Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: W. Yao, R. Li, J. Li, J. Sun and M. Ye, *Green Chem.*, 2019, DOI: 10.1039/C9GC00653B.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/green-chem

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9GC00653B

Journal Name

COMMUNICATION

NHC Ligand–Enabled Ni–Catalyzed Reductive Coupling of Alkyne and Imine Using Isopropanol as Reductant

Received 00th January 20xx,
Accepted 00th January 20xx

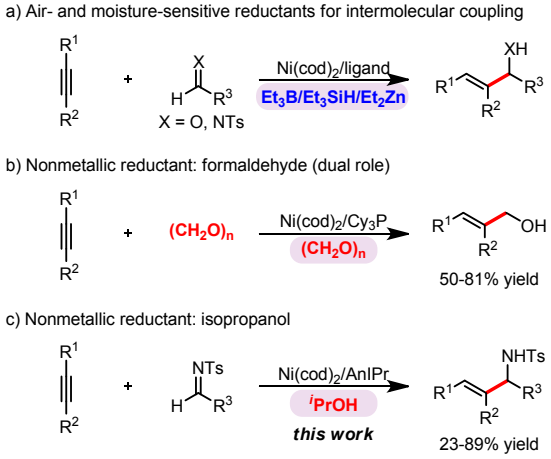
DOI: 10.1039/x0xx00000x

www.rsc.org/

Wei-Wei Yao[a], Ran Li [a], Jiang-Fei Li [a], Juan Sun[b], Mengchun Ye[a*]

A nickel-catalyzed reductive coupling of alkyne and imine using readily available isopropanol as the reducing agent was developed. The use of sterically bulky and electron-rich carbene ligand (AnIPr) significantly promotes the reaction, providing various multi-substituted allylic amines in 23–89% yield. And the corresponding chiral ligand (AnIPr-3) can afford the products in 51–95% ee.

Construction of allylic alcohols and allylic amines through nickel-catalyzed reductive coupling of alkynes and carbonyls or imines has attracted wide research interests during past decades.[1,2] However, owing to high susceptibility of nickel catalysts to reaction conditions,[3,4] the selection of reducing agent has been always an important and challenging issue. Especially for intermolecular reductive couplings of alkynes and carbonyls, existing endeavors mainly rely on the use of air- and moisture-sensitive reducing agents such as Et_3B[5], Et_3SiH[6] and Et_2Zn[7,8] (Scheme 1a).[9] However, these reducing agents are generally pyrophoric and highly mass intensive, leading to high cost and stoichiometric amounts of metallic waste. Therefore, the development of inexpensive and environmentally-friendly non-metallic reducing agents for nickel-catalyzed reductive couplings is highly desirable.[10,11] To date, the sole nonmetallic reducing agent in the reductive coupling of alkyne and carbonyl was reported by Krische and co-workers, who used formaldehyde as both substrate and reductant (Scheme 1b).[12] However, this dual role of formaldehyde resulted into a severe restriction of substrates, meaning that formaldehyde was the only selection of carbonyls. Therefore, the development of more commonly-used non-metallic reducing agent that possesses higher efficiency and broader compatibility of substrates in nickel-catalyzed reductive couplings still remains an elusive challenge. Herein we report a nickel-catalyzed reductive coupling of alkyne and imine, in which easy-to-handle and low-cost isopropanol is used as reducing agent for the first time (Scheme 1c). The bulky and electron-rich *N*-heterocycle carbene (NHC) AnIPr proves crucial to the reaction efficiency and selectivity.



Scheme 1 Ni-catalyzed reductive coupling of alkynes with carbonyls and imines.

