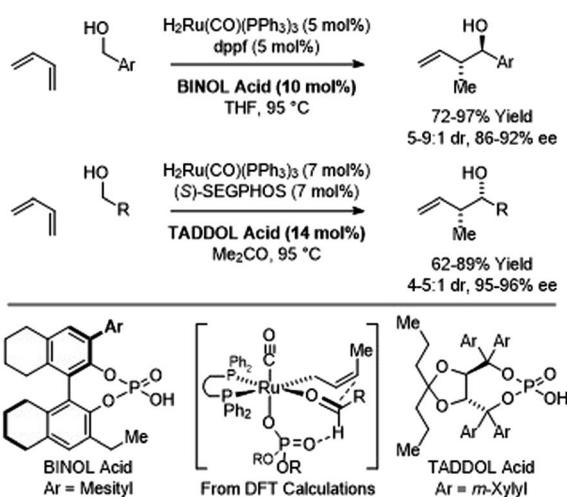


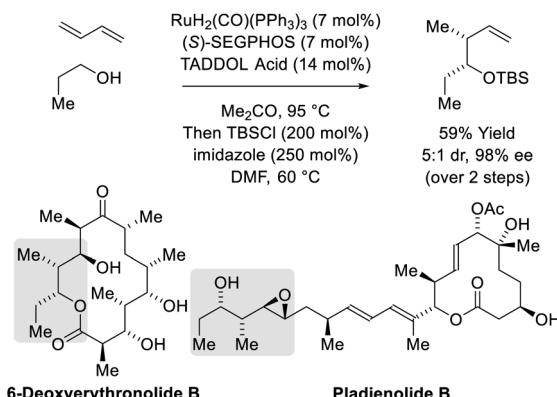
Scheme 1 *syn*-Diastereo- and enantioselective silaprene-mediated crotylation of primary alcohols.Scheme 2 *syn*-Diastereo- and enantioselective silaprene-mediated crotylation of primary alcohols for the total synthesis of trienomycins A and F.

obtained using ruthenium catalysts bound by chiral BINOL-derived phosphate counterions (Scheme 3).^{18b} However, these processes were restricted to benzylic alcohols. Interestingly, using the corresponding chiral tartaric acid-derived phosphate

counterion in combination with (*S*)-SEGPHOS, *syn*-diastereo- and enantioselective crotylations could be achieved (Scheme 3).^{18c} It was postulated that the more Lewis basic tartaric acid-derived phosphate counterion forms a contact ion pair with ruthenium, retarding the rate of isomerization of the kinetic (*Z*)- σ -crotylruthenium haptomer (formed by hydroruthenation of the *s-cis* conformer of butadiene) with respect to carbonyl addition. Computational studies suggest the transition state for aldehyde addition leading to the *syn*-diastereomer is stabilized by a formyl hydrogen bond.^{20,22} The *syn*-diastereoselective butadiene-mediated conversion of lower alcohols to higher branched alcohols was utilized in total syntheses of 6-deoxyerythronolide B²³ and pladienolide B (Scheme 4).²⁴

In more recent work, it was found that iodide-bound ruthenium-JOSIPHOS complexes catalyze the coupling of primary alcohols with butadiene to generate diastereo- and enantiomerically enriched products of *anti*-crotylation (Scheme 5).^{18d} This catalytic system displays broad scope and is of greater practicality, as it does not require chiral counterions and the JOSIPHOS ligand is commercially available. One remarkable feature of the ruthenium-JOSIPHOS-catalyzed primary alcohol-butadiene C–C coupling relates to the ability to affect C–C coupling of primary alcohols in the presence of unprotected secondary alcohols without the need for hydroxyl protecting groups, which is attributed to the relatively rapid kinetics of

Scheme 3 Chiral counterion-directed *anti*- and *syn*-diastereo- and enantioselective butadiene-mediated crotylations of primary alcohols.



Scheme 4 *syn*-Diastereo- and enantioselective butadiene-mediated crotylation of primary alcohols in the total synthesis of 6-deoxyerythronolide B and pladienolide B.

