ChemComm

COMMUNICATION

View Article Online
View Journal

Published on 19 June 2020. Downloaded by Dalian Institute of Chemical Physics, CAS on 6/28/2020 1:09:48 AM.

Check for updates

Cite this: DOI: 10.1039/d0cc04002a

Received 8th June 2020,
Accepted 18th June 2020

DOI: 10.1039/d0cc04002a

rsc.li/chemcomm

Rhodium-catalyzed regio- and enantioselective allylic alkylation of pyrazol-5-ones with alkynes†

Ding-Wei Ji,[ab] Fan Yang,[a] Bing-Zhi Chen,[ab] Xiang-Ting Min,[ab] Chang-Sheng Kuai,[a] Yan-Cheng Hu[a] and Qing-An Chen*[a]

A rhodium-catalyzed asymmetric allylic alkylation of pyrazol-5-ones with internal alkynes is illustrated. In the presence of a chiral rhodium-hydride catalyst, functionalized heterocyclic products bearing an all-carbon quaternary stereogenic center were obtained in high yields with satisfactory enantioselectivities. This protocol also features good regiocontrol and a high atom economy without stoichiometric by-product formation.

Pyrazol-5-ones and related heterocycles are prevalent structural units in natural products and synthetic pharmaceutical molecules.[1] In particular, optically pure pyrazol-5-ones bearing all-carbon quaternary stereocenters exhibit remarkable biological activities in drug discovery (Fig. 1).[2] For instance, capromorelin tartrate is an orally active and potent growth hormone secretagogue (GHS).[2a,b] Spiropyrazolones I and II show good anti-tumor and anti-inflammatory properties, respectively.[2c,d] Therefore, numerous efforts have been devoted to the synthesis of these compounds.[3]

Owing to the versatility of the allyl group, transition-metal-catalyzed asymmetric allylic alkylations (AAAs) have been established as a powerful and reliable tool in organic transformations.[4,5] However, due to the existence of tautomeric forms,[6] the regio- and enantioselective allylation of pyrazol-5-ones is by no means an easy process (Scheme 1).[7] In 2013, Gong's group developed the first highly efficient asymmetric allylic alkylation of pyrazol-5-ones with allylic alcohols *via* cooperative catalysis (chiral Pd and chiral phosphoric acid)[7a] (Scheme 1a). Later, this cooperative strategy was extended by the same group to enantioselective allylic C–H alkylation of pyrazol-5-ones with allylarenes in the presence of an oxidant (Scheme 1b).[7b,e] In 2017, the Jiang group also reported a significant Pd-catalyzed asymmetric allylation of pyrazol-5-ones with alkoxyallenes in branched selectivities (Scheme 1c).[7c] Despite these important advances, the development of an effective and economic pathway to access chiral allylic pyrazol-5-ones with non-activated precursors under redox-neutral conditions is still highly appealing.

Since alkynes are easily accessible and bench-stable synthons in organic synthesis, the employment of alkynes as greener allyl precusors is becoming an attractive alternative for the buildup of molecular complexity.[8] In this context, elegant studies that employ terminal or internal alkynes in AAAs have been contributed by the Yamamoto, Breit, Krische and Dong groups.[9–11] However, the direct utilization of alkynes to construct all-carbon quaternary stereocenters is lacking. In 2017, Dong and co-workers reported the only example to generate vicinal quaternary and tertiary carbon stereocenters *via* an enantioselective coupling between α-branched aldehydes and alkynes.[9g] Besides, all the reported studies on rhodium-catalyzed AAAs with alkynes gave branched allylic products, and how to switch the regioselectivity is a challenging problem. Considering this synthetic importance together with our continuous investigation on metal-hydride catalysis,[12] we report herein a regio- and enantioselective allylation of pyrazol-5-ones with alkynes under atom-economical Rh-catalysis.