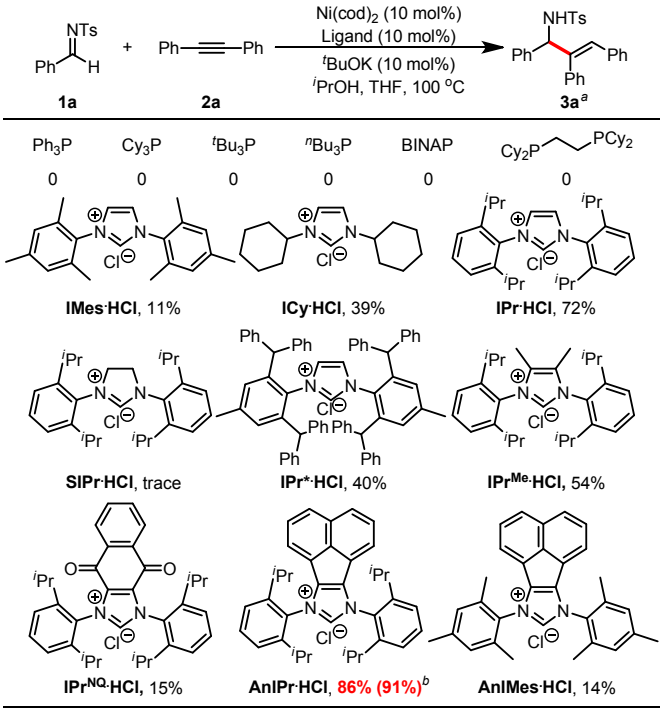
Kurahashi, Matsubara and co-workers developed an elegant coupling of primary alcohols and alkynes, in which the primary alcohol was proposed to protonate the formed 5-membered oxa-nickelacycle and then provide a β-hydride to complete the final reduction.[13] Inspired by this discovery, we envisioned that using a sterically-hindered secondary alcohol instead of primary alcohol to protonate an aza-nickelacycle[14] may suppress direct coupling of the alcohol and the alkyne, leading to alcohol-mediated reductive coupling of the alkyne and the imine.

Following this hypothesis, we selected aldimine **1a** and 1,2-diphenylethyne (**2a**) as model substrates to explore the alcohol-mediated nickel-catalyzed reductive coupling. Considering that isopropanol is not only the simplest secondary alcohol, but also it is regarded as green and recyclable reducing agent,[15] we commenced our study by using isopropanol as the reducing agent. When 1 equivalent of

[a] State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin, 300071, China. Email: mcye@nankai.edu.cn
[b] Department of Chemistry, Key Laboratory of Advanced Energy Materials Chemistry, College of Chemistry, Nankai University, Tianjin, 300071, China.
Electronic Supplementary Information (ESI) available: See DOI:

View Article Online DOI: 10.1039/C9GC00653B

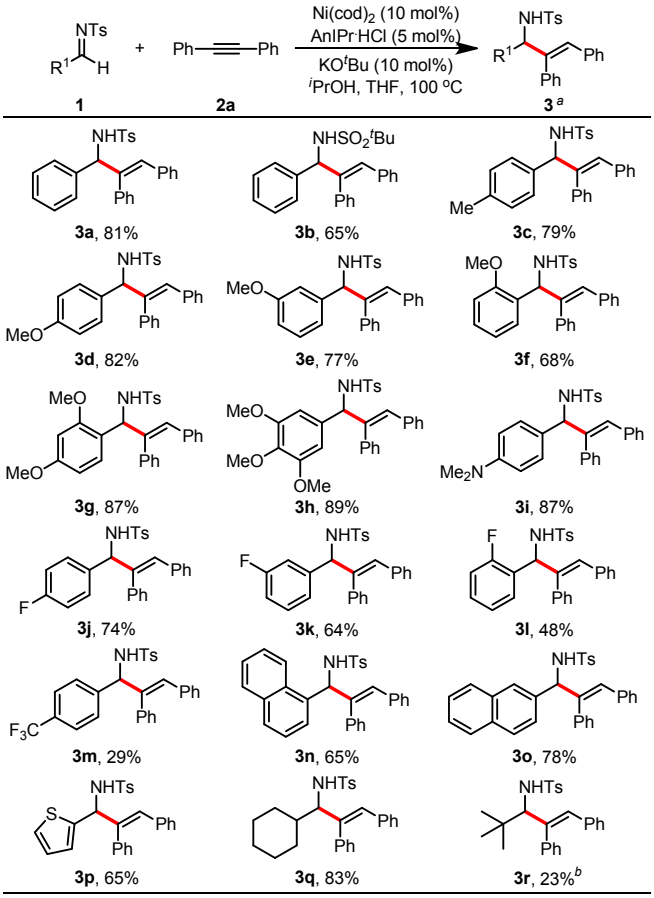
isopropanol was used, various commonly-used phosphines were completely ineffective (Scheme 2), whereas NHC ligands such as IMes·HCl and IPr·HCl did produce a trace amount of the expected allylic amine **3a** with sole *E*-selectivity. Furthermore, the reaction was found to be highly dependent on the amount of isopropanol. In case of IPr·HCl as the ligand, 5 equivalents of isopropanol can improve the yield to 7%. Further increasing the amount of isopropanol to 65 equivalents (0.5 mL) led to 72% yield. However, no better yield can be obtained by varying various reaction parameters including solvent, temperature, alcohol structure, substrate ratio and catalyst type (see Table S1–S6). So we then turned to modify the structure of carbene ligands. A broad range of carbenes were synthesized and examined, and the results showed that saturated carbene (SIPr·HCl) and sterically bulky carbene (IPr*·HCl) were not good. Similarly, electron-rich carbene (IPr^{Me}·HCl, 54%) and electron-deficient carbene (IPr^{NQ}·HCl, 15%) also cannot afford better result than IPr·HCl.



