Synthetic Methods

International Edition: DOI: 10.1002/anie.201812379
German Edition: DOI: 10.1002/ange.201812379

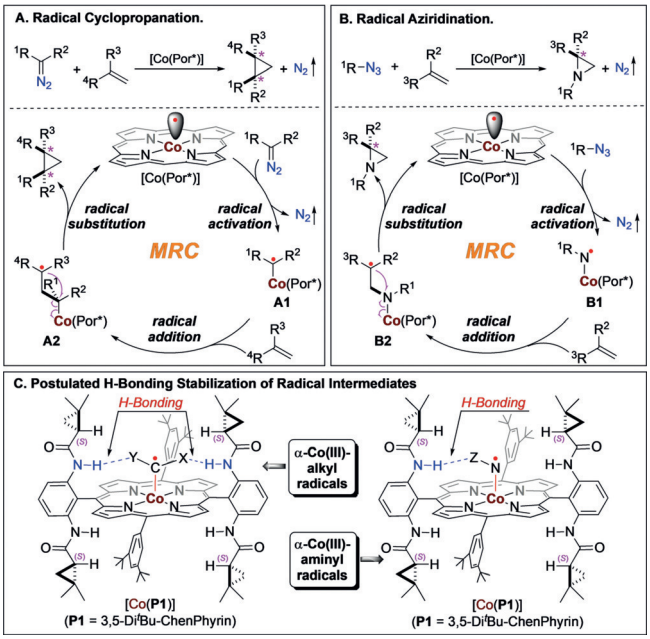
Next-Generation D_2-Symmetric Chiral Porphyrins for Cobalt(II)-Based Metalloradical Catalysis: Catalyst Engineering by Distal Bridging

*Yang Hu[+], Kai Lang[+], Jingran Tao, McKenzie K. Marshall, Qigan Cheng, Xin Cui, Lukasz Wojtas, and X. Peter Zhang**

Abstract: *Novel D_2-symmetric chiral amidoporphyrins with alkyl bridges across two chiral amide units on both sides of the porphyrin plane (designated "HuPhyrin") have been effectively constructed in a modular fashion to permit variation of the bridge length. The Co^{II} complexes of HuPhyrin, [Co(HuPhyrin)], represent new-generation metalloradical catalysts where the metal-centered d-radical is situated inside a cavity-like ligand with a more rigid chiral environment and enhanced hydrogen-bonding capability. As demonstrated with cyclopropanation and aziridination as model reactions, the bridged [Co(HuPhyrin)] functions notably different from the open catalysts, exhibiting significant enhancement in both reactivity and stereoselectivity. Furthermore, the length of the distal alkyl bridge can have a remarkable influence on the catalytic properties.*

Homolytic radical chemistry has been increasingly explored for the development of alternative bond-breaking and bond-forming tools that may shape the state of the art of organic synthesis.[1,2] Despite significant advancements in this endeavor, general strategies for addressing the enduring issues of controlling reactivity and selectivity in radical reactions, particularly enantioselectivity, remain to be uncovered. Among recent progresses,[3] metalloradical catalysis (MRC), which explores the use of metalloradical complexes as open-shell catalysts for catalytically generating organic radical intermediates as well as controlling subsequent homolytic radical transformations, has emerged as a conceptually new approach.[4,5] In this context, Co^{II} complexes of porphyrins, as 15e stable metalloradicals, have exhibited unusual efficiency in radical activation of diazo compounds to generate the fundamentally new α-Co^{III}-alkyl radicals **A1** (Scheme 1 A).[6] The resulting Co-stabilized C-centered radical intermediates can undergo radical addition to alkenes for generation of γ-Co^{III}-alkyl radicals (**A2**), which subsequently undergo intramolecular homolytic radical substitution (*3-exo-tet* radical cyclization) to produce cyclopropanes and regenerate the Co^{II}-based metalloradicals. The outcome of this Co^{II}-based metalloradical catalysis (Co^{II}-MRC) is the revelation of an unprecedented catalytic pathway for olefin cyclopropanation, and it operates by a stepwise radical mechanism (Scheme 1 A).[7] In parallel, the application of Co^{II}-MRC to organic azides has resulted in the disclosure of a new radical pathway for catalytic olefin aziridination involving α-Co^{III}-aminyl radicals (**B1**)[8] and γ-Co^{III}-alkyl radicals (**B2**) as key intermediates (Scheme 1 B).[9] Despite their underlying radical mechanisms, catalytic transformations by Co^{II}-MRC can be rendered stereoselective because the radical intermediates involved are no longer "free" but controlled by the catalysts.[7,9,10] In practice, the formidable challenge associated with controlling the stereoselectivity of radical reactions can essentially be translated into a solvable problem of catalyst design and development.