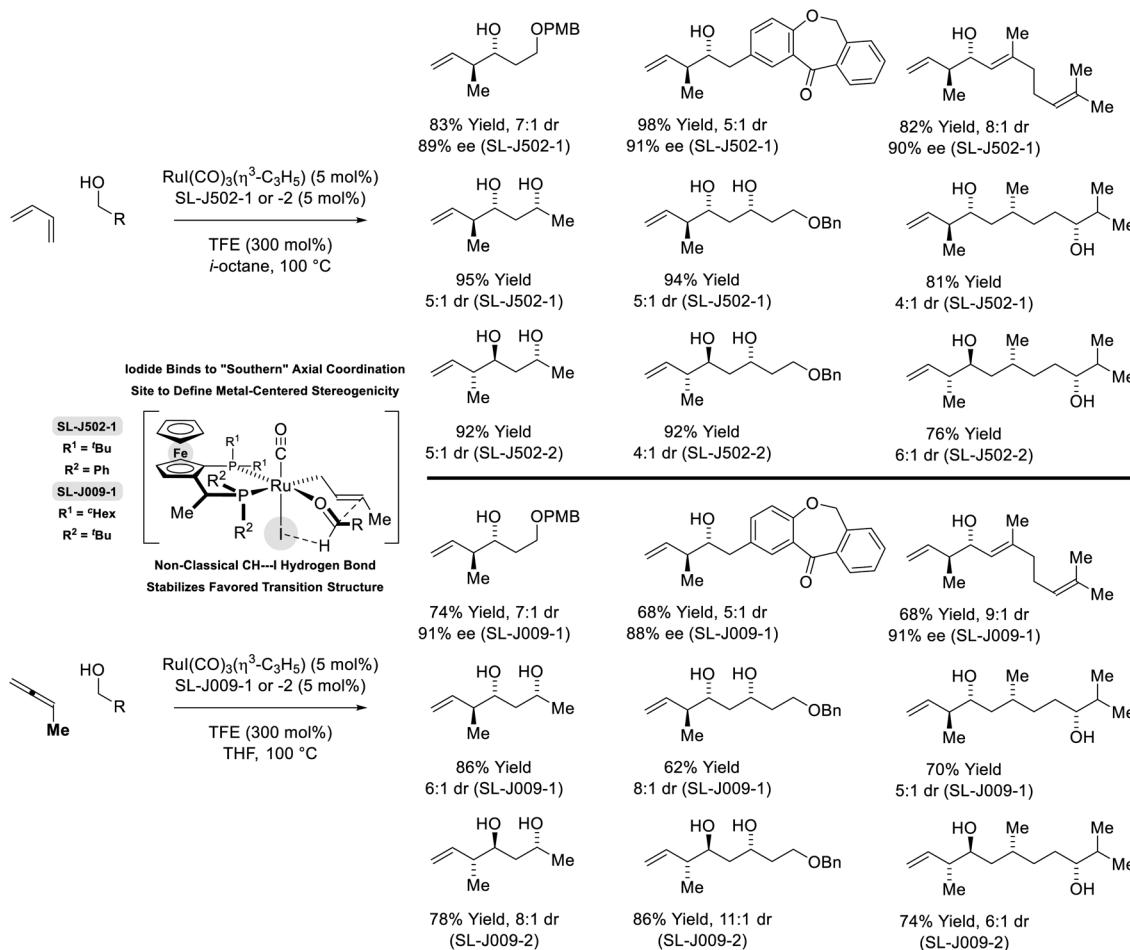
primary alcohol dehydrogenation. As supported by experimental and computational studies, iodide-bound ruthenium-JOSIPHOS complexes (unlike the corresponding chloride or bromide complexes) enforce high levels of enantioselectivity by defining the stereogenic center at ruthenium and through formation of a formyl CH···I hydrogen-bond that stabilizes the

favored transition state for carbonyl addition.²² Nearly identical reaction conditions were effective in couplings of primary alcohols with methylallene to form a duplicate set of diastereo- and enantiomerically enriched products. These processes represent an alternative to the longstanding use of discrete allylmetal reagents in enantioselective carbonyl crotylation.²⁵

