Rhodium(III)-Catalyzed C–H Alkenylation/Directing Group Migration for the Regio- and Stereoselective Synthesis of Tetrasubstituted Alkenes

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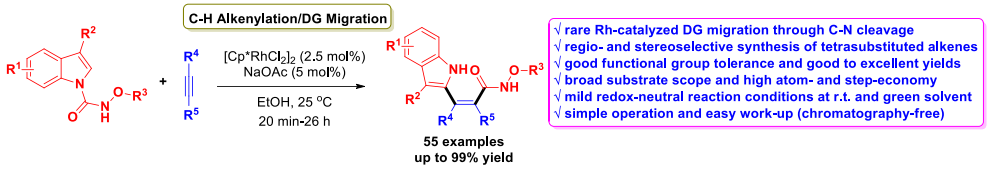
Supporting Information Placeholder

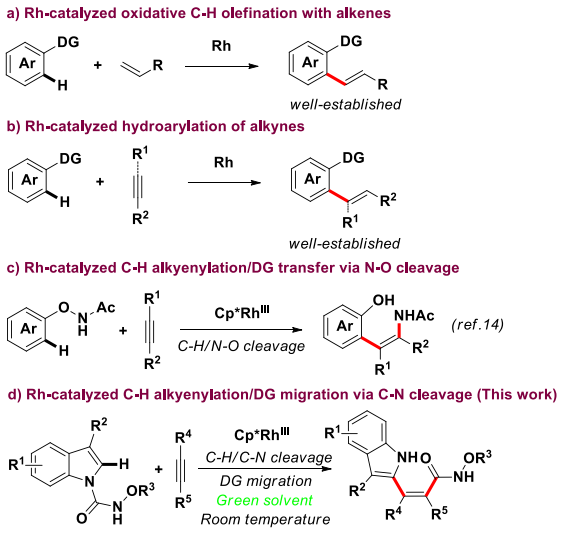


ABSTRACT: An efficient Rh(III)-catalyzed C–H alkenylation/directing group migration cascade between indoles and alkynes for the assembly of tetrasubstituted alkenes is reported. The carbamoyl directing group migrates to the carbon of the alkene moiety of the products through the rare Rh-catalyzed C–N bond cleavage after the C–H alkenylation step and thus acts as an internal amidation reagent. This protocol shows broad substrate scope, excellent regio-/stereoselectivity and good to excellent yields.

The tetrasubstituted alkene motif is considered as a privileged structure because of its large presence in pharmaceutical agents. Representative examples of active pharmaceutical ingredients possessing a tetrasubstituted alkene scaffold include Tamoxifen,[1] squalene synthetase inhibitor P-3622,[2] Diethylstilbestrol,[3] Imrecoxib[4] and Nifedipine[5] (Figure S1 in Supporting Information). Therefore, the synthesis of tetrasubstituted alkenes has captured wide attention of the scientific community. However, despite the remarkable achievements made,[6] the synthesis of tetrasubstituted alkenes remains a challenging area as it faces the challenges of achieving high regio- and stereoselectivity in such a congested structure. The three-component reaction of internal alkynes, organometallic reagents and electrophiles through a carbometalation/cross-coupling sequence constitutes a conventional and classic strategy to tetrasubstituted alkenes.[7] Nevertheless, this strategy involves the employment of stoichiometric organometallic reagents under harsh reaction conditions, which makes it not eco-friendly and cost-effective. Apparently, the development of straightforward and efficient approaches for the synthesis of tetrasubstituted alkenes is still highly demanding.

With the assistance of directing groups (DGs), transition metal-catalyzed C–H alkynylation, which constitutes an efficient method to prepare multi-substituted alkenes, has received much attention.[8-13] Particularly, direct C–H alkenylation including oxidative C–H olefination with alkenes[14,15] and hydroarylation of alkynes[16,17] *via* rhodium catalysis has contributed significantly in multi-substituted alkene synthesis. However, monosubstituted alkenes were generally employed in Rh-catalyzed oxidative C–H olefination to achieve high reactivity and stereoselectivity, thus mainly affording disubstituted alkenes (Scheme 1a). In Rh-catalyzed hydroarylation of alkynes, the alkenyl-metal species formed by C–H activation and

Scheme 1. Rh-catalyzed C–H alkynylation.