Initially, we began our investigations with coupling of pyrazol-5-one **1a** and commercially available 1-phenyl-1-propyne **2a**. As highlighted in Table 1, after examining a range of achiral bisphosphine ligands, we found that the bite angle of the ligands exhibited a significant influence on the efficiency of this allylic

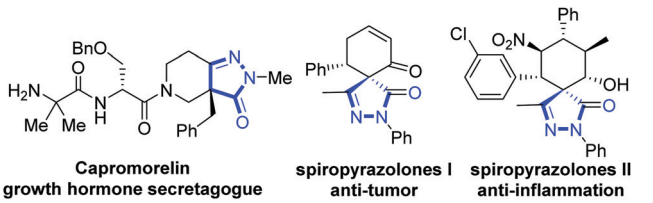


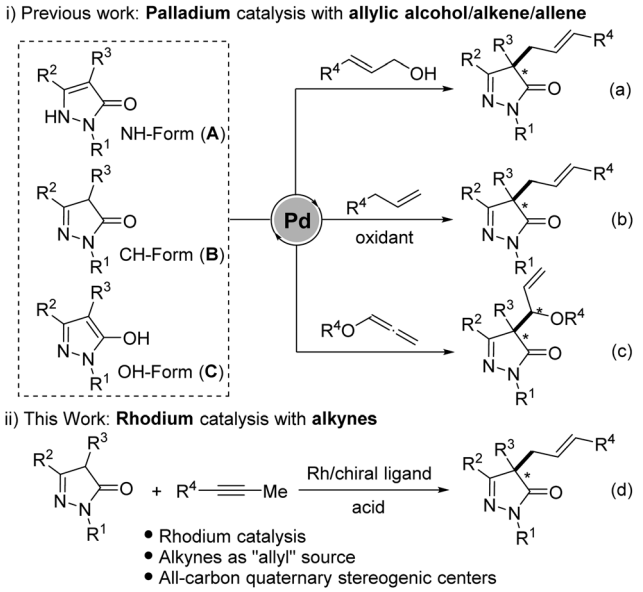
Fig. 1 Bioactive molecules containing pyrazol-5-one skeletons.

[a] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: qachen@dicp.ac.cn; Web: http://www.lbcs.dicp.ac.cn

[b] University of Chinese Academy of Sciences, Beijing 100049, P. R. China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0cc04002a

Published on 19 June 2020. Downloaded by Dalian Institute of Chemical Physics, CAS on 6/28/2020 1:09:48 AM.

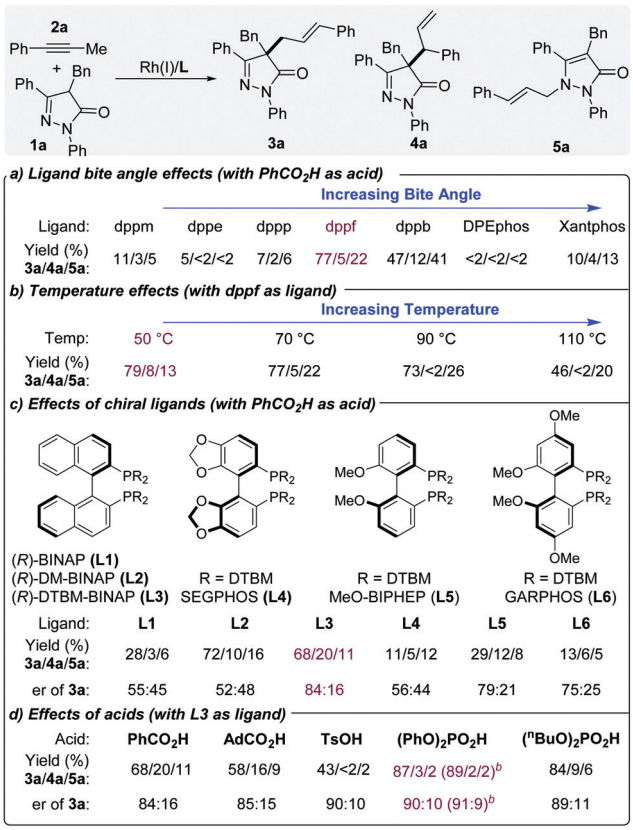


Scheme 1 Transition-metal-catalyzed AAAs of pyrazol-5-ones.