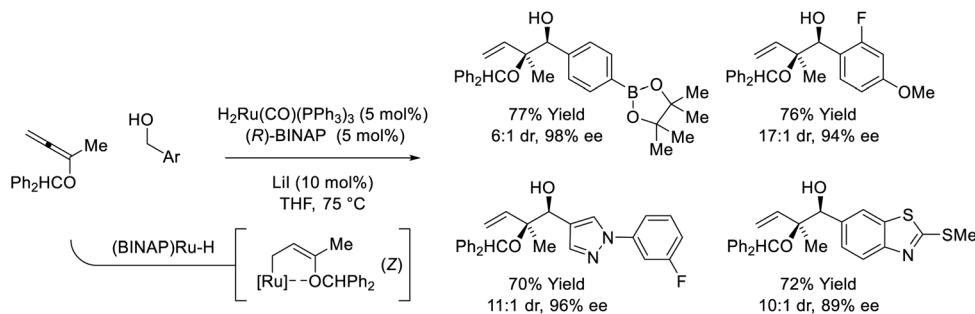
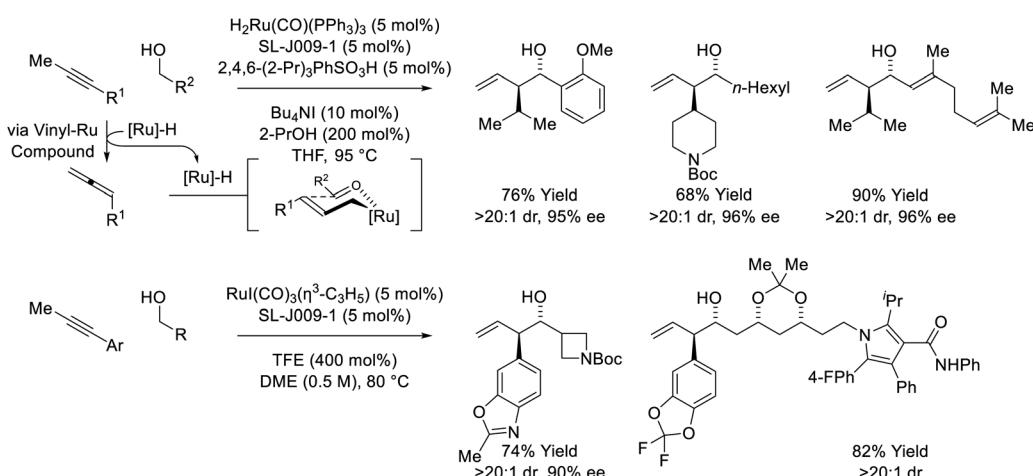
Ruthenium-BINAP-catalyzed couplings of primary benzylic alcohols with the indicated 1,1-disubstituted alkoxyallene enables formation of enantiomerically enriched *syn-sec,tert*-diols (Scheme 6).²⁶ Unusual *syn*-diastereoselectivity is attributed to internal chelation of the benzhydryl oxygen to ruthenium, which directs formation of (Z)- σ -(alkoxy)allylruthenium isomers that participate in stereospecific carbonyl addition through chair-like transition structures. Low conversion was observed in attempted reactions of aliphatic alcohols, however, 2-propanol-mediated reductive couplings of alkyl-substituted aldehydes were achieved in good yield (not shown).

III. Enantioselective reactions of alcohols with alkyne pronucleophiles

The first reported use of alkyne pronucleophiles in the enantioselective ruthenium-catalyzed conversion of lower alcohols to



Scheme 5 *anti*-Diastereo- and enantioselective crotylation of primary alcohols by the C4 feedstocks 1,2- and 1,3-butadiene.

Scheme 6 *syn*-Diastereo- and enantioselective alkoxyallene-mediated conversion of primary alcohols to *syn*-*sec*,*tert*-homoallylic diols.Scheme 7 *anti*-Diastereo- and enantioselective alkyne-mediated conversion of primary alcohols to branched homoallylic secondary alcohols.