Scheme 2 Conditions optimization. [a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), ^{i}PrOH (0.5 mL) in THF (0.5 mL) under N_2 for 18 h; yields were determined by ^{1}H NMR. [b]AnIPr·HCl (5 mol%).

However, AnIPr·HCl with more electron-rich and sterically bulky backbone significantly enhanced the yield to 86%. Notably, decreasing the ligand loading to 5 mol% led to a slightly better yield (91%), but further reducing to 2.5 mol% was a little detrimental (86% yield). Notably, decreasing the loading of nickel to 5 mol% also gave a lower yield (87%). Although this result was repeated many times, the exact reason was unknown. We speculated that the ratio of metal and ligand could have an influence on the induction of catalytic species. The same backbone with IMes only afforded 14% yield (AnIMes·HCl), suggesting that the reactivity was highly sensitive to steric hindrance of the carbene ligand.

With the optimized reaction conditions in hand, we first explored a series of aldimines to test the generality of the reaction (Scheme 3). The sulfonyl protecting group on N atom of the imine was requisite to the reaction efficiency (**3a** and **3b**), and other kinds of protecting groups such as Boc, Cbz and Bz were ineffective. The electronic property of phenyl ring of aldimines has substantial effect on the reaction. Generally, more electron-rich phenyl ring would result into higher yield. For example, various arylaldimines bearing electron-donating groups on the phenyl ring such as Me (**3c**), MeO (**3d–3h**) and Me_2N (**3i**) provided the corresponding products in 68–89% yields.

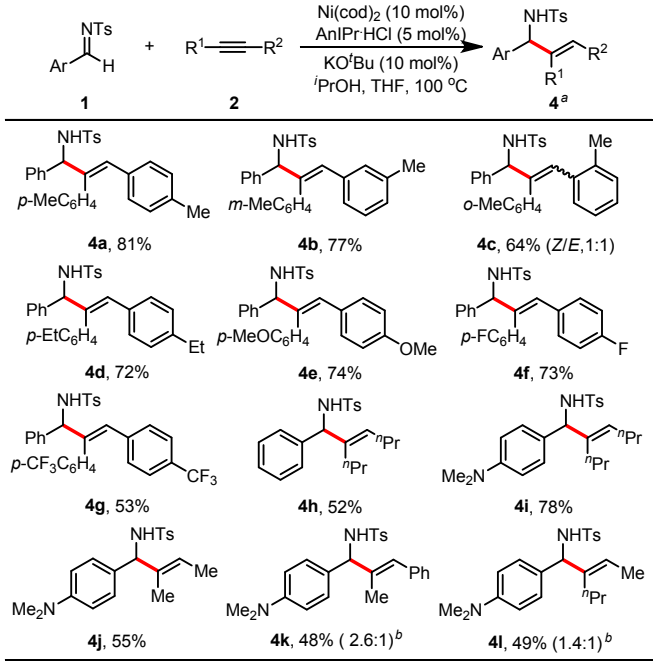


Scheme 3 [a]Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), ^{i}PrOH (1.0 mL) in THF (1.0 mL) under N_2 for 18 h; yields of isolated products. [b]AnIPr·HCl (5 mol%).