alkylation (Table 1a). The ligands with a moderate bite angle such as dppf and dppb showed good reactivities but produced a mixture of **3a**, **4a**, and **5a**. Although a higher temperature diminished the regioselectivity, an enhanced result was achieved when the reaction was conducted at 50 °C (Table 1b). Based on these preliminary results, we turned our attention to enantioselective control. The linear **3a** was obtained as a major product in 28% yield and 55 : 45 er with (*R*)-BINAP (**L1**) as the ligand and $PhCO_2H$ as the acid co-catalyst (Table 1c). Delightfully, the bulky ligand bearing the DTBM-phosphine substituent (**L3**) showed better performance in both reactivity and enantioselectivity and the reaction delivered **3a** in 68% yield and 84 : 16 er. The other axial ligands such as SEGPHOS (**L4**), MeO-BIPHEP (**L5**), and GARPHOS (**L6**) provided lower reactivities and selectivities. The good performance of the ligand **L3** was probably ascribed to its bulky substituents and comparably large dihedral angle. Futher evaluation of acids indicated that $(PhO)PO_2H$ was the best acid additive in terms of regio- and enantioselectivity as well as reactivity (Table 1d). Eventually, decreasing the temperature to 35 °C led to the product **3a** in 89% yield with >19 : 1 rr and 91 : 9 er. The disfavoring of branched selectivity might be attributed to steric hindrance.

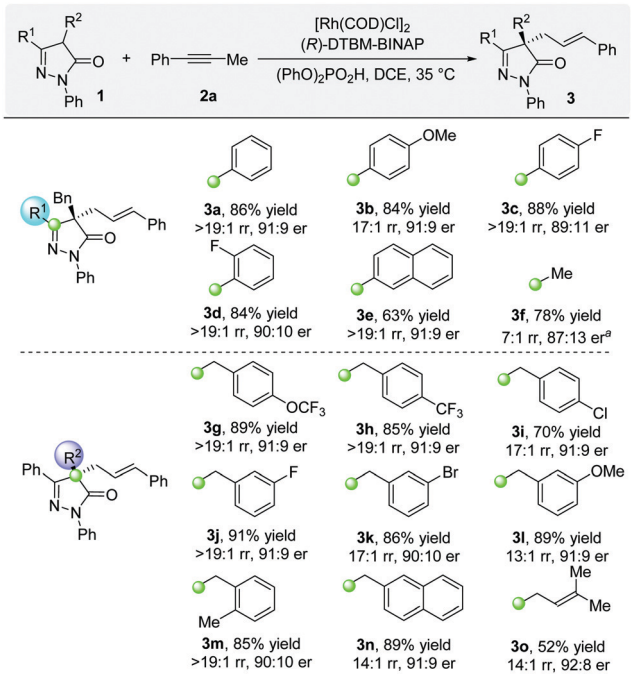
With the optimized reaction conditions in hand, we next investigated the scope of pyrazol-5-ones (Table 2). Generally, various pyrazol-5-ones were allowed to react with alkyne **2a** and gave the corresponding products in satisfactory yields and selectivities. Pyrazol-5-ones bearing different aryl substituents at the C5 position (R^1) all proceeded smoothly under the current reaction conditions, leading to the products **3a** to **3e**

Table 1 Optimization of the reaction conditions[a]



[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), ligand (5.0 mol%), acid (20 mol%), DCE (0.25 M), 50 °C, 18 h. In all cases, the yield was determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard, and er was determined by chiral HPLC. [b] 35 °C, 3 d.

Table 2 Scope of pyrazol-5-one substrates



Reaction conditions: **1** (0.10 mmol), **2a** (0.20 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2PO_2H$ (20 mol%), DCE (0.25 M), 35 °C, 3 d. In all cases, the isolated yields were given; the rr was determined by ^1H NMR analysis of the crude reaction mixture, and er was determined by chiral HPLC. [a] The absolute configuration was assigned by comparing the optical rotation in the literature (ref. 7*a*).

This journal is © The Royal Society of Chemistry 2020

Published on 19 June 2020. Downloaded by Dalian Institute of Chemical Physics, CAS on 6/28/2020 1:09:48 AM.