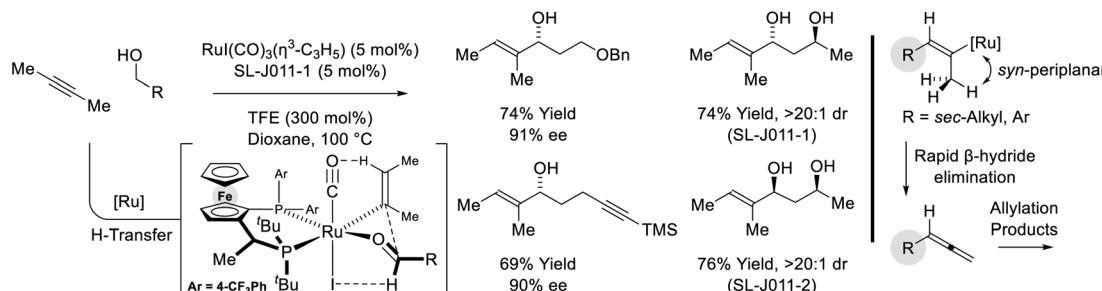
higher alcohols takes advantage of a dual catalytic cycle in which alkyne-to-allene isomerization (*via* hydrometallation- β -hydride elimination) is followed by allene-mediated carbonyl allylation to deliver branched homoallylic secondary alcohols (Scheme 7).^{27a} In these processes, iodide-bound ruthenium-JOSIPHOS catalysts are generated *in situ* through the acid-base reaction of $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$ with 2,4,6-(2-*Pr*)₃PhSO₃H, followed by substitution of the sulfonate counterion with iodide. Chloride and bromide-containing catalysts were inferior. As previously indicated (*vide supra*, Scheme 5), iodide defines the stereogenic center at ruthenium and stabilizes the favored transition state for carbonyl addition through formyl CH \cdots I hydrogen-bonding with the transient aldehyde. Several improvements to this catalytic system were subsequently made. Replacement of 2,4,6-(*i*Pr)₃PhSO₃H with 4-NO₂PhSO₃H resulted in >50% increase in isolated yield in reactions of 1-aryl-1-propynes, although catalyst loadings of 10 mol% remained necessary (not shown).^{27b} The use of the iodide-containing precatalyst $\text{Rui}(\text{CO})_3(\eta^3\text{-C}_3\text{H}_5)$ in combination with trifluoroethanol (TFE) provided the most effective catalytic system for the reaction of primary alcohols with 1-aryl-1-propynes to form products of carbonyl *anti*-(α -aryl)allylation.^{27c} In this process, TFE catalyses exchange of the homoallylic ruthenium

alkoxide with reactant alcohol, mitigating issues of product inhibition.

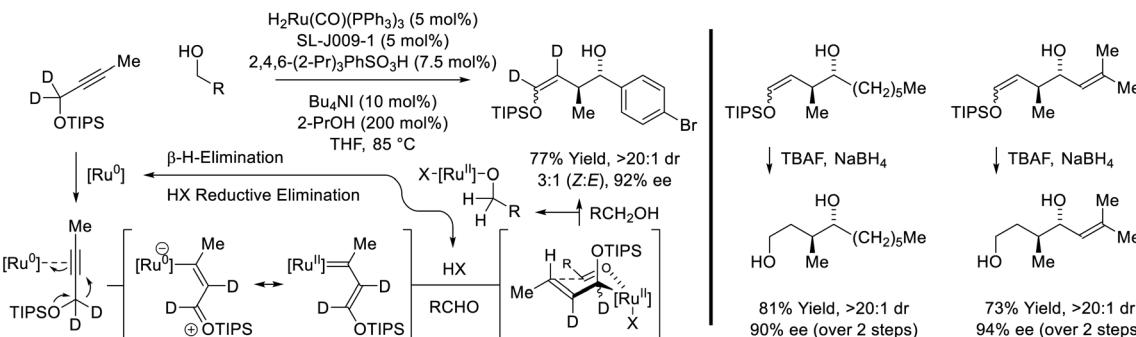
Remarkably, when the latter conditions are applied to 2-butyne, alkyne-to-allene isomerization is interrupted at the stage of intermediate vinylruthenium species *via* carbonyl addition to form products of alkenylation (Scheme 8).^{28,29} This divergent reactivity suggests acetylenic substituents larger than methyl (*i.e.* aryl or *sec*-alkyl) stabilize a *syn*-periplanar conformation of the carbon-ruthenium and propargylic C-H bonds, reducing the entropy of activation for β -hydride elimination to accelerate allene formation. The conversion of 2-butyne and primary alcohols to secondary allylic alcohols is highly chemoselective and proceeds in the presence of silyl-substituted alkynes and unprotected secondary alcohols. The indicated stereochemical model invokes a formyl CH \cdots I hydrogen-bond^{22,27c} and a ruthenium CH \cdots O=C[Ru] hydrogen-bond³⁰ in the favored transition state for carbonyl addition.

Yet another mode of reactivity is observed in connection with the couplings of trialkylsilyl propargyl ethers and primary alcohols (Scheme 9).³¹ Under conditions essentially identical to those used in the coupling *sec*-alkyl propynes (*vide supra*, Scheme 7),^{27a} alkyne-to-allene isomerization is not observed. Rather, as corroborated by deuterium labeling studies, alkyne coordination by zero-valent ruthenium triggers a 1,2-hydride





Scheme 8 Enantioselective conversion of primary alcohols and 2-butyne to secondary allylic alcohols.