Since the first introduction in 2004[7a] and later expanded,[7c–d] the family of D_2-symmetric chiral amidoporphyrins (D_2-Por*) have proven particularly effective in controlling the reactivity as well as stereoselectivity of various radical transformations by Co^{II}-MRC.[7,9,10] In additon to the



Scheme 1. Radical pathways for cyclopropanation and aziridination.

[*] Dr. K. Lang,[+] Prof. Dr. X. P. Zhang
Department of Chemistry, Merkert Chemistry Center, Boston College
Chestnut Hill, MA 02467 (USA)
E-mail: peter.zhang@bc.edu
Dr. Y. Hu,[+] J. Tao, M. K. Marshall, Q. Cheng, Dr. X. Cui, Dr. L. Wojtas
Department of Chemistry, University of South Florida
Tampa, FL 33620 (USA)
[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201812379.

pocket-like chiral environment with tunable electronic and steric properties, the effectiveness of this family of ligands in supporting Co^{II}-MRC is also attributed to the postulated hydrogen-bonding interactions between NH units of the amides on the amidoporphyrin ligand as the hydrogen-bond donors and the substituents on the C- or N-centered radical moiety as the hydrogen-bond acceptors, as illustrated (Scheme 1C) with the common metalloradical catalyst [Co(**P1**)] (**P1**: 3,5-Di^{t}Bu-ChenPhyrin).[7a] While existing D_2-symmetric chiral amidoporphyrins have been successfully applied in a number of catalytic radical processes, the need to design the next generation of MRC catalysts with improved catalytic properties has become increasingly evident. In addition to addressing the limitations of existing systems, it may open windows for discovering new catalytic radical transformations. To this end, we envisioned the new D_2-Por* having bridges across the two chiral amide units on both sides of the porphyrin plane, where the metal-centered radicals are situated inside a cavity-like chiral environment (Figure 1).[11,12] Besides offering an additional dimension for fine-tuning steric, electronic, and chiral properties, the bridged amidoporphyrins are expected to possess enhanced hydrogen-bonding capability as a result of the rigidification of the chiral amide units. Herein, we report the first construction of such porphyrin ligands (designated "HuPhyrin"), having different alkyl bridges (Figure 1). As an initial demonstration with asymmetric radical cyclopropanation and aziridination as model reactions, Co^{II} complexes of HuPhyrin ([Co(HuPhyrin)]) exhibit notably different catalytic properties from the Co^{II} catalysts supported by the open analogue of D_2-Por*.

