C–H Activation

International Edition: DOI: 10.1002/anie.201507744
German Edition: DOI: 10.1002/ange.201507744

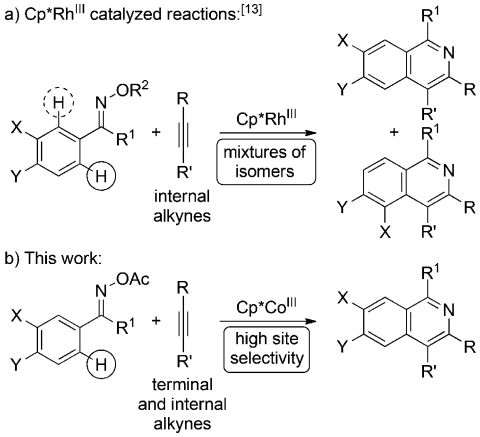
# $Cp^*Co^{III}$ Catalyzed Site-Selective C–H Activation of Unsymmetrical *O*-Acyl Oximes: Synthesis of Multisubstituted Isoquinolines from Terminal and Internal Alkynes

*Bo Sun, Tatsuhiko Yoshino, Motomu Kanai,* and Shigeki Matsunaga**

***Abstract:*** *The synthesis of isoquinolines by site-selective C–H activation of O-acyl oximes with a $Cp^*Co^{III}$ catalyst is described. In the presence of this catalyst, the C–H activation of various unsymmetrically substituted O-acyl oximes selectively occurred at the sterically less hindered site, and reactions with terminal as well as internal alkynes afforded the corresponding products in up to 98% yield. Whereas the reactions catalyzed by the $Cp^*Co^{III}$ system proceeded with high site selectivity (15:1 to 20:1), use of the corresponding $Cp^*Rh^{III}$ catalysts led to low selectivities and/or yields when unsymmetrical O-acyl oximes and terminal alkynes were used. Deuterium labeling studies indicate a clear difference in the site selectivity of the C–H activation step under $Cp^*Co^{III}$ and $Cp^*Rh^{III}$ catalysis.*

The transition-metal-catalyzed functionalization of C–H bonds is an atom-[1] and step-economic[2] organic transformation that has emerged over the last two decades.[3] A directing-group-assisted C–H bond activation process to form metallacyclic intermediates is frequently used to realize regio- and chemoselective transformations of selected C–H bonds. Among the numerous catalysts explored in this field, $Cp^*Rh^{III}$ ($Cp^*$ = pentamethylcyclopentadienyl) complexes are often employed for the directing-group-assisted functionalization of aromatic C–H bonds owing to their high reactivity, generality, and functional-group compatibility.[4] The high cost of $Cp^*Rh^{III}$ complexes, however, can be an obstacle to future large-scale applications for producing valuable materials and biologically active compounds. In 2013, we thus began to investigate $Cp^*Co^{III}$ catalysis as an inexpensive alternative to $Cp^*Rh^{III}$ catalysis.[5,6] Since then, we and other groups have shown that several $Cp^*Co^{III}$ complexes indeed catalyze various C–H bond functionalization reactions[7] that have already been established with $Cp^*Rh^{III}$ catalysts. On the other hand, reports on the unique catalytic activity of $Cp^*Co^{III}$ in comparison with $Cp^*Rh^{III}$ are still limited.[8] Our group utilized the high nucleophilicity of alkenyl $Co^{III}$ species in a one-pot pyrroloindolone synthesis.[8a] Glorius et al. capitalized on the high Lewis acidity of a cationic $Co^{III}$ catalyst to produce 6*H*-pyrido[2,1-*a*]isoquinolin-6-ones.[8b] More recently, we[8c] and the Glorius group[8d] independently utilized the oxophilic properties of $Co^{III}$ for the dehydrative C–H allylation with free allylic alcohols. Herein, we describe our efforts to further explore the unique catalytic activity of $Cp^*Co^{III}$ over $Cp^*Rh^{III}$ catalysts. $Cp^*Co^{III}$ catalysts were found to exhibit superior site selectivity in the C–H activation of unsymmetrically substituted *O*-acyl oximes, which enables the formation of multisubstituted isoquinolines from terminal and internal alkynes.