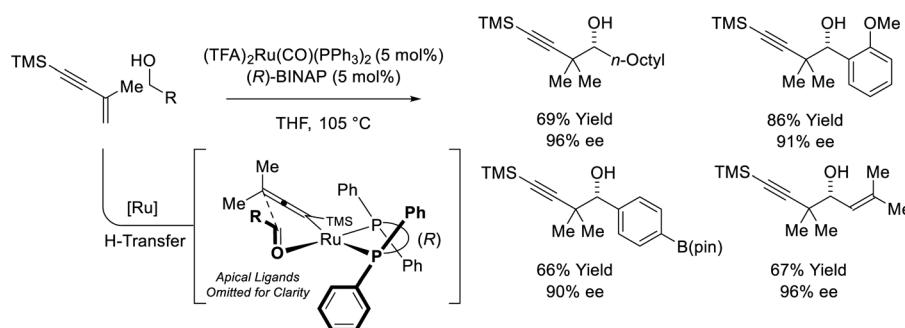
Scheme 9 anti-Diastereo- and enantioselective conversion of primary alcohols and trialkylsilyl propargyl ethers to branched secondary alcohols.

shift to form a vinyl carbene, which upon protonation, generates a siloxy- π -allylruthenium nucleophile. Aldehyde addition by way of the indicated σ -allylruthenium haptomer delivers branched homoallylic alcohols that incorporate enol silyl ethers. Silyl deprotection-reduction of the crude reaction products provides the corresponding 1,4-diols with excellent control of regio-, diastereo- and enantioselectivity.

IV. Enantioselective reactions of alcohols with enyne pronucleophiles

The first examples of enyne-mediated carbonyl propargylation were reported from the present authors laboratory.^{32–34} The first enantioselective ruthenium-catalyzed conversion of 1,3-enynes

and primary alcohols to form homopropargylic secondary alcohol was achieved using the chiral ruthenium complex assembled from $(\text{TFA})_2\text{Ru}(\text{CO})(\text{PPh}_3)_2$ and (R) -BINAP (Scheme 10).^{32c} The resulting secondary homopropargyl alcohols bearing *gem*-dimethyl groups are formed with excellent levels of enantiomeric enrichment. In this process, hydrogen transfer from the primary alcohol to the 1,3-enyne generates a prochiral allenylruthenium nucleophile, which engages the transient aldehyde in carbonyl addition by way of the indicated closed transition structure. In support of this mechanism, the reaction of $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ with 1,3-enynes to form an isolable σ -allenylruthenium complex characterized by single crystal X-ray diffraction has been described.³⁵ This protocol represents an alternative to the longstanding use of discrete allenylmetal reagents in enantioselective carbonyl propargylation.³⁶



Scheme 10 Enantioselective conversion of primary alcohols and 2-butyne to secondary allylic alcohols.



V. Conclusion and future outlook

Ruthenium complexes are the prototypical hydrogen transfer catalysts and they continue to facilitate an ever-increasing array of chemical processes. As described in this perspective article, a new reactivity mode in the field of ruthenium catalysis is represented by the emerging class of chemical transformations in which alcohol dehydrogenation triggers reductive generation of aldehyde-organometal pairs that combine to affect byproduct-free carbonyl addition. Such reactions enable direct conversion of lower alcohols to higher alcohols and allow abundant π -unsaturated feedstocks to serve as surrogates to stoichiometric organometallic reagents. Discovered and developed wholly in the present authors laboratory, processes of this type raise numerous other possibilities. Beyond continued efforts to adapt this concept to other types of carbonyl additions (alkylations,³⁷ vinylations,³⁸ alkynylations, and arylation), methods for the direct conversion of lower amine to higher amines (hydroaminoalkylation)³⁹ represents an important challenge that merits further attention. It is the authors' hope that the present state of the art summary will expedite progress toward this and other challenges in this growing area of research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research.