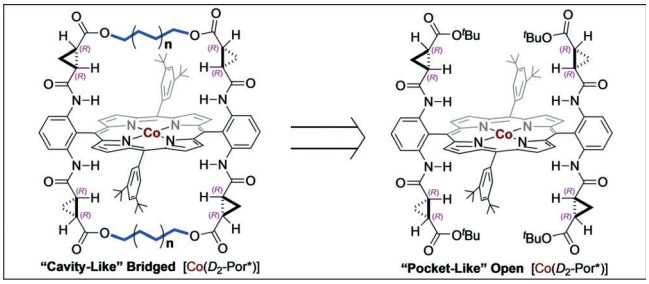
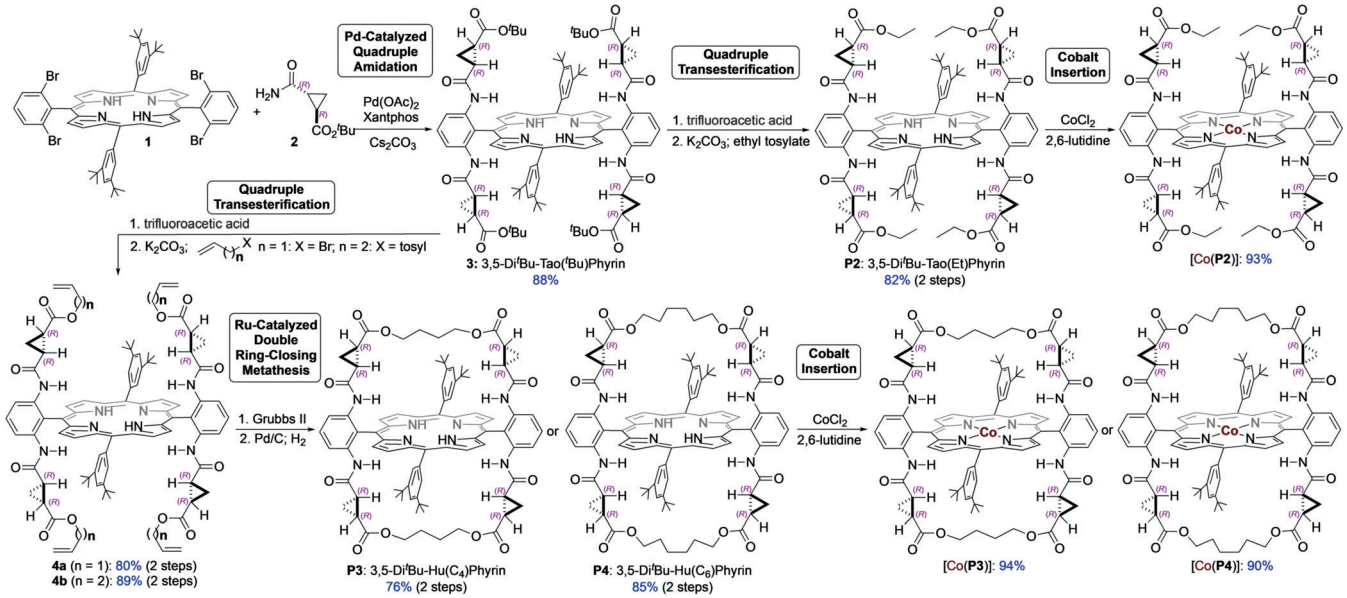


Figure 1. Creation of cavity-like chiral environment by bridging.

For construction of the bridges, 3,5-Di^{t}Bu-Tao(^{t}Bu)Phyrin (**3**; Scheme 2), a new D_2-symmetric chiral amidoporphyrin that carries *tert*-butyl ester moieties, was selected as the scaffold structure, considering that the ester functionalities in **3** may serve as convenient handles for building the bridges. Following the previously established procedure,[7a] **3** was prepared in 88% yield by Pd-catalyzed quadruple amidation reaction of the tetrabromoporphyrin **1** with the optically pure chiral amide **2**[7b] (Scheme 2). The *tert*-butyl esters in **3** could readily undergo transesterification, involving the first generation of the corresponding porphyrin carboxylic acids by hydrolysis and then subsequent O-alkylation with either alkyl halides or tosylates. For example, the use of ethyl tosylate afforded 3,5-Di^{t}Bu-Tao(Et)Phyrin (**P2**) in 82% yield for the two-step transformation, and was metallated to form the Co^{II} complex [Co(**P2**)] in 93% yield. When the transesterification operation was carried out with allyl bromide and homoallyl tosylate, **4a** and **4b** were formed in 80 and 89% yields, respectively. With the second-generation Grubbs catalyst, **4a** and **4b** underwent ring-closing metathesis to form olefin-bridged porphyrins as a non-consequential mixture of *cis* and *trans* isomers. They were directly hydrogenated to form the alkyl-bridged porphyrins **P3** (3,5-Di^{t}Bu-Hu(C_4)Phyrin) and **P4** (3,5-Di^{t}Bu-Hu(C_6)Phyrin) in 76 and 85% yields, respectively. The five-step synthesis was accomplished in high overall yields (54% for **P3** and 67% for **P4**). Metallation gave Co^{II} complexes [Co(**P3**)] and [Co(**P4**)] in 94 and 90% yields, respectively, on a scale of hundreds of milligrams.