The isoquinoline framework is an important structural motif found in a series of biologically active natural products and pharmaceuticals.[9] Cyclization reactions of oxime derivatives and alkynes by C–H activation to give isoquinolines without any external oxidants[10,11] have been developed using various transition-metal catalysts.[12–14] For example, Chiba and co-workers reported a $Cp^*Rh^{III}$ catalyzed annulation reaction of *O*-acyl oximes with internal alkynes (Scheme 1 a).[13a] Zhao, Jia, Li, and co-workers also reported a similar reaction of oximes under $Cp^*Rh^{III}$ catalysis.[13b] However, in both cases, the substrate scope was limited to internal alkynes.[13,15] Moreover, the site selectivity in the C–H activation step leading to a metallacycle was also problematic when unsymmetrical *meta*-substituted oxime derivatives were used. Only very few substrates bearing




***Scheme 1.*** $Cp^*Rh^{III}$ and $Cp^*Co^{III}$ catalyzed isoquinoline syntheses; site selectivity with unsymmetrical oxime derivatives and alkynes.

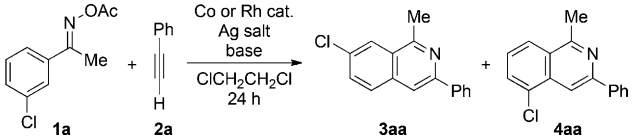
[*] B. Sun, Prof. Dr. M. Kanai
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: kanai@mol.f.u-tokyo.ac.jp
Dr. T. Yoshino, Prof. Dr. S. Matsunaga
Faculty of Pharmaceutical Sciences
Hokkaido University
Kita-ku, Sapporo 060-0812 (Japan)
E-mail: smatsuna@pharm.hokudai.ac.jp
Dr. T. Yoshino, Prof. Dr. S. Matsunaga
ACT-C (Japan) Science and Technology Agency (Japan)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507744.

methyl or alkoxy groups reacted with sufficient site selectivity in previously reported transition-metal-catalyzed isoquinoline syntheses from oxime derivatives.[13,14] We hypothesized that steric repulsion between the Cp* ligand and the substrate would be larger with the $Cp^*Co^{III}$ than with the $Cp^*Rh^{III}$ catalyst as the ionic radius of cobalt is smaller than that of rhodium. Thereby, $Cp^*Co^{III}$ would efficiently differentiate between the two *ortho* positions in unsymmetrical *meta*-substituted oxime derivatives.

We optimized the reaction conditions using *meta*-chloro-substituted *O*-acyl oxime **1a** and terminal alkyne **2a** as the model substrates (Table 1). A cationic benzene complex, $[Cp^*Co(C_6H_6)][PF_6]_2$ combined with KOAc at 120 °C afforded the desired annulated product **3aa** and its isomer **4aa** in 46% yield and good selectivity (**3aa**/**4aa** = 14:1; entry 1). The less hindered C–H bond was thus selectively functionalized under $Cp^*Co^{III}$ catalysis. In situ generation of an active catalyst using $[Cp^*Co(CO)I_2]$ and cationic Ag salts led to higher reactivity (entries 2–5), and $AgSbF_6$ afforded the best result (82% yield, 17:1 selectivity; entry 5). Other bases were less effective (entries 6–8). In the absence of KOAc, the yield of **3aa** decreased (55% yield; entry 9). We also evaluated the catalytic activity of $Cp^*Rh^{III}$ complexes under several conditions to investigate the difference between $Co^{III}$ and $Rh^{III}$. Under the reaction conditions reported for internal alkynes (acetate bases in MeOH,[13a,b] 60–80 °C), no reaction occurred (entries 10 and 11). When $AgSbF_6$ and carboxylate/carbonate bases were used in 1,2-dichloroethane at 120 °C, the annulated products were obtained in 9–28% yield, but the C–H activation proceeded with poor site selectivity in all cases (entries 13–16).