References

- 1 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.
- 2 M. A. Stoffels, F. J. R. Klauck, T. Hamadi, F. Glorius and J. Leker, *Adv. Synth. Catal.*, 2020, **362**, 1258–1274.
- 3 N. Schneider, D. M. Lowe, R. A. Sayle, M. A. Tarselli and G. A. Landrum, *J. Med. Chem.*, 2016, **59**, 4385–4402.
- 4 For recent reviews on hydrogen auto-transfer for the conversion of lower alcohols to higher alcohols, see: (a) S. W. Kim, W. Zhang and M. J. Krische, *Acc. Chem. Res.*, 2017, **50**, 2371–2380; (b) R. S. Doerkens, C. C. Meyer and M. J. Krische, *Angew. Chem., Int. Ed.*, 2019, **58**, 14055–14064; (c) C. G. Santana and M. J. Krische, *ACS Catal.*, 2021, **11**, 5572–5585.
- 5 For selected reviews on “borrowing hydrogen” processes that result in hydroxyl substitution, see: (a) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (b) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358–2364; (c) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703; (d) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853–1864; (e) Q. Yang, Q. Wang and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305–2329; (f) H. Aitchison, R. L. Wingad and D. F. Wass, *ACS Catal.*, 2016, **6**, 7125–7132; (g) A. Quintard and J. Rodriguez, *Chem. Commun.*, 2016, **52**, 10456–10473; (h) B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595–1607; (i) T. Kwok, O. Hoff, R. J. Armstrong and T. J. Donohoe, *Chem.-Eur. J.*, 2020, **26**, 12912–12926.
- 6 For selected general reviews on ruthenium-catalyzed hydrogen transfer processes, see: (a) U. Matteoli, P. Frediani, M. Bianchi, C. Botteghi and S. Gladiali, *J. Mol. Catal.*, 1981, **12**, 265–319; (b) S. I. Murahashi and T. Naota, *Adv. Met.-Org. Chem.*, 1994, **3**, 225–254; (c) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97–102; (d) S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201–2237; (e) Y. Ahn, S.-B. Ko, M.-J. Kim and J. Park, *Coord. Chem. Rev.*, 2008, **252**, 647–658; (f) M. C. Warner, C. P. Casey and J.-E. Bäckvall, *Top. Organomet. Chem.*, 2011, **37**, 85–125; (g) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249–260; (h) C. Gunanathan and D. Milstein, *Chem. Rev.*, 2014, **114**, 12024–12087; (i) J. Zhang, B. Guo, D. J. Young and H.-X. Li, *Dalton Trans.*, 2020, **49**, 15527–15547; (j) V. Ritleng and J. G. de Vries, *Molecules*, 2021, **26**, 4076–4121.
- 7 J. Halpern, J. F. Harrod and B. R. James, *J. Am. Chem. Soc.*, 1961, **83**, 753–754.
- 8 Y. Sasson and J. Blum, *Tetrahedron Lett.*, 1971, **12**, 2167–2170.
- 9 A. Dobson and S. D. Robinson, *Inorg. Chem.*, 1977, **16**, 137–142.
- 10 For oxidative esterification and oxidative amidation of primary alcohols, see: (a) Y. Blum, D. Reshef and Y. Shvo, *Tetrahedron Lett.*, 1981, **22**, 1541–1544; (b) S.-I. Murahashi, K.-I. Ito, T. Naota and Y. Maeda, *Tetrahedron Lett.*, 1981, **22**, 5327–5330; (c) T. Naoto and S.-I. Murahashi, *Synlett*, 1991, **10**, 693–694. Also see: (d) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792.
- 11 Alcohol amination *via* metal-catalyzed hydrogen auto-transfer was reported contemporaneously by Wantanabe and Grigg using ruthenium and rhodium catalysts, respectively: (a) Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667–2670; (b) R. Grigg, T. R. B. Mitchell, S. Suthivaiyakit and N. Tongpenyai, *J. Chem. Soc., Chem. Commun.*, 1981, 611–612.
- 12 (a) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta and H. Takaya, *J. Am. Chem. Soc.*, 1986, **108**, 7117–7119; (b) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562–7563.
- 13 The first metal-catalyzed hydrogen auto-transfer reactions to convert lower alcohols to higher alcohols employed catalysts based on iridium and ruthenium: (a) J. F. Bower, E. Skucas, R. L. Patman and M. J. Krische, *J. Am. Chem. Soc.*, 2007, **129**, 15134–15135; (b) F. Shibahara, J. F. Bower and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 6338–6339.
- 14 This reactivity pattern appears quite unique. To our knowledge, the closest precedent is the ruthenium-catalyzed conversion of primary alcohols and allyl acetate





to α,β -unsaturated enones: T. Kondo, T. Mukai and Y. Watanabe, *J. Org. Chem.*, 1991, **56**, 487.

15 For earlier reviews on ruthenium-catalyzed hydrogen auto-transfer for the conversion of lower alcohols to higher alcohols, see: (a) F. Shibahara and M. J. Krische, *Chem. Lett.*, 2008, **37**, 1102–1107; (b) J. Moran and M. J. Krische, *Pure Appl. Chem.*, 2012, **84**, 1729–1739; (c) F. Perez, S. Oda, L. M. Geary and M. J. Krische, *Top. Curr. Chem.*, 2016, **374**, 365–387.