In contrast, arylaldimines with electron-withdrawing groups such as F (**3j–3l**) and CF_3 (**3m**) significantly decreased the yield. The steric hindrance of the phenyl ring also has a little influence. For example, various aryl rings with *o*-MeO (**3f**) and *o*-F (**3l**) resulted in lower yields than those bearing *p*-MeO (**3d**) and *p*-F (**3j**). Naphthyl (**3n** and **3o**) and heteroaryl (**3p**) were also tolerant to this reaction, providing the corresponding products in 65–78% yield. Alkylaldimines were also compatible, but the reaction was highly sensitive to the stability of imines under reaction conditions. Relatively stable cyclohexyl

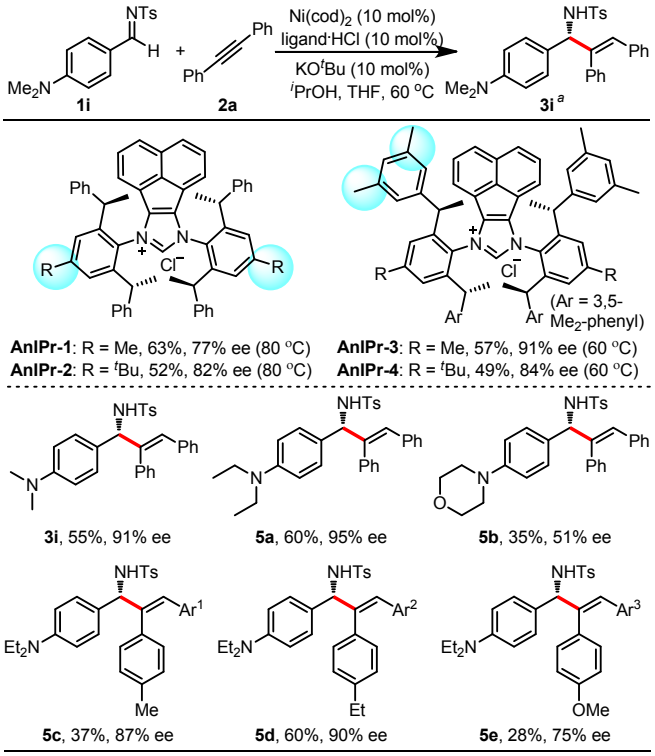
aldimine gave 83% yield (**3q**), whereas *tert*-butyl imine only led to 23% yield owing to its easy decomposition during the reaction (**3r**).

Next, various alkynes including symmetric and asymmetric alkynes bearing either aryl or alkyl substituents were examined (Scheme 4). Results showed electronic property of aryl ring of diaryl alkynes did not have big influence on the reaction. Various electron-withdrawing groups (CF_3, F) and electron-donating groups (Me, Et, OMe) (**4a–4g**) provided the corresponding products in 53–81% yield. Notably, sterically hindered aryl alkyne provided a mixture of *Z*- and *E*-allylic amines with a 1:1 ratio (**4c**). We reasoned that steric hindrance of phenyl ring resulted into an inversion of alkene configuration after the ring opening of the nickelacycle. Dialkyl alkynes also worked well in this reaction, but provided a slightly lower yield (**4h–4l**). The use of more electron-rich aldimine significantly increased the yield (**4h** *vs* **4i**). Notably, asymmetric dialkyl alkynes led to a mixture of two regioisomers with a ratio varying from 1.4:1 to 2.6:1, suggesting that the regioselectivity control of isopropanol-mediated reductive coupling would be more difficult than previously reported reactions.



Scheme 4 Base-free hydroboration of arylalkene. [a]Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), ^{i}PrOH (1.0 mL) in THF (1.0 mL) under N_2 for 18 h; yields of isolated products. [b]Regioisomeric ratios are shown in parentheses.

We also tried to investigate asymmetric control of the reaction. Owing to the fact that the reaction is pretty sensitive to electronic and steric factors of carbene ligands, it is quite challenging for us to select chiral carbene ligands. Various chiral backbones were first tested, but these saturated carbenes provided low yields and low ees (see Table S8). In addition, chiral side chains derived from chiral acids and amines were installed on the aryl ring of the carbene, but they almost inhibited the reaction. Inspired by recent elegant work on chiral carbenes,[16] we turned to survey a series of chiral full carbon side chains. As shown in Scheme 5, both AnIPr-1 and AnIPr-2 significantly improved the enantioselectivity at 80 °C, and further increasing steric hindrance of the aryl ring led to 87% ee (AnIPr-3). Finally, lowering the temperature to 60 °C gave the optimal ee (91%). However, combining the feature of AnIPr-2 and AnIPr-3 led to AnIPr-4, only providing a slight decrease of ee. Notably, although less amounts of ligand could benefit the yield, the ee of the product would slightly decrease. And thus, equal ratio of nickel and ligand was used for all asymmetric experiments. The absolute configuration of **3i** was assigned to be *S* by single-crystal X-ray analysis.