Scheme 2. Synthesis of D_2-symmetric chiral bridged amidoporphyrins and cobalt(II) complexes.

To examine the bridging effect on the conformation of D_2-Por*, the ^{1}H NMR spectra of C_4-bridged **P3** and C_6-bridged **P4** were analyzed and compared to their open counterparts **P2** and **P1**, respectively. As illustrated by the low-field region of their ^{1}H NMR spectra (Figure 2), both the line width and

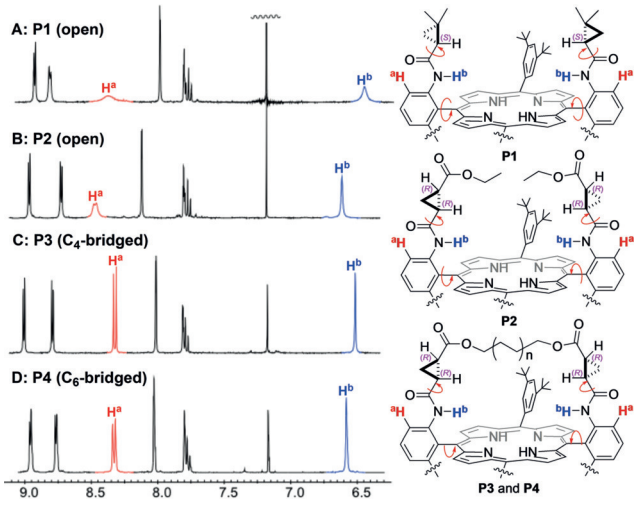


Figure 2. Low-field region of the ^{1}H NMR spectra of chiral amidoporphyrins.

chemical shift of the signals corresponding to the aromatic protons H^a and the amide protons H^b vary significantly. Although existing D_2-Por*, as represented by **P1**, has a relatively defined configuration that directs the *ortho* chiral amide units toward the center of the porphyrin where Co^{II} is situated, they bear a certain degree of conformational flexibility owing to the existence of rotational freedom between the *meso*-phenyl rings and the porphyrin plane, as well as between the *trans* amides and the cyclopropyl groups. This rotational freedom is manifested by the broad H^a and H^b signals at $\delta = 8.45$ and 6.52 ppm, respectively (Figure 2A). Because of steric effects of CO_2Et, the H^a and H^b signals in **P2** became less broad and shift to the lower field at $\delta = 8.55$ and 6.69 ppm, respectively, (Figure 2B). As a result of the bridging, both H^a ($\delta = 8.41$ ppm) and H^b ($\delta = 6.60$ ppm) signals in **P3** were notably sharpened, signifying the rigidification of the conformational freedom (Figure 2C). Similar, but slightly less sharp were the H^a ($\delta = 8.44$ ppm) and H^b ($\delta =$ 6.66 ppm) signals in **P4**, indicating reduced rigidification in conformation upon elongation of the bridge from C_4 to C_6 (Figure 2D). Consequently, the more rigid conformation in **P3** and **P4** should enhance the hydrogen-bonding capability of the chiral amide units for stabilizing catalytic intermediates.