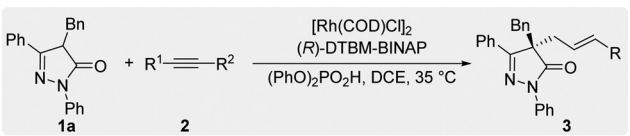
in moderate to good yields (63–88%) with good selectivities. The substrate having a methyl group at the C5 position of the pyrazolones was also compatible and delivered the product **3f** in 78% yield with 7 : 1 rr and 87 : 13 er. Substituents at the quaternary carbon position were then examined. The electronic nature of the substituents (electron-donating or electron-withdrawing groups) on the benzyl ring exerted no significant impact on the yields and selectivities (**3g–3n**). Various groups such as 4-OCF_3, 4-CF_3, 4-Cl and 3-F could be well tolerated and the corresponding products **3g–3j** were obtained in 70–91% yields with 91 : 9 er. Notably, the bromo group, which is easily eliminated under palladium catalysis, remained intact under the current reaction conditions, and the product **3k** was produced in 86% yield with 17 : 1 rr and 90 : 10 er. The substrates bearing a sterically hindered group (**3m**) or a naphthyl group (**3n**) also reacted well with **2a** and generated the products in good yields and selectivities. To our delight, prenyl-substituted pyrazol-5-one was also applicable under the current conditions and led to the product **3o** in 52% yield with 14 : 1 rr and 92 : 8 er.

Next, the generality of alkynes was tested (Table 3). The substrates possessing electron-withdrawing groups at the 4-position of the phenyl ring all reacted with **1a** smoothly and provided the allylic products in 53–79% yield with >19 : 1 rr and 91 : 9 to 92 : 8 er (entries 1–4). In comparison, the alkynes with electron-donating groups at the para position of phenyl were a bit sluggish in the current protocol (entries 5 and 6). However, good yield and regioselectivity could be observed when the methyl group was located at the meta-position of the phenyl ring (entry 7). Due to the steric hindrance, a decrease in the yield and enantioselectivity was observed when *o*-methylphenyl substituted alkyne was used (entry 8). On replacing the phenyl group with a naphthyl group, the target allylic product was furnished in 92% yield with >19 : 1 rr and 89 : 11 er (entry 9). 2-Thienyl derived alkyne was also suitable for this reaction and led to **3y** in 25% yield (entry 10). Unfortunately, subjecting 2-butyne to coupling with **2a** under the standard conditions only gave the product **3z** in 15% yield with low regio- and enantioselectivity (entry 11). Finally, 16% yield of **3a** was obtained with the terminal alkyne as a substrate and the selectivities were well maintained (entry 12).

To probe the possibility of the allene intermediate, the pre-synthesized phenylallene **6** was subjected to coupling with pyrazol-5-one **2a** under the standard conditions, and the product **3a** was indeed observed with a comparable er, albeit in a low yield (Scheme 2a). This result also suggests that alkynes could serve as good allene surrogates in some catalytic reactions.[9d] Then an isotopic-labeling study was performed. When the deuterated alkyne **2a**-d_3 was employed as a substrate, the deuterium atom was found to incorporate into the α-, β-, and γ-positions of the allyl unit (Scheme 2b). This observation indicates that a reversible hydrometallation might be involved during the allene formation. Additional control experiments showed that the products **3a** and **5a** remained intact under the standard reaction conditions, while 14% of **4a** was found to be transformed into **5a** (Scheme 2c). The isomerization reaction from **4a** to **5a** presumably resulted from an aza-cope rearrangement process.[9i] This result also indicates that the selectivity of the product **3a** does not derive from the isomerization of **4a** or **5a**.

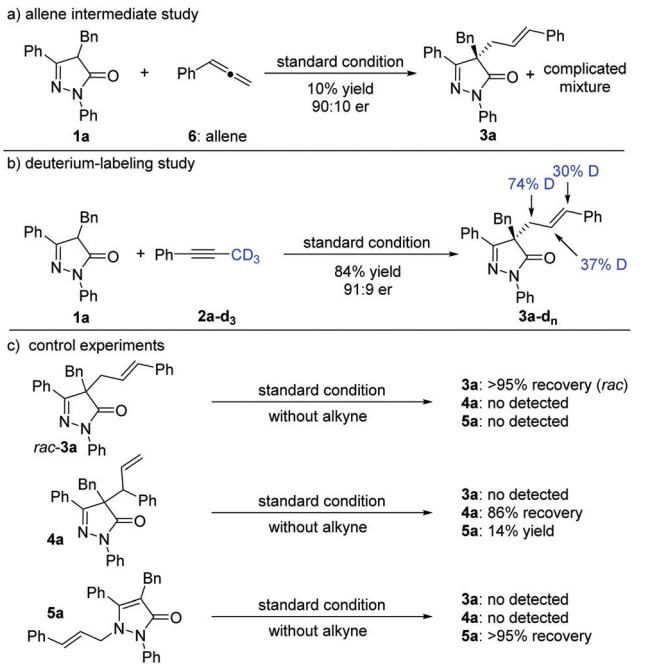
On the basis of the literature[7a–c,9] and our observations, we proposed a pathway *via* tandem Rh-catalysis (Fig. 2). First, the oxidative addition of the Brønsted acid with a Rh(I) precursor generates Rh(III)-hydride species **A**. Then the *syn*-migratory insertion of alkyne **2a** into Rh(III)–H **A** affords the vinyl-Rh intermediate **B**. The following β-hydride elimination from **B** gives the allene **6** intermediate and regenerates the Rh(III)–H