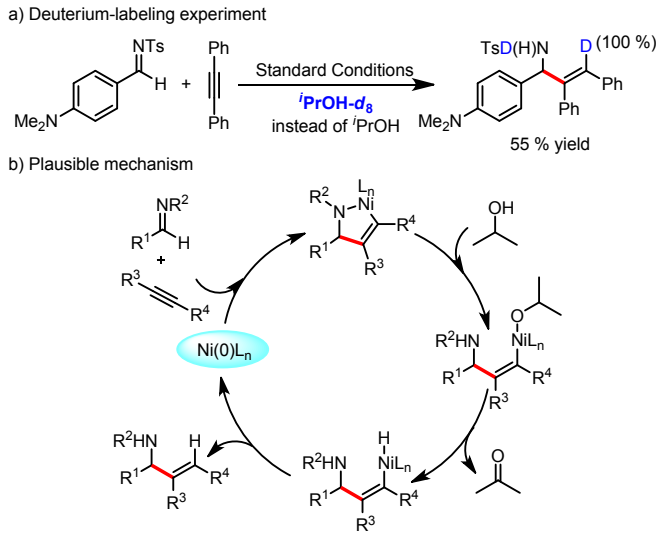
Scheme 5 [a]Reaction conditions: imine (0.12 mmol), alkyne (0.1 mmol), ^{i}PrOH (1.5 mL) in THF (1.5 mL) under N_2 for 18 h; ee was determined by chiral HPLC. ^{1}H NMR yield for ligand screening (top part) and isolated yield for substrate scope using AnIPr-3 as the ligand at 60 °C (bottom part). Ar_1 = *p*-Me-phenyl; Ar_2 = *p*-Et-phenyl; Ar_3 = *p*-MeO-phenyl.

Based on the optimized conditions, we examined the substrate scope. Amino group on the aryl ring of imines was found to be critical for the enantioselective control. No amino group led to either low yield or low ee (see Table S10). We reasoned that the mutual repulsion of amino group with the side chain of the ligand could be critical to the enantioselective recognition. Diethylamino group gave the better result (**5a**, 60% yield, 95% ee) than dimethylamino (**3i**) and morpholino group (**5b**). However, different from AnIPr, sterically bulky AnIPr-3 resulted into a narrow range of alkynes. In comparison with *p*-Me- (**5c**) and *p*-Et- (**5d**) substituted diaryl alkynes that still gave good yield and ee, electron-rich (**5e**) and electron-deficient diaryl alkynes led to lower ee and yield. Although the

View Article Online
DOI: 10.1039/C9GC00657B

preliminary result is still not quite satisfactory, it provides helpful insights for the future chiral ligand design in nickel-catalyzed reductive coupling reactions.

To clarify the hydride source, a deuterium-labeling experiment was conducted. When d_8-isopropanol was used as the reductant in the reaction, completely D-transfer into the product was observed, suggesting that the hydride was completely from isopropanol (Scheme 6a). Based on the reported information that the cyclometallation of nickel, alkyne and aldehyde or imine could be easily formed, a plausible mechanism was proposed in Scheme 6b. The nickelacycle that was formed *via* cyclometallation was protonated by isopropanol to generate a ring-opening intermediate, which proceeded sequential β-H elimination and reductive elimination to provide the desired product.



Scheme 6 Proposed mechanism.

Conclusions

In summary, we have developed a nickel-catalyzed reductive coupling of alkynes and imines using inexpensive and readily available isopropanol as the reducing agent for the first time. The method affords an economical and environment-friendly pathway for the synthesis of multi-substituted allylic amines. The discovery that uses bulky and electron-rich *N*-heterocycle carbene (AnIPr·HCl) to promote the reaction provides a helpful insight into the future development of relevant reactions in our lab.

Acknowledgment

We thank the National Natural Science Foundation of China (21672107 and 21871145) for financial support.