***Table 1:*** Optimization studies and control experiments.[a]



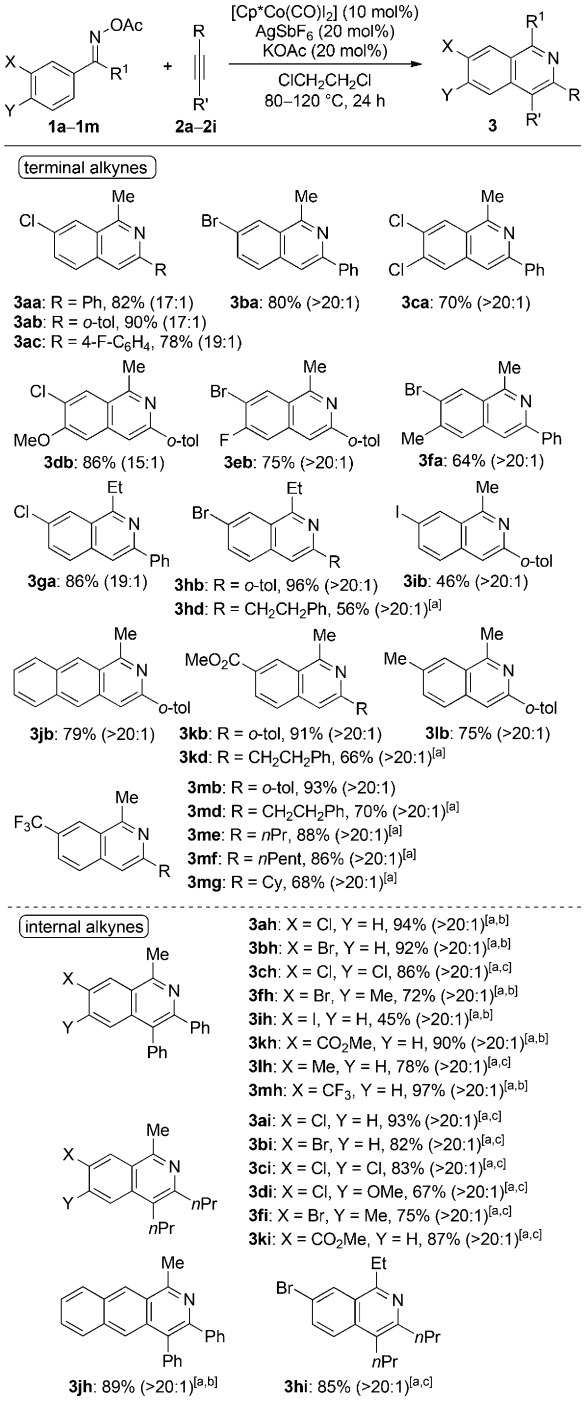

| Entry | Catalyst (mol%) | Ag salt (mol%) | Base (mol%) | *T* [°C] | Yield [%][b] | **3**/**4** |
|---|---|---|---|---|---|---|
| 1 | $[Cp^*Co(C_6H_6)][PF_6]_2$ (10) | – | KOAc (20) | 120 | 46 | 14:1 |
| 2 | $[Cp^*Co(CO)I_2]$ (10) | $AgPF_6$ (20) | KOAc (20) | 120 | 73 | 17:1 |
| 3 | $[Cp^*Co(CO)I_2]$ (10) | $AgBF_4$ (20) | KOAc (20) | 120 | 65 | 19:1 |
| 4 | $[Cp^*Co(CO)I_2]$ (10) | $AgNTf_2$ (20) | KOAc (20) | 120 | 70 | 16:1 |
| 5 | $[Cp^*Co(CO)I_2]$ (10) | $AgSbF_6$ (20) | KOAc (20) | 120 | 82[c] | 17:1 |
| 6 | $[Cp^*Co(CO)I_2]$ (10) | $AgSbF_6$ (20) | $K_2CO_3$ (20) | 120 | 71 | 13:1 |
| 7 | $[Cp^*Co(CO)I_2]$ (10) | $AgSbF_6$ (20) | CsOAc (20) | 120 | 63 | 19:1 |
| 8 | $[Cp^*Co(CO)I_2]$ (10) | $AgSbF_6$ (20) | CsOPiv (20) | 120 | 64 | 17:1 |
| 9 | $[Cp^*Co(CO)I_2]$ (10) | $AgSbF_6$ (20) | – | 120 | 55 | 17:1 |
| 10[d] | $[\{Cp^*RhCl_2\}_2]$ (2.5) | – | NaOAc (30) | 60 | trace | n.d. |
| 11[d] | $[\{Cp^*RhCl_2\}_2]$ (2.5) | – | CsOAc (30) | 80 | trace | n.d. |
| 12 | $[\{Cp^*RhCl_2\}_2]$ (5) | $AgSbF_6$ (20) | KOAc (20) | 80 | trace | n.d. |
| 13 | $[\{Cp^*RhCl_2\}_2]$ (5) | $AgSbF_6$ (20) | KOAc (20) | 120 | 11 | 1:1.3 |
| 14 | $[\{Cp^*RhCl_2\}_2]$ (5) | $AgSbF_6$ (20) | $K_2CO_3$ (20) | 120 | 9 | 1:1.6 |
| 15 | $[\{Cp^*RhCl_2\}_2]$ (5) | $AgSbF_6$ (20) | CsOAc (20) | 120 | 28 | 1:1.3 |
| 16 | $[\{Cp^*RhCl_2\}_2]$ (5) | $AgSbF_6$ (20) | CsOPiv (20) | 120 | 13 | 1:1.3 |