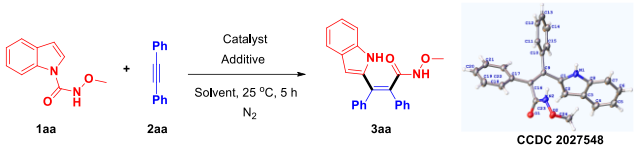


successive alkyne insertion preferentially underwent proto-demetalation to construct a C(sp^2)–H bond, thus providing di- or trisubstituted alkenes (Scheme 1b). Moreover, it should be noted that the DGs in these two types of reactions only acted as the auxiliary groups which help to enhance reactivity and site selectivity. It is quite appealing but also challenging to achieve the further utilization of the DG such as migration to the carbon of the alkene moiety of the products to form an extra C–C or C-heteroatom bond in Rh-catalyzed C–H alkyenylation, which makes the formation of tetrasubstituted alkenes possible. In this context, only one example was reported by Lu and Liu who pioneered an intriguing furnishment of tetrasubstituted enamides through Rh-catalyzed C–H alkyenylation and the following DG transfer *via* N–O bond cleavage (Scheme 1c)[18]. To the best of our knowledge, Rh-catalyzed C–H functionalization involving DG migration through the cleavage of C–N bond remains unprecedented.[19] Based on our experience in functional group migration *via* C–N bond cleavage[20] and together with our interest in rhodium catalysis,[21] we herein reported an efficient Rh(III)-catalyzed C–H alkenylation and DG migration *via* C–N bond cleavage for the synthesis of tetrasubstituted alkenes containing the privileged indole moiety (Scheme 1d). In this reaction, the carbamoyl directing group (CONHOMe)[22] not only played as the auxiliary group, but also acted as an internal amidation reagent which migrated to the alkene moiety of the products to deliver the tetrasubstituted α,β-unsaturated amides.

Initially, we optimized the reaction conditions using compounds **1aa** and **2aa** as the model substrates (Table 1). With NaOAc as the additive, different metal catalysts were screened in DCE at 25 °C for 5 h under N_2 atmosphere (entries 1-6). To our delight, $[Cp^*RhCl_2]_2$ could catalyze this C–H alkenylation/DG migration cascade highly stereoselectively, providing the *cis*-adduct **3aa** as the only stereoisomer in a high yield. Subsequently, various solvents were investigated (entries 7-16). The results showed the green solvent EtOH[23] turned out to be the best of choice (entry 14), in which the desired tetrasubstituted alkene **3aa** precipitated out as white solids and could be simply collected by filtration in a quantitative yield (>99%). Next, a variety of additives were screened in EtOH.[24] Among them, CsOAc and $Zn(OAc)_2$ were also found to be effective additives, with which high yields (92-97%) and stereoselectivities of **3aa** were observed (entries 17-18). Delightfully, when 1.1 equivalent of **2aa** or 2.5 mol% $[Cp^*RhCl_2]_2$ or 5 mol% NaOAc was used, no impacts on the yield or stereoselectivity were observed (entries 19-21). A survey of the reaction time revealed the reaction could complete in 20 minutes (entry 22). Besides, product **3aa** was still obtained in an excellent yield and *cis*-stereoselectivity under air atmosphere (entry 23). At last, blank experiments showed the reaction could not occur with single catalyst or additive (entries 24-25). Notably, no *trans*-stereoisomer was observed when optimizing the reaction conditions, suggesting the exclusive *cis*-stereoselectivity of this process.

Next, we investigated the general applicability of the C–H alkenylation/DG migration sequence. At first, the substrate scope of indoles was explored (Scheme 2). In general, a variety of indoles **1** carring diverse substituents at R^1, R^2 and R^3 could interact with **2aa** to produce tetrasubstituted alkenes **3** with high yields and excellent *cis*-stereoselectivities. For instance, the reactions of halogenated indoles with **2aa** could complete within 30 minutes in a highly *cis*-selective manner to

Table 1. Optimization of the reaction conditions[a]