Table 3 Scope of alkyne substrates



Entry	R^1	R^2	Yield of **3** (%)	rr	er
1	4-FC_6H_4	Me	**3p**, 74	>19 : 1	91 : 9
2	4-ClC_6H_4	Me	**3q**, 79	>19 : 1	91 : 9
3	4-BrC_6H_4	Me	**3r**, 77	>19 : 1	92 : 8
4	4-$CF_3C_6H_4$	Me	**3s**, 53	>19 : 1	92 : 8
5	4-MeC_6H_4	Me	**3t**, 43	>19 : 1	89 : 11
6	4-$MeOC_6H_4$	Me	**3u**, 39	>19 : 1	88 : 12
7	3,5-$Me_2C_6H_3$	Me	**3v**, 87	>19 : 1	89 : 11
8	2-MeC_6H_4	Me	**3w**, 30	>19 : 1	87 : 13
9	2-Naphthyl	Me	**3x**, 92	>19 : 1	89 : 11
10	2-Thienyl	Me	**3y**, 25	15 : 1	90 : 10
11	Me	Me	**3z**, 15	2 : 1	54 : 46
12	Benzyl	H	**3a**, 16	>19 : 1	91 : 9

Reaction conditions: **1a** (0.10 mmol), **2** (0.20 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2PO_2H$ (20 mol%), DCE (0.25 M), 35 °C, 3 d. In all cases, the isolated yields were given; the rr was determined by ^1H NMR analysis of the crude reaction mixture, and er was determined by chiral HPLC.



Scheme 2 Mechanistic studies.

Published on 19 June 2020. Downloaded by Dalian Institute of Chemical Physics, CAS on 6/28/2020 1:09:48 AM.

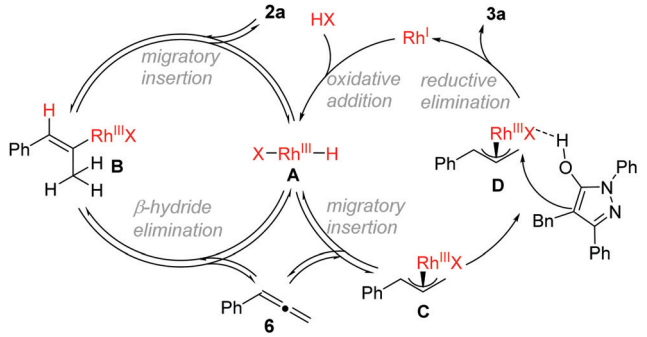


Fig. 2 Proposed mechanism.

species **A**. Next, the reinsertion of the terminal allene **6** into Rh(III)–H yields the chiral π-allyl rhodium complex **C**, which shows hydrogen-bonding interaction with the enol form of pyrazolone **1a**. Then the enol motif undergoes nucleophilic attack at the carbon center to deliver the allylic product **3a** and generate Rh(I) species.

In summary, we have described a rhodium-catalyzed enantioselective allylic alkylation of pyrazol-5-ones with internal alkynes. With the assistance of rhodium-hydride catalysis, functionalized heterocyclic products bearing an all-carbon-substituted quaternary stereogenic center were formed in high yields with good regio- and enantiocontrol. This method provides an atom-economical paradigm for exploiting asymmetric allylic alkylations of other heterocyclic ketones.