[a] Reactions were run using **1a** (0.15 mmol) and **2a** (0.18 mmol) in $ClCH_2CH_2Cl$ unless otherwise noted. [b] Combined yield of **3aa** and **4aa** determined by $^1H$ NMR analysis with 1,1,2,2-tetrachloroethane as the internal standard. [c] Yield of isolated product after column chromatography on silica gel. [d] The reaction was run in MeOH (reaction conditions reported in Ref. [13a,b]).

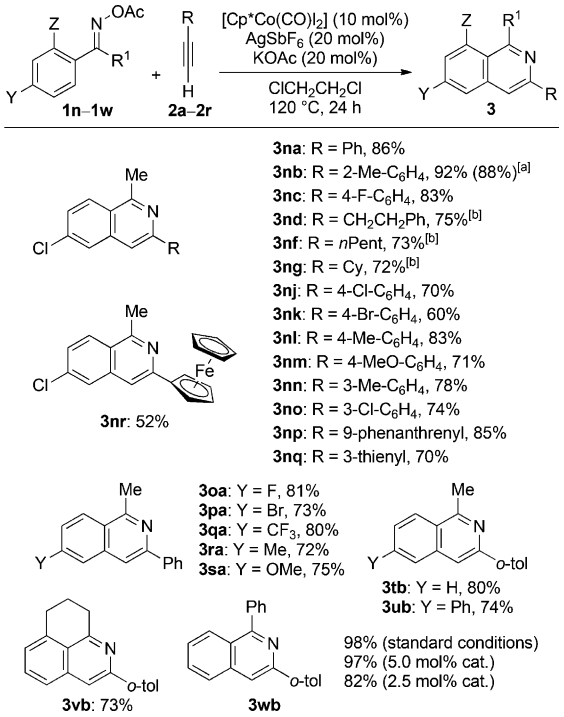
The scope of unsymmetrically substituted *O*-acyl oximes **1** is summarized in Scheme 2. *O*-Acyl oximes bearing halogen substituents at the *meta* position generally reacted with high site selectivity, and the less hindered C–H bond was functionalized (**3aa**–**3ib**). A second substituent in the *para* position (Y in **1**) did not affect the selectivity or reactivity (**3ca**, **3db**, **3eb**, **3fa**). Various substituents at the *meta* position, such as ester, methyl, and $CF_3$ groups, were compatible with the reaction, and high site selectivity was observed with terminal aryl alkyne **2b**. When the reaction conditions were slightly modified and CsOAc was used as the base, the terminal alkyl alkynes **2d**–**2g** also afforded the corresponding products with high site selectivity (>20:1) and in good to moderate yields (**3hd**, **3kd**, **3md**–**3mg**). We also evaluated the reactivity of the $Cp^*Rh^{III}$ catalyst with several terminal alkynes and unsymmetrical *O*-acyl oximes, but the yields and/or site selectivities were much less satisfactory (**3db**/**4db**: 38%, 1:1.7; **3eb**/**4eb**: 62%, 1:1.2; **3hb**/**4hb**: 18%, 1.1:1; **3kb**/**4kb**: 9%, >20:1; **3lb**/**4lb**: 30%, >20/:1; **3mb**/**4mb**: trace, n.d.; **3md**/**4md**: 6%, >20:1). In a previous report, the use of the $Cp^*Rh^{III}$ catalyst had also resulted in low site selectivity when *meta*-bromo-substituted *O*-acyl oxime **1b** and internal alkyne **2h** were employed (**3bh**/**4bh** = 2.7:1).[13a] The $Cp^*Co^{III}$ catalyst exhibited much superior site selectivity with both aryl and alkyl internal alkynes (**2h** and **2i**), and a broad range of unsymmetrically substituted *O*-acyl oximes were converted into the desired products **3ah**–**3ki** with >20:1 site selectivity and in 45–97% yield.