X-ray diffraction analysis unveiled the structural details of **P3** and **P4**, including the double alkyl bridges and associated dual cavities (Figure 3). The 38- and 42-membered macrocyclic structures in **P3** and **P4**, respectively, created by the double ring-closing olefin metathesis, are bisected by the porphyrin core. In addition to the porphyrin ring, the macrocycles consist of multiple small rings (2 benzenes and 4 cyclopropanes) and functional groups (4 amides and 4

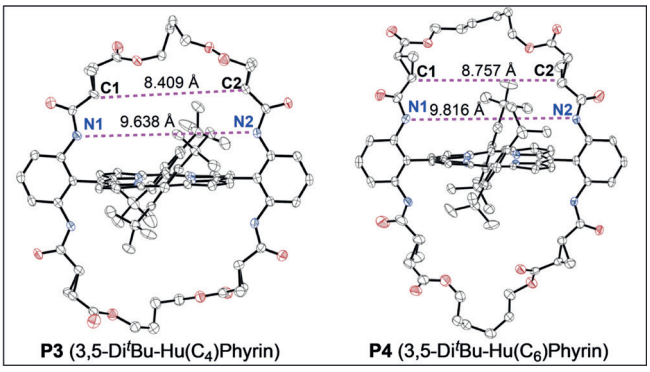
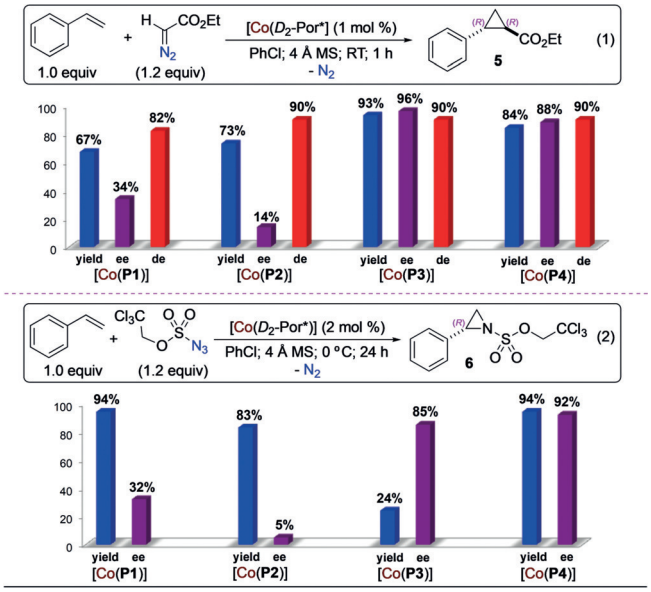


Figure 3. X-ray structures of bridged amidoporphyrins.[17] Thermal ellipsoids are shown at 50% probability. The distances between N1 and N2 and between C1 and C2 are averaged values of those on both sides of the porphyrin plane.

esters). As shown, **P4** contains a significantly larger cavity than **P3**. The observation that the cavity size can be varied by a simple change in the bridge length suggests a new dimension for catalyst engineering.

The bridging effect on the catalytic performance of [Co(D_2-Por*)] was demonstrated with cyclopropanation[13] and aziridination[14] as two model reactions. The catalytic reactions by bridged catalysts [Co(**P3**)] and [Co(**P4**)] were conducted in direct comparison with the open catalysts [Co(**P1**)] and [Co(**P2**)]. Asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA) [Scheme 3, Eq. (1)] was carried out at room temperature using 1 mol% catalyst, in the absence of additives, using the alkene as the limiting reagent and without slow addition of the diazo reagent,[15] a practical condition that is atypical for other catalytic systems. Within only 1 hour, [Co(**P3**)] catalyzed the efficient formation of the cyclopropane **5** in high yield (93%) with high diastereoselectivity (90% *de*) and excellent enantioselectivity



Scheme 3. Bridging effect on Co^{II}-catalyzed radical cyclopropanation and aziridination.