16 For selected reviews on the general topic of metal-catalyzed carbonyl reductive coupling, see: (a) J. Montgomery, *Angew. Chem. Int. Ed.*, 2004, **43**, 3890–3908; (b) M. J. Krische and H.-Y. Jang, in *Comprehensive Organometallic Chemistry III*, ed. P. Mingos, and R. Crabtree, Elsevier, Oxford, 3rd edn, 2006, vol. 10, ch. 4, pp. 493–536; (c) M. J. Krische, *Top. Curr. Chem.*, 2007, **279**, 77–104; (d) M. Kimura and Y. Tamaru, *Top. Curr. Chem.*, 2007, **279**, 173–207; (e) T. Moragas, A. Correa and R. Martin, *Chem.-Eur. J.*, 2014, **20**, 8242–8258; (f) K. D. Nguyen, B. Y. Park, T. Luong, H. Sato, V. J. Garza and M. J. Krische, *Science*, 2016, **354**, aah5133; (g) M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.*, 2018, **118**, 6026–6052; (h) E. Ortiz, J. Z. Shezaf, Y.-H. Chang and M. J. Krische, *ACS Catal.*, 2022, **12**, 8164–8174.

17 For ruthenium-catalyzed diene-alcohol C–C couplings to form secondary homoallylic alcohols, see ref. 13 and following studies: (a) H. Han and M. J. Krische, *Org. Lett.*, 2010, **12**, 2844–2846; (b) J. C. Leung, L. M. Geary, T.-Y. Chen, J. R. Zbieg and M. J. Krische, *J. Am. Chem. Soc.*, 2012, **134**, 15700–15703; (c) T.-Y. Chen and M. J. Krische, *Org. Lett.*, 2013, **15**, 2994–2997; (d) B. Y. Park, T. P. Montgomery, V. J. Garza and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 16320–16323.

18 For enantioselective ruthenium-catalyzed diene-alcohol C–C couplings to form higher homoallylic alcohols, see: (a) J. R. Zbieg, J. Moran and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 10582–10586; (b) J. R. Zbieg, E. Yamaguchi, E. L. McInturff and M. J. Krische, *Science*, 2012, **336**, 324–327; (c) E. L. McInturff, E. Yamaguchi and M. J. Krische, *J. Am. Chem. Soc.*, 2012, **134**, 20628–20631; (d) E. Ortiz, B. J. Spinello, Y. Cho, J. Wu and M. J. Krische, *Angew. Chem. Int. Ed.*, 2022, **61**, e202212814.

19 M. Pantin, J. G. Hubert, T. Söhnel, M. A. Brimble and D. P. Furkert, *J. Org. Chem.*, 2017, **82**, 11225–11229.

20 For computational studies of chiral counterion-directed enantioselective ruthenium-catalyzed diene-alcohol C–C couplings to provide higher homoallylic alcohols, see: M. N. Grayson, M. J. Krische and K. N. Houk, *J. Am. Chem. Soc.*, 2015, **137**, 8838–8850.

21 (a) D. J. Del Valle and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 10986–10989; (b) T. T. Schempp and M. J. Krische, *J. Am. Chem. Soc.*, 2022, **144**, 1016–1022.

22 For selected studies of formyl CH hydrogen bonds, see ref. 20 and following reports: (a) E. J. Corey and T. W. Lee, *Chem. Commun.*, 2001, 1321–1329; (b) T. S. Thakur, M. T. Kirchner, D. Bläser, R. Boese and G. R. Desiraju, *Phys. Chem. Chem. Phys.*, 2011, **13**, 14076–14091.

23 X. Gao, S. K. Woo and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 4223–4226.

24 M. Yoo and M. J. Krische, *Angew. Chem., Int. Ed.*, 2021, **60**, 13923–13928.

25 For selected reviews on the use of allylmetal reagents in carbonyl allylation and crotylation, see: (a) S. E. Denmark and J. Fu, *Chem. Rev.*, 2003, **103**, 2763–2794; (b) D. G. Hall, *Synlett*, 2007, **11**, 1644–1655; (c) M. Yus, J. C. González-Gómez and F. Foubelo, *Chem. Rev.*, 2011, **111**, 7774–7854; (d) H.-X. Huo, J. R. Duvall, M.-Y. Huang and R. Hong, *Org. Chem. Front.*, 2014, **1**, 303–320; (e) K. Spielmann, G. Niel, R. M. de Figueiredo and J.-M. Campagne, *Chem. Soc. Rev.*, 2018, **47**, 1159–1173.