As the $Cp^*Rh^{III}$ complex exhibited only modest to poor reactivity with terminal alkynes,[15,16] we further examined the synthetic utility of the $Cp^*Co^{III}$ catalyst with various terminal alkynes and symmetrical *O*-acyl oximes. Aryl, alkyl, heteroaryl, and ferrocenyl terminal alkynes reacted smoothly with *O*-acyl oxime **1n**, giving the products **3na**–**3nr** in 52–92% yield (Scheme 3). The reaction could also be run on gram scale without difficulty, and **3nb** was then obtained in 88% yield. Regarding the scope of symmetrical *O*-acyl oximes, **1o**–**1u** gave **3oa**–**3ub** in 72–81% yield. The *ortho*-substituted bicyclic *O*-acyl oxime **1v** gave **3vb** in 73% yield, and the benzophenone-derived *O*-acyl oxime **1w** also afforded the corresponding product in excellent yield (**3wb**, 98%). With **1w** and **2b**, we attempted to reduce the catalyst loading. The reaction proceeded smoothly with 5.0 mol% of the cobalt catalyst, and **3wb** was obtained in 97% yield. Decreasing the

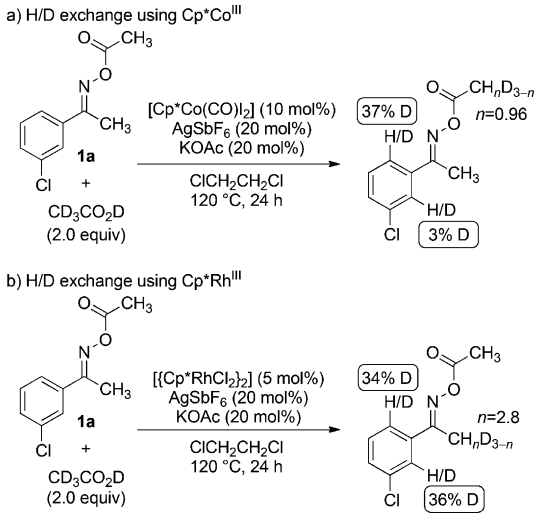
  




***Scheme 2.*** Variation of unsymmetrical *O*-acyl oximes **1**. Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), $[Cp^*Co(CO)I_2]$ (10 mol%), $AgSbF_6$ (20 mol%), and KOAc (20 mol%) in $ClCH_2CH_2Cl$ at 120°C for 24 h unless otherwise noted. Combined yields of isolated **3** and its regioisomer **4** are given. The numbers in parentheses correspond to the ratios of **3**/**4** determined by $^1H$ NMR analysis of the crude mixture. [a] CsOAc (20 mol%) instead of KOAc. **1** (0.10 mmol) and **2** (0.15 mmol) were used. [b] 80°C. [c] 100°C. Cy = cyclohexyl.




***Scheme 3.*** Variation of terminal alkynes **2**. Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), $[Cp^*Co(CO)I_2]$ (10 mol%), $AgSbF_6$ (20 mol%), and KOAc (20 mol%) in $ClCH_2CH_2Cl$ at 120°C for 24 h unless otherwise noted. Yields of isolated **3** after purification by column chromatography on silica gel are given. [a] The yield in parentheses was obtained using **1n** (5.0 mmol, 1.06 g) and **2b** (6.0 mmol). [b] CsOAc (20 mol%) instead of KOAc. **1** (0.10 mmol) and **2** (0.15 mmol) were used.