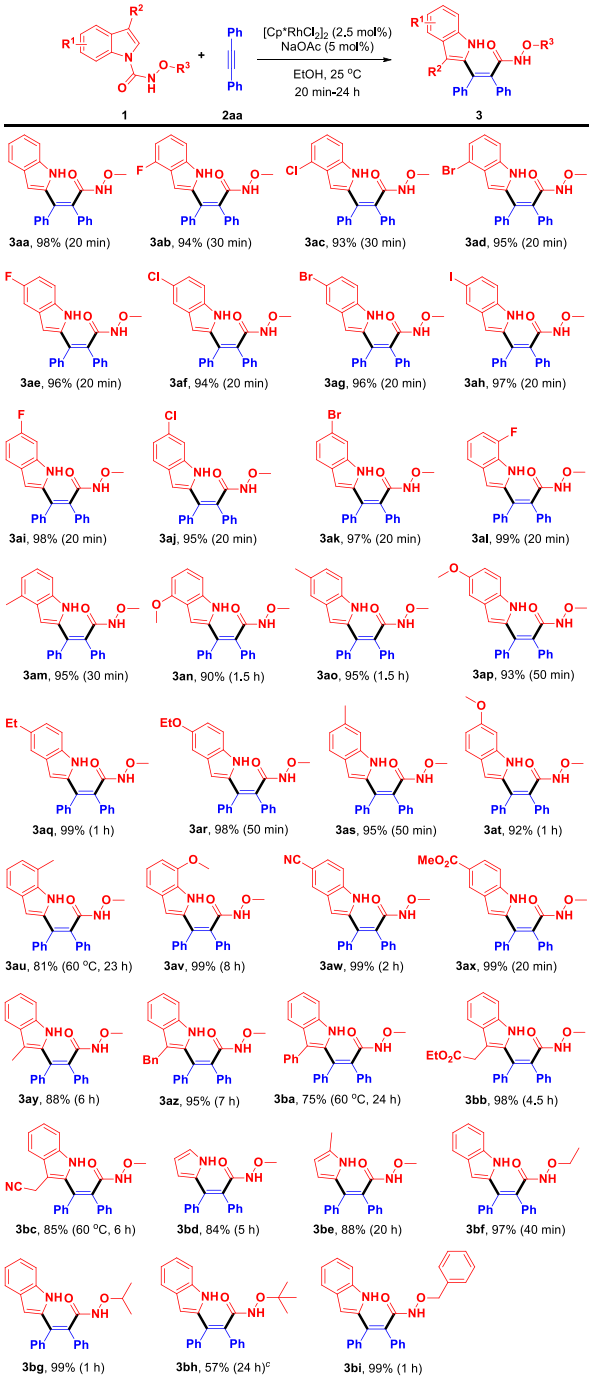


Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$MnBr(CO)_5$	NaOAc	DCE	0
2	$Pd(OAc)_2$	NaOAc	DCE	0
3	$Cu(OAc)_2$	NaOAc	DCE	0
4	$CoCp_2^*PF_6$	NaOAc	DCE	0
5	$Ni(OTf)_2$	NaOAc	DCE	0
6	$[Cp^*RhCl_2]_2$	NaOAc	DCE	92
7	$[Cp^*RhCl_2]_2$	NaOAc	Toluene	88
8	$[Cp^*RhCl_2]_2$	NaOAc	CH_2Cl_2	93
9	$[Cp^*RhCl_2]_2$	NaOAc	THF	97
10	$[Cp^*RhCl_2]_2$	NaOAc	Acetone	87
11	$[Cp^*RhCl_2]_2$	NaOAc	Dioxane	92
12	$[Cp^*RhCl_2]_2$	NaOAc	CH_3CN	93
13	$[Cp^*RhCl_2]_2$	NaOAc	MeOH	85
14	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	>99
15	$[Cp^*RhCl_2]_2$	NaOAc	DMF	66
16	$[Cp^*RhCl_2]_2$	NaOAc	DMSO	84
17	$[Cp^*RhCl_2]_2$	CsOAc	EtOH	92
18	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	EtOH	97
19[c]	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	>99
20[c,d]	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	99
21[c,d,e]	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	99
22[c,d,e,f]	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	98
23[c,d,e,f,g]	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	98
24[c,d]	$[Cp^*RhCl_2]_2$	-	EtOH	0
25[c,e]	-	NaOAc	EtOH	0

[a]Reaction conditions: **1aa** (0.25 mmol, 1.0 equiv.), **2aa** (0.325 mmol, 1.3 equiv.), catalyst (5 mol%), additive (0.25 mmol, 1.0 equiv.), solvent (4.0 mL), 25 °C, 5 h, N_2. [b]Isolated yield. [c]**2aa** (0.275 mmol, 1.1 equiv.) was used. [d]2.5 mol% $[Cp^*RhCl_2]_2$ was used. [e]5 mol% NaOAc was used. [f]The reaction was run for 20 min. [g]The reaction was performed under air.