Financial support from the Dalian Institute of Chemical Physics (DICPI201902), the National Natural Science Foundation of China (21702204), and the Liaoning Revitalization Talents Program (XLYC1807181) is acknowledged.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 G. Varvounis, *Pyrazol-3-ones. Part IV: Synthesis and Applications*, Academic Press, New York, 2009.
2 (*a*) P. A. Carpino, B. A. Lefker, S. M. Toler, L. C. Pan and J. R. Hadcock, *et al.*, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3279; (*b*) P. A. Carpino, B. A. Lefker, S. M. Toler, L. C. Pan and J. R. Hadcock, *et al.*, *Bioorg. Med. Chem.*, 2003, **11**, 581; (*c*) Y. Zhang, S. Wu, S. Wang, K. Fang and G. Dong, *et al.*, *Eur. J. Org. Chem.*, 2015, 2030; (*d*) S. Wu, Y. Li, G. Xu, S. Chen and Y. Zhang, *et al.*, *Eur. J. Med. Chem.*, 2016, **115**, 141.
3 (*a*) X. Bao, S. Wei, X. Qian, J. Qu, B. Wang, L. Zou and G. Ge, *Org. Lett.*, 2018, **20**, 3394; (*b*) J. Zhou, W. J. Huang and G. F. Jiang, *Org. Lett.*, 2018, **20**, 1158; (*c*) H. Li, R. Gontla, J. Flegel, C. Merten, S. Ziegler, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2019, **58**, 307; (*d*) X.-L. Liu, X. Zuo, J.-X. Wang, S.-Q. Chang, Q.-D. Wei and Y. Zhou, *Org. Chem. Front.*, 2019, **6**, 1485; (*e*) X. Xu, Y. He, J. Zhou, X. Li, B. Zhu and J. Chang, *J. Org. Chem.*, 2020, **85**, 574.
4 For a book, see: U. Kazmaier, *Transition Metal Catalyzed Enantioselective Allylic Substitution*, Springer, Heidelberg, 2012.
5 For selected reviews, see: (*a*) B. M. Trost and D. L. VanVranken, *Chem. Rev.*, 1996, **96**, 395; (*b*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (*c*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (*d*) N. A. Butt and W. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 7929; (*e*) Q. Cheng, H. F. Tu, C. Zheng, J. P. Qu, G. Helmchen and S. L. You, *Chem. Rev.*, 2019, **119**, 1855.
6 Z. P. Chen, M. W. Chen, L. Shi, C. B. Yu and Y. G. Zhou, *Chem. Sci.*, 2015, **6**, 3415.
7 For examples, see: (*a*) Z. L. Tao, W. Q. Zhang, D. F. Chen, A. Adele and L. Z. Gong, *J. Am. Chem. Soc.*, 2013, **135**, 9255; (*b*) H. C. Lin, P. S. Wang, Z. L. Tao, Y. G. Chen, Z. Y. Han and L. Z. Gong, *J. Am. Chem. Soc.*, 2016, **138**, 14354; (*c*) H. Zhou, Z. Wei, J. Zhang, H. Yang, C. Xia and G. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 1077; (*d*) K. Yang, X. Bao, S. Liu, J. Xu, J. Qu and B. Wang, *Eur. J. Org. Chem.*, 2018, 6469; (*e*) L.-F. Fan, P.-S. Wang and L.-Z. Gong, *Org. Lett.*, 2019, **21**, 6720; (*f*) G. Wu, H. Xu, Z. Liu, Y. Liu, X. Yang, X. Zhang and Y. Huang, *Org. Lett.*, 2019, **21**, 7708.
8 For reviews, see: (*a*) P. Koschker and B. Breit, *Acc. Chem. Res.*, 2016, **49**, 1524; (*b*) A. M. Haydl, B. Breit, T. Liang and M. J. Krische, *Angew. Chem., Int. Ed.*, 2017, **56**, 11312; (*c*) M. B. Thoke and Q. Kang, *Synthesis*, 2019, 2585.