***Scheme 4.*** H/D exchange experiments under a) $Cp^*Co^{III}$ catalysis and b) $Cp^*Rh^{III}$ catalysis.

catalyst loading to 2.5 mol% resulted in diminished reactivity, but an acceptable yield (82%) was still achieved.

The high site selectivity of the C–H bond activation step under $Cp^*Co^{III}$ catalysis in comparison with $Cp^*Rh^{III}$ catalysis was confirmed by deuterium exchange experiments (Scheme 4). When *O*-acyl oxime **1a** was subjected to the optimized reaction conditions using $Cp^*Co^{III}$ in the presence of $CD_3CO_2D$, selective deuterium incorporation was observed at the less hindered position (37%D vs. 3%D;

Scheme 4a). On the other hand, the Cp*Rh$^{III}$ catalyst promoted non-selective H/D exchange under the same conditions (34% D vs. 36% D; Scheme 4b). These results clearly indicate that the Cp*Co$^{III}$ catalyst differentiates more efficiently between the substituents in unsymmetrical *meta*-substituted *O*-acyl oximes than Cp*Rh$^{III}$. We assume that the steric repulsion between the Cp* ligand and the substrate is larger with the Cp*Co$^{III}$ catalyst than with the Cp*Rh$^{III}$ catalyst as the ionic radius of cobalt is smaller than that of rhodium.[17] However, further mechanistic studies are required to clarify the precise origin of the high site selectivity.

Possible reaction pathways to form isoquinolines **3** are shown in Figure 1. Coordination of *O*-acyl oxime **1a** to the

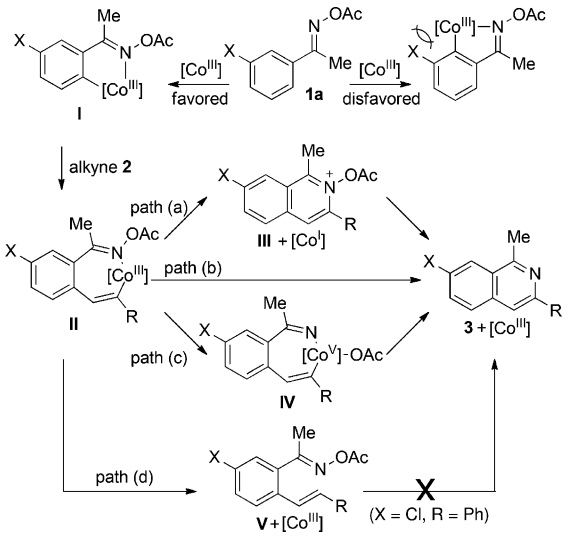



***Figure 1.*** Possible reaction pathways for the formation of isoquinolines under Cp*Co$^{III}$ catalysis.

Co$^{III}$ center, followed by acetate-assisted C–H activation[18] at the sterically less hindered site leads to the five-membered metallacycle **I**. Alkyne insertion leads to a common intermediate (**II**). Path a combines reductive elimination of the C–N bond to form the *N*-acetoxy isoquinolinium cation **III** with subsequent reduction of intermediate **III** by the resulting Co$^{I}$ species. In path b, a concerted C–N bond formation and N–O bond cleavage process would provide isoquinoline **3** and regenerate the catalyst.[11a] Path c involves formal oxidative addition of the N–O bond to the Co$^{III}$ center to give Co$^{V}$ species **IV**,[7o] which undergoes reductive elimination leading to **3**. At present, it is difficult to determine which pathway is more plausible under Cp*Co$^{III}$ catalysis. On the other hand, we can rule out that the reaction proceeds by 6π electrocyclization of *ortho*-alkenylated intermediate **V** (path d),[14b,19] because **3** was not obtained when the separately synthesized intermediate **V** (X = Cl, R = Ph) was subjected to the reaction conditions.