(96% *ee*). By comparing the results with those of [Co(**P1**)][15] and [Co(**P2**)] under the same reaction conditions, it is evident that [Co(**P3**)] is a superior catalyst for the reaction in terms of both reactivity and stereoselectivity, indicating the positive bridging effect on catalytic performance. While [Co(**P4**)] could also catalyze the reaction effectively, it differed in both reactivity (84 versus 93% yield) and enantioselectivity (88 versus 96% *ee*) from [Co(**P3**)]. Enantioselective radical aziridination of styrene with trichloroethoxysulfonyl azide ($TcesN_3$) [Scheme 3, Eq. (2)] was carried out at 0°C for 24 hours with 2 mol% catalyst loading, in the absence of additives, with the alkene as the limiting reagent.[16] While both [Co(**P1**)] and [Co(**P2**)] could generate the desired aziridine **6** in high yields, the enantioselectivities were inferior.[16] Under the same reaction conditions, [Co(**P3**)] resulted in dramatic improvement in enantioselectivity (85% *ee*), but a considerable decrease in reactivity (24% yield). Switching from [Co(**P3**)] to [Co(**P4**)] led to further improvement in enantioselectivity (92% *ee*) while significantly enhancing the reactivity (94% yield). Considering that [Co(**P3**)] and [Co(**P4**)] differ only in the length of the distal bridge by merely two methylene units, the observed ligand effect is truly remarkable and may have an important implication in catalyst design and development.

In summary, we have introduced the new-generation D_2-Por*, containing alkyl bridges across the two chiral amide units on both sides of the porphyrin plane. The bridged D_2-Por* can be efficiently constructed in a modular fashion by a five-step synthesis featuring double ring-closing olefin metathesis in high overall yields. They have more rigid, cavity-like chiral environments, the shape and size of which can be adjusted by variation of the bridge length. As demonstrated with two model reactions, bridged [Co(D_2-Por*)] exhibits notably different catalytic reactivity and stereoselectivity to that of the existing nonbridged catalysts. Furthermore, our results indicate subtle alteration on the distal bridge can have a profound effect on catalytic performance, signifying the importance of cavity manipulation in catalyst engineering. This study opens the door to further applications of Co^{II}-MRC for the development of new stereoselective radical reactions

Acknowledgements

We are grateful for financial support by NIH (R01-GM102554) and in part by NSF (CHE-1624216).

Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral porphyrinoids · cobalt · ligand design · metalloradical catalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2019**, *58*, 2670–2674
Angew. Chem. **2019**, *131*, 2696–2700

[1] D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*, Wiley-VCH, Weinheim, **2008**.

[2] a) M. P. Plesniak, H. M. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 0077; b) N. Kern, M. P. Plesniak, J. J. W. McDouall, D. J. Procter, *Nat. Chem.* **2017**, *9*, 1198; c) F. Dénès, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* **2014**, *114*, 2587; d) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2003**, *103*, 3263; e) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.

[3] a) T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem.* **2014**, *6*, 702; b) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014; c) D. Meyer, P. Renaud, *Angew. Chem. Int. Ed.* **2017**, *56*, 10858; *Angew. Chem.* **2017**, *129*, 10998; d) C. Morrill, C. Jensen, X. Just-Baringo, G. Grogan, N. J. Turner, D. J. Procter, *Angew. Chem. Int. Ed.* **2018**, *57*, 3692; *Angew. Chem.* **2018**, *130*, 3754.

[4] a) H. Miyabe, A. Kawashima, E. Yoshioka, S. Kohtani, *Chem. Eur. J.* **2017**, *23*, 6225; b) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58; *Angew. Chem.* **2016**, *128*, 58; c) H. Pellissier, H. Clavier, *Chem. Rev.* **2014**, *114*, 2775.

[5] a) A. Gansäuer, C.-A. Fan, F. Keller, J. Keil, *J. Am. Chem. Soc.* **2007**, *129*, 3484; b) A. Gansäuer, L. Shi, M. Otte, *J. Am. Chem. Soc.* **2010**, *132*, 11858; c) S. Hildebrandt, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9719; *Angew. Chem.* **2016**, *128*, 9871; d) N. Funken, F. Mühlhaus, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 12030; *Angew. Chem.* **2016**, *128*, 12209; e) Y.-Q. Zhang, E. Vogelsang, Z.-W. Qu, S. Grimme, A. Gansäuer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12654; *Angew. Chem.* **2017**, *129*, 12828.

[6] a) W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2010**, *132*, 10891; b) H. Lu, W. I. Dzik, X. Xu, L. Wojtas, B. de Bruin, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 8518.