26 M. Xiang, D. Pfaffinger, E. Ortiz, G. A. Brito and M. J. Krische, *J. Am. Chem. Soc.*, 2021, **143**, 8849–8854.

27 (a) T. Liang, K. D. Nguyen, W. Zhang and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 3161–3164; (b) M. Xiang, A. Ghosh and M. J. Krische, *J. Am. Chem. Soc.*, 2021, **143**, 2838–2845; (c) E. Ortiz, J. Z. Shezaf, Y.-H. Chang, T. P. Gonçalves, K.-W. Huang and M. J. Krische, *J. Am. Chem. Soc.*, 2021, **143**, 16709–16717.

28 E. Ortiz, Y.-H. Chang, J. Z. Shezaf, W. Shen and M. J. Krische, *J. Am. Chem. Soc.*, 2022, **144**, 8861–8869.

29 The coupling of 2-butyne with primary alcohols to form racemic products of carbonyl alkenylation was previously described: R. L. Patman, M. R. Chaulagain, V. M. Williams and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 2066–2067.

30 An exhaustive survey of X-ray diffraction data reveal CH...O≡C[Ru] hydrogen-bonds are conserved across diverse vinylruthenium carbonyl complexes. These hydrogen bonds are $< 2.96 \text{ \AA}$ in length, which is significantly shorter than the $< 3.2 \text{ \AA}$ distance usually observed for CH...O hydrogen bonds. See ref. 27 for primary literature references.

31 T. Liang, W. Zhang, T.-Y. Chen, K. D. Nguyen and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 13066–13071.

32 For ruthenium-catalyzed coupling of 1,3-enynes with primary alcohols to form secondary homopropargylic alcohols, see: (a) R. L. Patman, V. M. Williams, J. F. Bower and M. J. Krische, *Angew. Chem., Int. Ed.*, 2008, **47**, 5220–5223; (b) L. M. Geary, J. C. Leung and M. J. Krische, *Chem.-Eur. J.*, 2012, **18**, 16823–16827; (c) K. D. Nguyen, D. Herkommmer and M. J. Krische, *J. Am. Chem. Soc.*, 2016, **138**, 5238–5241.

33 For iridium- and rhodium-catalyzed coupling of 1,3-enynes or propargyl chlorides with primary alcohols to form secondary homopropargylic alcohols, see: (a) L. M. Geary, S. K. Woo, J. C. Leung and M. J. Krische, *Angew. Chem., Int. Ed.*, 2012, **51**, 2972–2976; (b) S. K. Woo, L. M. Geary and M. J. Krische, *Angew. Chem., Int. Ed.*, 2012, **51**, 7830–7834; (c) T. Liang, S. K. Woo and M. J. Krische, *Angew. Chem., Int. Ed.*, 2016, **55**, 9207–9211.

34 For a review on carbonyl propargylation via alcohol-mediated hydrogen auto-transfer, see: B. R. Ambler, S. K. Woo and M. J. Krische, *ChemCatChem*, 2019, **11**, 324–332.

35 Y. Wakatsuki, H. Yamazaki, Y. Maruyama and I. Shimizu, *J. Chem. Soc., Chem. Commun.*, 1991, 261–263.

36 For selected reviews on the use of allenylmetal reagents in carbonyl propargylation, see: (a) J. A. Marshall, *Chem. Rev.*, 1996, **96**, 31–48; (b) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914–1937; (c) H. M. Wisniewska and E. R. Jarvo, *J. Org. Chem.*, 2013, **78**, 11629–11636; (d) T. Thaima, F. Zamani, C. J. T. Hyland and S. G. Pyne, *Synthesis*, 2017, **49**, 1461–1480.

37 For use of ethylene and α -olefins as alkylmetal equivalents in carbonyl addition from alcohol proelectrophiles, see: (a) E. Yamaguchi, J. Mowat, T. Luong and M. J. Krische, *Angew. Chem., Int. Ed.*, 2013, **52**, 8428–8431; (b) B. Y. Park, T. Luong, H. Sato and M. J. Krische, *J. Org. Chem.*, 2016, **81**, 8585–8594.

38 For vinyl transfer beyond use of alkyne pronucleophiles, see: B. Y. Park, T. Luong, H. Sato and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 7652–7655.

39 For late transition metal-catalyzed hydroaminoalkylation beyond directing groups, see: T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 1798–1801.