yield the corresponding products **3ab-3al** in excellent yields (93-99%). Similarly, electron-rich indoles underwent this transforantion smoothly to give the *cis*-adducts **3am-3av** exclusively in 81-99% yields. Likewise, electron-deficient indoles smoothly added to **2aa** to deliver the *cis*-adducts **3aw-3ax** in quantitative yields (99%). Gratifyingly, when Me, Bn, Ph, CH_2CO_2Et or CH_2CN was introduced at the C3 position of the indole substrates, the desired products **3ay-3bc** were also prepared in high yields (75-98%) and perfect *cis*-stereoselectivities. Moreover, this protocol was also compatible with *N*-carbamoyl pyrroles. They reacted successfully with **2aa** to furnish products **3bd-3be** in 84-88% yields without affecting the stereoselectivities. At last, the reactions of indoles with diverse alkyl substituents at R^3 (Et, *i*-Pr, *t*-Bu, Bn) also afforded products **3bf-3bi** in 57-99% yields and exclusive *cis*-stereoselectivities. The steric hindrance of the bulky directing group could lead to the lower yield of product **3bh**. It is noteworthy that the indicated products in

Scheme 2. Scope of indoles.[a,b]

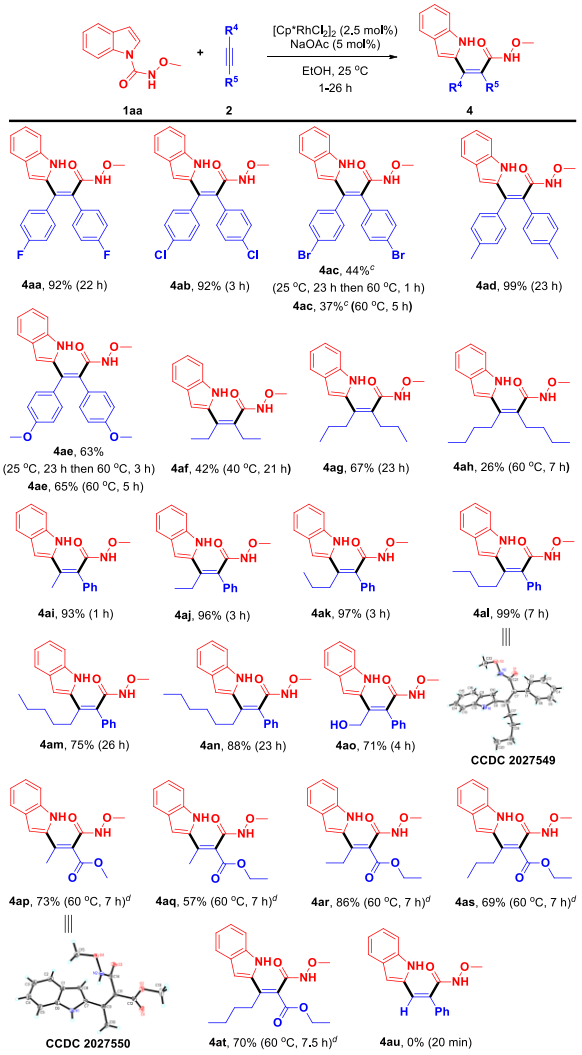


[a]Reaction conditions: **1** (0.25 mmol, 1.0 equiv.), **2aa** (0.275 mmol, 1.1 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (5 mol%), EtOH (4.0 mL), 25 °C, 20 min-24 h. [b]Isolated yield. [c]5 mol% $[Cp^*RhCl_2]_2$ and 10 mol% NaOAc were used.

Scheme 2 were obtained as single stereoisomers in all cases, indicating the excellent stereochemical control of this reaction.

Subsequently, the substrate scope of alkynes was studied (Scheme 3). Overall, the desired tetrasubstituted alkenes **4** were obtained with excellent regio-/stereoselectivities when various symmetrical and asymmetrical alkynes **2** were employed. For example, symmetrical diarylalkynes containing halogens and electron-donating groups or symmetrical

Scheme 3. Scope of alkynes.[a,b]



[a]Reaction conditions: **1aa** (0.25 mmol, 1.0 equiv.), **2** (0.275 mmol, 1.1 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (5 mol%), EtOH (4.0 mL), 25 °C, 1-26 h. [b]Isolated yield. [c]1,4-dioxane was used as the solvent. [d]The reaction was conducted in 1,4-dioxane with 5 mol% $[Cp^*RhCl_2]_2$ and 10 mol% NaOAc.