[7] a) Y. Chen, K. B. Fields, X. P. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 14718; b) Y. Chen, J. V. Ruppel, X. P. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 12074; c) S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042; d) X. Xu, H. Lu, J. V. Ruppel, X. Cui, S. Lopez de Mesa, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 15292; e) S. Fantauzzi, E. Gallo, E. Rose, N. Raoul, A. Caselli, S. Issa, F. Ragaini, S. Cenini, *Organometallics* **2008**, *27*, 6143; f) Y. Wang, X. Wen, X. Cui, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 1049; g) A. R. Reddy, F. Hao, K. Wu, C.-Y. Zhou, C. M. Che, *Angew. Chem. Int. Ed.* **2016**, *55*, 1810; *Angew. Chem.* **2016**, *128*, 1842; h) A. Chirila, B. G. Das, N. D. Paul, B. de Bruin, *ChemCatChem* **2017**, *9*, 1413; i) S. Roy, S. K. Das, B. Chattopadhyay, *Angew. Chem. Int. Ed.* **2018**, *57*, 2238; *Angew. Chem.* **2018**, *130*, 2260.

[8] V. Lyaskovskyy, A. I. Olivos Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2011**, *133*, 12264.

[9] a) V. Subbarayan, J. V. Ruppel, S. Zhu, J. A. Perman, X. P. Zhang, *Chem. Commun.* **2009**, 4266; b) L.-M. Jin, X. Xu, H. Lu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 5309; *Angew. Chem.* **2013**, *125*, 5417; c) H. Jiang, K. Lang, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9164.

[10] a) Y. Wang, X. Wen, X. Cui, X. P. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 4792; b) A. S. Karns, M. Goswami, B. de Bruin, *Chem. Eur. J.* **2018**, *24*, 5253; c) H. J. Lu, H. L. Jiang, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10192; *Angew. Chem.* **2010**, *122*, 10390; d) O. Villanueva, N. M. Weldy, S. B. Blakey, C. E. MacBeth, *Chem. Sci.* **2015**, *6*, 6672.

[11] a) B. Boitrel, A. Lecas, Z. Renko, E. Rose, *J. Chem. Soc. Chem. Commun.* **1985**, 1820; b) E. Rose, A. Lecas, M. Quelquejeu, A. Kossanyi, B. Boitrel, *Coord. Chem. Rev.* **1998**, *178*, 1407; c) B. Boitrel, V. Baveux-Chambenoît, P. Richard, *Eur. J. Inorg. Chem.* **2002**, 1666; d) P. Even, B. Boitrel, *Coord. Chem. Rev.* **2006**, *250*, 519; e) E. Gallo, E. Rose, B. Boitrel, L. Legnani, L. Toma, *Organometallics* **2014**, *33*, 6081; f) D. M. Carminati, D. Intrieri,

A. Caselli, S. Le Gac, B. Boitrel, L. Toma, L. Legnani, E. Gallo, *Chem. Eur. J.* **2016**, *22*, 13599.
[12] M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2014**, *43*, 1734.
[13] a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977; b) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911.
[14] a) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881; b) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905.
[15] While [Co(**P1**)] was previously demonstrated to be effective for cyclopropanation with different diazo compounds, including *tert*-butyl diazoacetate (*t*-BDA) (Ref [7]), use of the more common ethyl diazoacetate (EDA) was less efficient, even at longer reaction times (20 h) and in the presence of DMAP (0.5 equiv) as an additive, forming cthe yclopropane **5** in 82% yield with 78% *ee* and 94% *de* (Ref [7a]).
[16] The Co^{II} complex of 2,6-DiMeO-ZhuPhyrin was previously reported to catalyze the reaction, but required higher catalyst loading (5 mol%), longer reaction time (48 h), and excess styrene (5 equiv), as well as the use of 5 mol% $Pd(OAc)_2$ as an additive (Ref. [9a]). Under the current more desirable reaction conditions, it only led to aziridine **6** in 10% yield with 80% *ee.*
[17] CCDC 1891454 (**P3**) and 1891455 (**P4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: October 29, 2018
Accepted manuscript online: January 2, 2019
Version of record online: February 4, 2019