In summary, we have demonstrated the unique catalytic activity of the Cp*Co$^{III}$ complex for the synthesis of multi-substituted isoquinolines from *O*-acyl oximes and terminal as well as internal alkynes by site-selective C–H bond activation. The Cp*Co$^{III}$ catalyst exhibited much higher site selectivity for unsymmetrical *O*-acyl oximes and higher reactivity towards terminal alkynes than the Cp*Rh$^{III}$ catalyst. An oxidizing directing group bearing an N–O bond was successfully utilized as an internal oxidant in this process. Further mechanistic studies as well as investigations to apply the unique catalytic activity of Cp*Co$^{III}$ to other processes are actively ongoing in our laboratory.[20]

## Acknowledgements

This work was supported in part by the ACT-C program from JST, a Grant-in-Aid for Scientific Research on Innovative Areas, The Asahi Glass Foundation, and the Naito Foundation (S.M.).

**Keywords:** C–H activation · cobalt · isoquinolines · transition-metal catalysis

**How to cite:** *Angew. Chem. Int. Ed.* **2015**, *54*, 12968–12972
*Angew. Chem.* **2015**, *127*, 13160–13164

[1] B. M. Trost, *Science* **1991**, *254*, 1471.
[2] P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197.
[3] For selected recent reviews on C–H bond functionalization, see: a) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260; b) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; d) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; e) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; f) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; g) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588; h) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068.
[4] For reviews on Cp*Rh$^{III}$ catalyzed C–H functionalization, see: a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; b) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; d) S. Chiba, *Chem. Lett.* **2012**, *41*, 1554; e) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; f) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; g) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308.
[5] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207; *Angew. Chem.* **2013**, *125*, 2263.
[6] For reviews on cobalt-catalyzed C–H bond functionalization reactions, see: a) N. Yoshikai, *Synlett* **2011**, 1047; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208; for a review on first-row transition-metal-catalyzed C–H bond functionalization reactions, see: c) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087.
[7] a) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142; b) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491; c) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722; d) T. M. Figg, S. Park, J. Park, S. Chang, D. G. Musaev, *Organometallics* **2014**, *33*, 4076; e) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490; f) P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853; g) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635; *Angew. Chem.* **2015**, *127*, 3706; h) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Chem. Commun.* **2015**, *51*, 4659; i) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660; j) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551;

*Angew. Chem.* **2015**, *127*, 8671; k) J. R. Hummel, J. A. Ellman, *Org. Lett.* **2015**, *17*, 2400; l) Y. Suzuki, B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Tetrahedron* **2015**, *71*, 4552; m) M. Moselage, N. Sauermann, J. Koeller, W. Liu, D. Gelman, L. Ackermann, *Synlett* **2015**, *26*, 1596; n) X.-G. Liu, S.-S. Zhang, J.-Q. Wu, Q. Li, H. Wang, *Tetrahedron Lett.* **2015**, *56*, 4093; o) Z.-Z. Zhang, B. Liu, C.-Y. Wang, B.-F. Shi, *Org. Lett.* **2015**, *17*, 4094.

[8] a) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424; b) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 4508; *Angew. Chem.* **2015**, *127*, 4591; c) Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2015**, *54*, 9944; *Angew. Chem.* **2015**, *127*, 10082; d) T. Gensch, S. Vásquez-Céspedes, D.-G. Yu, F. Glorius, *Org. Lett.* **2015**, *17*, 3714.

[9] For reviews, see: a) K. W. Bentley, *The Isoquinoline Alkaloids*, *Vol. 1*, Hardwood Academic, Amsterdam, **1998**; b) K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395; c) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444.

[10] For reviews on oxidative C–H bond functionalization reactions without external oxidants, see: a) F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1977; *Angew. Chem.* **2011**, *123*, 2021; b) J. Mo, L. Wang, Y. Liu, X. Cui, *Synthesis* **2015**, 439; c) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155.