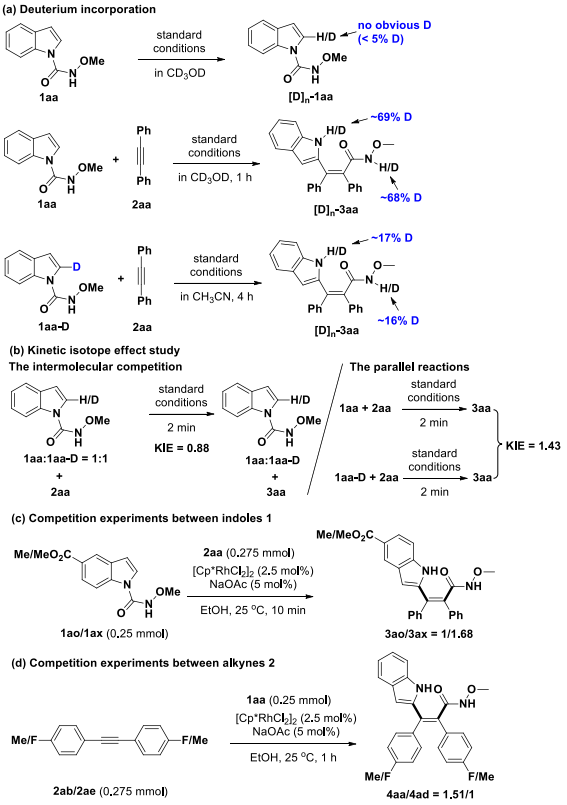
dialkylalkynes reacted smoothly with **1aa** to produce the *cis*-adducts **4aa**-**4ah** in 26-99% yields. Pleasingly, a variety of asymmetrical alkyl/aryl alkynes could undergo this reaction to deliver the corresponding *cis*-adducts **4ai**-**4ao** in high yields (71-99%) with excellent regioselectivities, in which the indole fragment was exclusively attached to the less hindered carbon of the alkyne moiety. Similarly, the addition of **1aa** to various asymmetrical alkyl/ester alkynes also took place successfully, providing products **4ap**-**4at** in a *cis*-selective way and good to high yields (57-86%). Besides, terminal alkynes like phenylacetylene failed to react with **1aa** to afford the desired adduct **4au** under standard conditions.[25] This indicates terminal alkynes are not suitable alkyne conponents for this reaction. It should be noted that the indicated products in Scheme 3 were obtained as single isomers in all cases, suggesting the excellent regio- and stereoselectivities of this process.

To demonstrate the synthetic practicality of this reaction, we carried out the model reaction on a gram scale. Impressively,

product **3aa** collected by a simple filtration as white solids was still obtained in an excellent yield (96%),[26] suggesting the industrial perspective of this reaction.

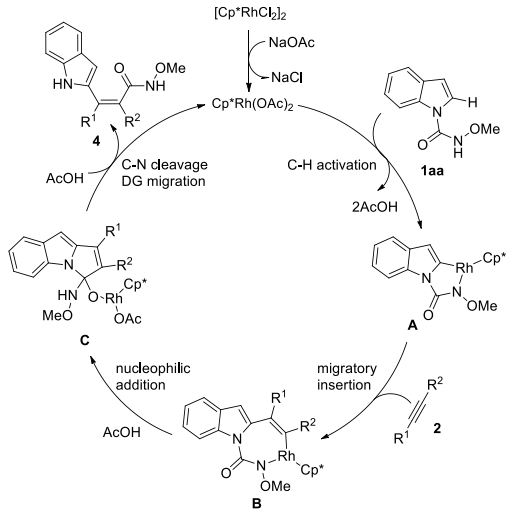
To investigate the role of the DG, the reactions of five 1*H*-indole-1-carboxamides carrying different substituents on the amide nitrogen with **2aa** were independently studied (Scheme S1 in Supporting Information). The results showed the free hydrogen and alkoxyl group attached to the amide nitrogen were both essential. To probe the reaction mechanism, isotope labelling experiments and kinetic isotope effect (KIE) experiments were performed (Scheme 4). First, treatment of **1aa** with CD_3OD resulted in no apparent deuteration (<5% D) at the C2 position of **1aa** under standard conditions. Subsequently, the reaction of **1aa** with **2aa** in CD_3OD gave the deuterated **3aa** with 68% and 69% deuterium incorporation at amide N and indole N positions, respectively. In addition, the reaction of deuterated **1aa-D** with **2aa** in CH_3CN provided the deuterated **3aa** with 16% and 17% deuteration at amide N and indole N positions, respectively. The intermolecular competition reaction and two parallel reactions gave two low KIE values of 0.88 and 1.43, respectively. These data indicated the C–H cleavage step was unlikely involved in the rate-determining step. Additionally, intermolecular competition experiment was performed using electronically different indoles **1ao** and **1ax**, and the ratio of the desired products **3ao**/**3ax** was 1/1.68. This suggested that electron-deficient indole was preferred and a concerted metalation/deprotonation (CMD) mechanism was likely involved in the step of C–H cleavage.[27] Meanwhile, when alkyne **2ab** was used to compete with **2ae**, a 1.51:1 mixture of the products **4aa** and **4ad** was obtained. This indicated the electron-rich alkyne was favored.