Notes and references

1 For related reviews on Ni-catalyzed reductive couplings, see: (a) H. A. Reichard, M. McLaughlin, M. Z. Chen and G. C. Micalizio, *Eur. J. Org. Chem.,* 2010, 391; (b) J. Montgomery and G. J. Sormunen, *Top. Curr. Chem.,* 2007, **279**, 1; (c) R. M. Moslin, K. Miller-Moslin, T. F. Jamison, *Chem. Commun.*, 2007, 4441; (d) J. Montgomery, *Angew. Chem. Int. Ed.,* 2004, **43**, 3890; (e) M. Jeganmohan and C.-H. Cheng, *Chem. Eur. J.,* 2008, **14**, 10876; (f) E. P. Jackson, H. A. Malik, G. J. Sormunen, R. D. Baxter, P. Liu, H. Wang, A.-R. Shareef and J. Montgomery, *Acc. Chem. Res.,* 2015, **48**, 1736. (g) E. A. Standley, S. Z. Tasker, K. L. Jensen and T. F. Jamison, *Acc. Chem. Res.,* 2015, **48**, 1503.

2 For selected reviews on allylic compound applications, see: (a) E. M. Skoda, G. C. Davis and P. Wipf, *Org. Process Res. Dev.,* 2012, **16**, 26; (b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.,* 2008, **108**, 2796; (c) E. Skucas, M. -Y. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.,* 2007, **40**, 1394; (d) R. C. Schnur and M. L. Corman, *J. Org. Chem.,* 1994, **59**, 2581.

3 For selected examples on nickel catalysis, see: (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature,* 2014, **509**, 299; (b) X. Wang, Y. Dai and H. Gong, *Top. Curr. Chem.,* 2016, **374**, 1; (c) V. P. Ananikov, *ACS Catal.,* 2015, **5**, 1964; (d) J. A. Garduno, A. Arevalo and J. J. Garcia, *Dalton Trans.,* 2015, **44**, 13419.

4 For reviews on metallic reducing agents, see: E. Richmond and J. Moran, *Synthesis,* 2018, **50**, 499.

5 (a) W.-S. Huang, J. Chan and T. F. Jamison, *Org. Lett.,* 2000, **2**, 4221; (b) T. Luanphaisarnnont, C. O. Ndubaku and T. F. Jamison, *Org. Lett.,* 2005, **7**, 2937; (c) K. M. Miller, W.-S. Huang and T. F. Jamison, *J. Am. Chem. Soc.,* 2003, **125**, 3442.

6 (a) G. M. Mahandru, G. Liu and J. Montgomery, *J. Am. Chem. Soc.,* 2004, **126**, 3698; (b) K. Sa-ei and J. Montgomery, *Org. Lett.,* 2006, **8**, 4441; (c) M. R. Chaulagain, G. J. Sormunen and J. Montgomery, *J. Am. Chem. Soc.,* 2007, **129**, 9568; (d) H. A. Malik, G. J. Sormunen and J. Montgomery, *J. Am. Chem. Soc.,* 2010, **132**, 6304; (e) H. Wang, G. Lu, G. J. Sormunen, H. A. Malik, P. Liu and J. Montgomery, *J. Am. Chem. Soc.,* 2017, **139**, 9317.

7 For Et_2Zn-mediated intramolecular cyclization, see: (a) E. Oblinger and J. Montgomery, *J. Am. Chem. Soc.,* 1997, **119**, 9065; (b) X.-Q. Tang and J. Montgomery, *J. Am. Chem. Soc.,* 1999, **121**, 6098; (c) X.-Q. Tang and J. Montgomery, *J. Am. Chem. Soc.,* 2000, **122**, 6950; (d) B. Knapp-Reed, G. M. Mahandru and J. Montgomery, *J. Am. Chem. Soc.,* 2005, **127**, 13156; (e) J. Montgomery, *Acc. Chem. Res*., 2000, **33**, 467.

8 C.-Y. Zhou, S.-F. Zhu, L.-X. Wang and Q.-L. Zhou, *J. Am. Chem. Soc.,* 2010, **132**, 10955.

9 For the use of stoichiometric Cr reagent in the coupling of alkyne and aldehyde, see: K. Takai, S. Sakamoto and T. Isshiki, *Org. Lett.,* 2003, **5**, 653.