[11] For selected examples of $Cp^*Rh^{III}$ catalyzed redox-neutral C–H bond activation/annulation reactions that employ directing groups that concomitantly function as internal oxidants, see: a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; c) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449; d) P. C. Too, T. Noji, Y. J. Lim, X. Li, S. Chiba, *Synlett* **2011**, 2789; e) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science* **2012**, *338*, 500; f) B. Ye, N. Cramer, *Science* **2012**, *338*, 504; g) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592; h) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66; i) D. Zhao, Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 12426; *Angew. Chem.* **2013**, *125*, 12652; j) B. Liu, C. Song, C. Sun, S. Zhou, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 16625; k) C. Wang, Y. Huang, *Org. Lett.* **2013**, *15*, 5294; l) S.-C. Chuang, P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 5750; m) X. Huang, J. Huang, C. Du, X. Zhang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12970; *Angew. Chem.* **2013**, *125*, 13208; n) X.-C. Huang, X.-H. Yang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 1025; o) L. Zheng, R. Hua, *Chem. Eur. J.* **2014**, *20*, 2352; p) U. Sharma, Y. Park, S. Chang, *J. Org. Chem.* **2014**, *79*, 9899; q) Z. Fan, S. Song, W. Li, K. Geng, Y. Xu, Z.-H. Miao, A. Zhang, *Org. Lett.* **2015**, *17*, 310.

[12] For examples of isoquinoline synthesis by C–H activation with stoichiometric amounts of external oxidants, see a review: a) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5705; for pioneering reports, see also: b) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141; c) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050.

[13] For $Cp^*Rh^{III}$ catalyzed isoquinoline syntheses by redox-neutral C–H functionalization of oxime derivatives, see: a) P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688; b) X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719; c) P. C. Too, S. H. Chua, S. H. Wong, S. Chiba, *J. Org. Chem.* **2011**, *76*, 6159; d) T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846; e) L. Zheng, J. Ju, Y. Bin, R. Hua, *J. Org. Chem.* **2012**, *77*, 5794; f) D. Zhao, F. Lied, F. Glorius, *Chem. Sci.* **2014**, *5*, 2869; for related work, see also: g) Y.-F. Wang, K. K. Toh, J.-Y. Lee, S. Chiba, *Angew. Chem. Int. Ed.* **2011**, *50*, 5927; *Angew. Chem.* **2011**, *123*, 6049; h) S. Zhang, D. Huang, G. Xu, S. Cao, R. Wang, S. Peng, J. Sun, *Org. Biomol. Chem.* **2015**, *13*, 7920; see also Refs. [11l, 11n].

[14] For isoquinoline syntheses from oxime derivatives using other transition-metal catalysts, see: a) T. Gerfaud, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 572; *Angew. Chem.* **2009**, *121*, 580; b) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359; c) Y. Yoshida, T. Kurahashi, S. Matsubara, *Chem. Lett.* **2011**, *40*, 1140; d) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032; e) C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190; f) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3703; g) C. Kornhaaß, C. Kuper, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1619.

[15] 1,3-Dienes were used as alternative substrates to overcome the difficulty associated with using terminal alkyl alkynes in combination with $Cp^*Rh^{III}$ catalysis: see Ref. [13f].

[16] A few terminal alkynes were successfully used as substrates in the reaction of benzophenone-derived oximes under $Ru^{II}$ catalysis; see Ref. [14d]. When we used a less reactive *meta*-substituted oxime and terminal alkyne **2a**, however, the $Ru^{II}$ catalyst $[\{RuCl_2(p\text{-cymene})\}_2]$ gave the corresponding isoquinolines in less than 5% yield and poor **3aa**/**4aa** ratios (1.2:1).

[17] The steric properties of substituted cyclopentadienyl ligands affect the site, regio-, and diastereoselectivity of $Rh^{III}$ catalyzed C–H activation reactions. For systematic studies of these effects in dihydroisoquinolone synthesis and cyclopropanation, see: a) T. K. Hyster, D. M. Dalton, T. Rovis, *Chem. Sci.* **2015**, *6*, 254; b) T. Piou, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 11292.

[18] For reviews on the concerted metalation–deprotonation mechanism, see: a) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315, and references therein.

[19] The $6\pi$ electrocyclization mechanism was proposed for $Rh^{I}$ catalysis; see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645; see also Ref. [14b].

[20] **Editorial Note (15.9.2015)**: Two very closely related papers were submitted almost simultaneously to this one; see: H. Wang, J. Koeller, W. Liu, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, DOI: 10.1002/chem.201503624 and M. Sen, D. Kalsi, B. Sundararaju, *Chem. Eur. J.* **2015**, *21*, DOI: 10.1002/chem.201503643.

Received: August 19, 2015
Published online: September 28, 2015