Scheme 4. Mechanistic studies.



On the basis of the preliminary mechanistic studies and previous studies,[14a,28] a proposed reaction mechanism was shown in Scheme 5. At first, the active rhodium complex $Cp^*Rh(OAc)_2$ was produced by exchanging the ligand . Then coordination of **1aa** to the rhodium complex forms a rhodacyclic intermediate **A**. Intermediate **B** was then generated through the migratory insertion of the alkyne into the Rh–C bond of intermediate **A**. The following intramolecular nucleophilic addition of Rh–C bond to the carbonyl group affords intermediate **C**. After C–N bond cleavage and protonation, it generates the desired tetrasubstituted alkenes **4** and the active rhodium catalyst.

Scheme 5. Proposed reaction mechanism.



In conclusion, a robust and highy efficient Rh(III)-catalyzed C–H alkenylation/directing group migration cascade between indoles and alkynes for the assembly of tetrasubstituted alkenes has been disclosed. This reaction features: a) rare Rh-catalyzed directing group migration through C–N bond cleavage, b) excellent regio- and stereoselectivity, c) broad substrate scope and good to excellent yields, d) good functional group tolerance and high atom- and step-economy, e) mild redox-neutral reaction conditions at room temperature and green solvent, f) simple operation and easy work-up (chromatography-free in most case). Further bioactivity studies of the tetrasubstituted alkenes containing an indole moiety are currently in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of substrates and products, and copies of ^1H, ^{13}C and ^{19}F NMR spectra (PDF)

X-ray crystal structure of compound **3aa**, **4al** and **4ap** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Beer, M. L.; Lemon, J.; Valliant, J. F. *J. Med. Chem.* **2010**, *53*, 8012–8020.

(2) (a) Morand, P.; Bagli, J. F.; Kraml, M.; Dubuc, J. *J. Med. Chem.* **1964**, *7*, 504–508. (b) Harwood, H. J. Jr.; Barbacci-Tobin, E. G.; Petras, S. F.; Lindsey, S.; Pellarin, L. D. *Biochem. Pharmacol.* **1997**, *53*, 839–864.

(3) Levenson, A. S.; Jordan, V. C. *Eur. J. Cancer.* **1999**, *35*, 1628–1639.

(4) Pei, Q.; Xie, J.-L.; Huang, J.; Liu, W.-Y.; Yang, X.-Y.; Wang, Y.; Li, W.; Tan, H.-Y.; Zhang, H.; Yang, G.-P. *Eur. J. Clin. Pharmacol.* **2019**, *75*, 1355–1360.

(5) Simon, A.; Levenson, J. *Expert. Opin. Pharmacother.* **2003**, *4*, 95–106.

(6) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745.

(7) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870.

(8) For selected reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (c) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886–896. (d) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468–3517. (e) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138–12204. (f) Manikandan, R.; Jeganmohan, M. *Chem. Commun.* **2017**, *53*, 8931–8947.

(9) For selected examples on Mn catalysis, see: (a) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264–1267. (b) Shi, L.; Zhong, X.; She, H.; Lei, Z.; Li, F. *Chem. Commun.* **2015**, *51*, 7136–7139. (c) Liu, B.; Li, J.; Hu, P.; Zhou, X.; Bai, D.; Li, X. *ACS Catal.* **2018**, *8*, 9463–9470. (d) Cembellín, S.; Dalton, T.; Pinkert, T.; Schäfers, F.; Glorius, F. *ACS Catal.* **2020**, *10*, 197–202.

(10) For selected examples on Co catalysis, see: (a) Gao, K.; Lee, P. S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251. (b) Ding, Z.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4698–4701. (c) Tanaka, R.; Ikemoto, H.; Kanai, M.; Yoshino, T.; Matsunaga, S. *Org. Lett.* **2016**, *18*, 5732–5735. (d) Wang, S.; Hou, J.-T.; Feng, M.-L.; Zhang, X.-Z.; Chen, S.-Y.; Yu, X.-Q. *Chem. Commun.* **2016**, *52*, 2709–2712. (e) Zhou, X.; Luo, Y.; Kong, L.; Xu, Y.; Zheng, G.; Lan, Y.; Li, X. *ACS Catal.* **2017**, *7*, 7296–7304. (f) Nakanowatari, S.; Mei, R.; Feldt, M.; Ackermann, L. *ACS Catal.* **2017**, *7*, 2511–2515. (g) Ikemoto, H.; Tanaka, R.; Sakata, K.; Kanai, M.; Yoshino, T.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 7156–7160.