10 For selected reviews on precious metal-catalyzed reductive coupling mediated by H_2 or H donors, see: (a) M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.,* 2018, **118**, 6026; (b) K. D. Nguyen, B. Y. Park, T. Luong, H. Sato, V. J. Garza and M. J. Krische, *Science,* 2016, **354**, aah5133; (c) J. Moran and M. J. Krische, *Pure Appl. Chem.,* 2009, **84**, 1729; (d) J. F. Bower, I. S. Kim, R. L. Patman and M. J. Krische, *Angew. Chem. Int. Ed.,* 2009, **48**, 34. For selected examples on Rh and Ir-catalyzed reductive coupling mediated by H_2 or H donors, see: (e) E. Skucas, J. R. Kong and M. J. Krische, *J. Am. Chem. Soc.,* 2007, **129**, 7242; (f) A. Barchuk, M.-Y. Ngai and M. J. Krische, *J. Am. Chem. Soc.,* 2007, **129**, 8432; (g) M.-Y. Ngai, A. Barchuk and M. J. Krische, *J. Am. Chem. Soc.,* 2007, **129**, 12644; (h) H.-Y. Jang, R. R. Huddleston and M. J. Krische, *J. Am. Chem. Soc.,* 2014, **126**, 4664; (i) M. J. Krische, *J. Am. Chem. Soc.,* 2005, **127**, 11269; (j) J.-R. Kong,; M.-Y. Ngai and M. J. Krische, *J. Am. Chem. Soc.,* 2006, **128**, 718; (k) V. Komanduri and M. J. Krische, *J. Am. Chem. Soc.,* 2006, **128**, 16448.

11 For our recent work on Lewis acid-catalyzed H transfer in the reaction of alkenes with aldehydes mediated by isopropanol,

View Article Online
DOI: 10.1039/C9GC00653B

see: (a) Y.-L. Zheng, Y.-Y. Liu, Y.-M. Wu, Y.-X. Wang, Y.-T. Lin and M. Ye, *Angew. Chem., Int. Ed.,* 2016, **55**, 6315; (b) Y.-L. Zheng, Y.-Y. Liu, X.-T. Xu, K. Zhang, M. Ye, *Asian J. Org. Chem.* 2018, **7**, 554; (c) Y.-L. Zheng, Y.-X. Luan, M. Ye, *Synlett*, 2016, **27**, 2401.

12 C. C. Bausch, R. L. Patman, B. Breit and M. J. Krische, *Angew. Chem. Int. Ed.,* 2011, **50**, 5687.

13 (a) K. Nakai, Y. Yoshida, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc,.* 2014, **136**, 7797. For its asymmetric version, see: (b) Y. Cai, J.-W. Zhang, F. Li, J.-M. Liu and S.-L. Shi, *ACS Catal.,* 2019, **9**, 1−6.

14 (a) M. Ohashi, Y. Hoshimoto and S. Ogoshi, *Dalton Trans.,* 2015, **44**, 12060; (b) S. Ogoshi, H. Ikeda and H. Kurosawa, *Angew. Chem. Int. Ed.,* 2007, **46**, 4930; (c) S. Ogoshi, H. Ikeda and H. Kurosawa, *Pure Appl. Chem.,* 2008, **80**, 1115; (d) Y. Hoshimoto, T. Ohata, M. Ohashi and S. Ogoshi, *Chem. Eur. J.,* 2014, **20**, 4105.

15 (a) D. Wang and D. Astruc, *Chem. Rev.,* 2015, **115**, 6621; (b) Y.-Y. Li, S.-L. Yu, W.-Y. Shen and J.-X. Gao, *Acc. Chem. Res.,* 2015, **48**, 2587; (c) R. H. Morris, *Acc. Chem. Res.,* 2015, **48**, 1494; (d) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.,* 1995, **117**, 7562; (e) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed.,* 1997, **36**, 285.

16 (a) Y. Cai, X.-T. Yang, S.-Q. Zhang, F. Li, Y.-Q. Li, L.-X. Ruan, X. Hong and S.-L. Shi, *Angew. Chem. Int. Ed.,* 2018, **57**, 1376; (b) J. Diesel, A. M. Finogenova and N. Cramer, *J. Am. Chem. Soc.,* 2018, **140**, 4489; (c) A. Albright and R. E. Gawley, *J. Am. Chem. Soc.,* 2011, **133**, 19680.