9 For selected examples under Rh-catalysis, see: (*a*) A. Lumbroso, P. Koschker, N. R. Vautravers and B. Breit, *J. Am. Chem. Soc.*, 2011, **133**, 2386; (*b*) U. Gellrich, A. Meissner, A. Steffani, M. Kahny, H. J. Drexler, D. Heller, D. A. Plattner and B. Breit, *J. Am. Chem. Soc.*, 2014, **136**, 1097; (*c*) K. Xu, V. Khakyzadeh, T. Bury and B. Breit, *J. Am. Chem. Soc.*, 2014, **136**, 16124; (*d*) Q.-A. Chen, Z. Chen and V. M. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 8392; (*e*) P. Koschker, M. Kahny and B. Breit, *J. Am. Chem. Soc.*, 2015, **137**, 3131; (*f*) Z. Liu and B. Breit, *Angew. Chem., Int. Ed.*, 2016, **55**, 8440; (*g*) F. A. Cruz and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1029; (*h*) F. A. Cruz, Y. Zhu, Q. D. Tercenio, Z. Shen and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 10641; (*i*) J. Kuang, S. Parveen and B. Breit, *Angew. Chem., Int. Ed.*, 2017, **56**, 8422; (*j*) W.-F. Zheng, Q.-J. Xu and Q. Kang, *Organometallics*, 2017, **36**, 2323; (*k*) J. Zheng and B. Breit, *Angew. Chem., Int. Ed.*, 2019, **58**, 3392; (*l*) L. Xie, H. Yang, M. Ma and D. Xing, *Org. Lett.*, 2020, **22**, 2007.
10 For selected examples under Pd-catalysis, see: (*a*) B. M. Trost, W. Brieden and K. H. Baringhaus, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1335; (*b*) I. Kadota, A. Shibuya, Y. S. Gyoung and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 10262; (*c*) I. Kadota, A. Shibuya, L. M. Lutete and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 4570; (*d*) L. M. Lutete, I. Kadota and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 1622; (*e*) S. Gao, Z. Wu, X. Fang, A. Lin and H. Yao, *Org. Lett.*, 2016, **18**, 3906; (*f*) C. J. Lu, H. Chen, D. K. Chen, H. Wang, Z. P. Yang, J. Gao and H. Jin, *Org. Biomol. Chem.*, 2016, **14**, 10833; (*g*) S. Gao, H. Liu, Z. Wu, H. Yao and A. Lin, *Green Chem.*, 2017, **19**, 1861; (*h*) S. Gao, H. Liu, C. Yang, Z. Fu, H. Yao and A. Lin, *Org. Lett.*, 2017, **19**, 4710; (*i*) G. Cera, M. Lanzi, D. Balestri, N. Della Ca, R. Maggi, F. Bigi, M. Malacria and G. Maestri, *Org. Lett.*, 2018, **20**, 3220; (*j*) X. Fang, Q. Li, R. Shi, H. Yao and A. Lin, *Org. Lett.*, 2018, **20**, 6084; (*k*) J. T. D. Lee and Y. Zhao, *Chem. – Eur. J.*, 2018, **24**, 9520; (*l*) Y. Minami, Y. Furuya and T. Hiyamera, *Asian J. Org. Chem.*, 2018, **7**, 1343; (*m*) Y. L. Su, L. L. Li, X. L. Zhou, Z. Y. Dai, P. S. Wang and L. Z. Gong, *Org. Lett.*, 2018, **20**, 2403; (*n*) Z. Wu, X. Fang, Y. Leng, H. Yao and A. Lin, *Adv. Synth. Catal.*, 2018, **360**, 1289; (*o*) J. Zheng and B. Breit, *Org. Lett.*, 2018, **20**, 1866.
11 For other metal catalysis, see: (*a*) Y. Obora, S. Hatanaka and Y. Ishii, *Org. Lett.*, 2009, **11**, 3510; (*b*) B. Y. Park, K. D. Nguyen, M. R. Chaulagain, V. Komanduri and M. J. Krische, *J. Am. Chem. Soc.*, 2014, **136**, 11902; (*c*) Q. A. Chen, F. A. Cruz and V. M. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 3157; (*d*) T. Liang, K. D. Nguyen, W. Zhang and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 3161; (*e*) T. Liang, W. Zhang, T. Y. Chen, K. D. Nguyen and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 13066; (*f*) T. Liang, W. Zhang and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 16024.
12 (*a*) D. W. Ji, Y. C. Hu, H. Zheng, C. Y. Zhao, Q. A. Chen and V. M. Dong, *Chem. Sci.*, 2019, **10**, 6311; (*b*) Y. C. Hu, D. W. Ji, C. Y. Zhao, H. Zheng and Q. A. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 5438; (*c*) D. W. Ji, G. C. He, W. S. Zhang, C. Y. Zhao, Y. C. Hu and Q. A. Chen, *Chem. Commun.*, 2020, DOI: 10.1039/d0cc02697b.