(11) For selected examples on Ni catalysis, see: (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147. (b) Nakanowatari, S.; Müller, T.; Oliveira, J. C. A.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 15891–15895.

(12) For selected examples on Ru catalysis, see: (a) Padala, K.; Jeganmohan, M. *Org Lett.* **2012**, *14*, 1134–1137. (b) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058–2061. (c) Zhang, L. Q.; Yang, S.; Huang, X.; You, J.; Song, F. *Chem. Commun.* **2013**, *49*, 8830–8832. (d) Lanke, V.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 2818–2821. (e) Reddy, M. C.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 481–483. (f) Li, B.; Ma, J.; Xie, W.; Song, H.; Xu, S.; Wang, B. *J. Org. Chem.* **2013**, *78*, 9345−9353. (g) Liang, L.; Fu, S.; Lin, D.; Zhang, X.-Q.; Deng, Y., Jiang, H.; Zeng, W. *J. Org. Chem.* **2014**, *79*, 9472–9480. (h) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 14573–14576. (i) Zhang, W.; Wei, J.; Fu, S.; Lin, D.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 1349–1352. (j) Lanke, V.; Bettadapur, K. R.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5496–5499. (k) Huang, L.; Biafora, A.; Zhang, G.; Bragoni, V.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6933–6937. (l) Zhang, J.; Shrestha, R.; Hartwig, J. F.; Zhao, P. *Nat. Chem.* **2016**, *8*, 1144–1151. (m) Li, M.; Yao, T.-Y.; Sun, S.-Z.; Yan, T.-X.; Wen, L.-R.; Zhang, L.-B. *Org. Biomol. Chem.* **2020**, *18*, 3158–3163. (n) Choi, I.; Messinis, A. M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2020**, *59*, 12534−12540.

(13) For selected examples on Pd catalysis, see: (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129. (b) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, *14*, 1854–1856. (c) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159–1162. (d) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452–6455. (e) García-Rubia, A.; Gómez, A. R.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511–6515. (f) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074. (g) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 6169–6173. (h) Kandukuri, S. R.; Schiffner, J. A.; Oestreich, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 1265–1269. (i) Xiao, Y.-L.; Zhang, B.; He, C.-Y.; Zhang, X. *Chem. Eur. J.* **2014**, *20*, 4532–4536. (j) Wang, Q.; Han, J.; Wang, C.; Zhang, J.; Huang, Z.; Shi, D.; Zhao, Y. *Chem. Sci.* **2014**, *5*, 4962–4967. (k) Zhao, F.; Jia, X.; Zhao, J.; Fei, C.; Liu, L.; Liu, G.; Wang, D.; Chen, F. *RSC Adv.* **2017**, *7*, 25031–25040.

(14) For selected reviews, see: (a) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212–11222. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (c) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (d) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (e) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. *Org. Chem. Front.* **2017**, *4*, 1435–1467.

(15) For selected examples, see: (a) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983. (b) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1064–1067. (c) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353. (d) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540–542. (e) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235–3237. (f) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372–2375. (g) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166–4169. (h) Schröder, N.; Besset, T.; Glorius, F. *Adv. Synth. Catal.* **2012**, *354*, 579–583. (i) Zhen, W.; Wang, F.; Zhao, M.; Du, Z.; Li, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 11819–11823. (j) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 7242–7245. (k) Li, B.; Ma, J.; Xie, W.; Song, H.; Xu, S.; Wang, B. *Chem. Eur. J.* **2013**, *19*, 11863–11868. (l) Wang, Y.; Li, C.; Li, Y.; Yin, F.; Wang, X.-S. *Adv. Synth. Catal.* **2013**, *355*, 1724–1728. (m) Zhang, X.-S.; Zhu, Q.-L.; Zhang, Y.-F.; Li, Y.-B.; Shi, Z.-J. *Chem. Eur. J.* **2013**, *19*, 11898–11903. (n) Chary, B. C.; Kim, S. *Org. Biomol. Chem.* **2013**, *11*, 6879–6882. (o) Zhang, T.; Wu, L.; Li, X. *Org. Lett.* **2013**, *15*, 6294–6297. (p) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12970−12974. (q) Sharma, S.; Han, S.; Kim, M.; Mishra, N. K.; Park, J.; Shin, Y.; Ha, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2014**, *12*, 1703–1706. (r) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 269–271. (s) Zhou, J.; Li, B.; Qian, Z.-C.; Shi, B.-F. *Adv. Synth. Catal.* **2014**, *356*, 1038–1046. (t) Yang, L.; Zhang, G.; Huang, H. *Adv. Synth. Catal.* **2014**, *356*, 1509–1515. (u) Parthasarathy, K.; Bolm, C. *Chem. Eur. J.* **2014**, *20*, 4896–4900. (v) Zhang, C.; Wang, M.; Fan, Z.; Sun, L.-P.; Zhang, A. *J. Org. Chem.* **2014**, *79*, 7626−7632. (w) Karthikeyan, J.; Yoshikai, N. *Org. Lett.* **2014**, *16*, 4224−4227. (x) Xu, L.; Zhang, C.; He, Y.; Tan, L.; Ma, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 321–325. (y) Lv, H.; Shi, J.; Huang, J.; Zhang, C.; Yi, W. *Org. Biomol. Chem.*

2017, *15*, 7088–7092. (z) Lin, W.; Li, W.; Lu, D.; Su, F.; Wen, T.-B.; Zhang, H.-J. *ACS Catal.* **2018**, *8*, 8070−8076.

(16) For selected reviews, see: Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. *Chem. Rev.* **2016**, *116*, 5894–5986.

(17) For selected examples, see: (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910–6911. (b) Sharma, S.; Han, S.; Shin, Y.; Mishra, N. K.; Oh, H.; Park, J.; Kwak, J. H.; Shin, B. S.; Jung, Y. H.; Kim, I. S. *Tetrahedron Lett.* **2014**, *55*, 3104–3107. (c) Li, T.; Wang, Z.; Chen, C.; Zhu, B. *Adv. Synth. Catal.* **2019**, *361***,** 2855–2863. (d) Fei, X.; Li, C.; Yu, X.; Liu, H. *J. Org. Chem.* **2019**, *84*, 6840−6850.

(18) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 6033–6037.

(19) The directing group migration is only achieved by the cleavage of N–O bond in the reported Rh-catalyzed C–H activation (C–H alkyenylation/alkylation/amination) reactions, see: (a) Zhang, X.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 10794–10798. (b) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. *Org. Lett.* **2015**, *17*, 5874–5877. (c) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86–90. (d) Datee, R. B.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4908–4911. (e) Hu, Z.; Tong, X.; Liu, G. *Org. Lett.* **2016**, *18*, 1702–1705. (f) Wang, X.; Gensch, T.; Lerchen, A.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 6506–6512. (g) Wu, Q.; Yan, D.; Chen, Y.; Wang, T.; Xiong, F.; Wei, W.; Lu, Y.; Sun, W.-Y.; Li, J. J.; Zhao, J. *Nat. Commun.* **2017**, *8*, 14227. (h) Wu, Y.; Chen, Z.; Yang, Y.; Zhu, W.; Zhou, B. *J. Am. Chem. Soc.* **2018**, *140*, 42–45.

(20) Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. *Org. Lett.* **2014**, *16*, 5124–5127.

(21) (a) Wu, X.; Wang, B.; Zhou, S.; Zhou, Y.; Liu, H. *ACS Catal.* **2017**, *7*, 2494–2499. (b) Wu, X.; Ji, H. *J. Org. Chem.* **2018**, *83*, 4650–4656. (c) Wu, X.; Ji, H. *Org. Lett.* **2018**, *20*, 2224–2227. (d) Wu, X.; Li, P.; Lu, Y.; Qiao, J.; Zhao, J.; Jia, X.; Ni, H.; Kong, L.; Zhang, X.; Zhao, F. *Adv. Synth. Catal.* **2020**, *362*, 2953–2960.

(22) For the first example of C–H functionalization directed by the CONHOMe group, see: Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 7190–7191. For a review on C–H functionalizations directed by the CONHOMe group, see: Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2016**, *55*, 10578–10599.

(23) Jessop, P. G. *Green Chem.* **2011**, *13*, 1391–1398.

(24) For more details on the screening of the additives, see Table S1 in supporting information.

(25) However, the C–H alkenylation product **4au'** was obtained instead with an acceptable yield when the same reaction was conducted in DCE with increased amount of the catalyst and additive for a longer time, details could be found in the supporting information.

(26) Detailed information for the gram scale experiment could be found in the supporting information.

(27) (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (c) Wang, H.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 7318–7322.

(28) Gulías, M.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 11000–11019.