How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 12392–12395
International Edition: doi.org/10.1002/anie.202004243
German Edition: doi.org/10.1002/ange.202004243

Asymmetric Catalysis

Complementing Pyridine-2,6-bis(oxazoline) with Cyclometalated N-Heterocyclic Carbene for Asymmetric Ruthenium Catalysis

*Long Li[+], Feng Han[+], Xin Nie[+], Yubiao Hong, Sergei Ivlev, and Eric Meggers**

In memory of Rolf Huisgen

Abstract: *A strategy for expanding the utility of chiral pyridine-2,6-bis(oxazoline) (pybox) ligands for asymmetric transition metal catalysis is introduced by adding a bidentate ligand to modulate the electronic properties and asymmetric induction. Specifically, a ruthenium(II) pybox fragment is combined with a cyclometalated N-heterocyclic carbene (NHC) ligand to generate catalysts for enantioselective transition metal nitrenoid chemistry, including ring contraction to chiral 2H-azirines (up to 97% ee with 2000 TON) and enantioselective C(sp^3)–H aminations (up to 97% ee with 50 TON).*

The demand for enantiopure chiral molecules in the chemical and pharmaceutical industry leads to a continued quest for efficient chiral metal catalysts for a wide variety of chemical transformations.[1] Typically, chiral ligands serve as the basis for the design of nonracemic chiral metal catalysts and a number of especially versatile chiral ligand families have been dubbed "privileged ligands".[2]

Pyridine-2,6-bis(oxazolines) (pybox), first reported by Nishiyama in 1989,[3] constitute a highly popular class of chiral ligands for asymmetric transition metal catalysis (Figure 1 a).[4] Their chirality stems from readily available chiral 2-amino alcohols and they serve as strongly coordinating tridentate ligands for a large variety of transition metals including lanthanides and actinides. The C_2 symmetry of the pybox ligand is desirable since it reduces the number of stereoisomers after substrate coordination and transition states during catalysis and leads to satisfactory enantioselectivities for many transformations. Conveniently, the pybox ligand is simply reacted with a metal salt of the organometallic precursor complex, often even in situ in the reaction mixture. However, the pybox ligand has a severe limitation, namely the fixation to three imine coordinating groups which, due to their significant π-backbonding properties, lead to a reduced electron density at the central metal. This may be desired for Lewis acid catalysis but not for transformations in which a higher electron density at the metal center is beneficial.

Here we introduce a strategy to increase the utility of chiral pybox metal complexes for asymmetric catalysis by complementing pybox with a cyclometalated ligand. Specifically, the addition of a cyclometalated N-heterocyclic carbene (NHC) ligand to a ruthenium pybox complex results in a strong modulation of the catalytic properties (Figure 1 b). This is demonstrated for the enantioselective isomerization of isoxazoles to chiral 2*H*-azirines with up to 97% *ee* and up to 2000 TON and for two enantioselective C(sp^3)–H amination reactions with up to 97% *ee* and 50 TON (Figure 1 c).

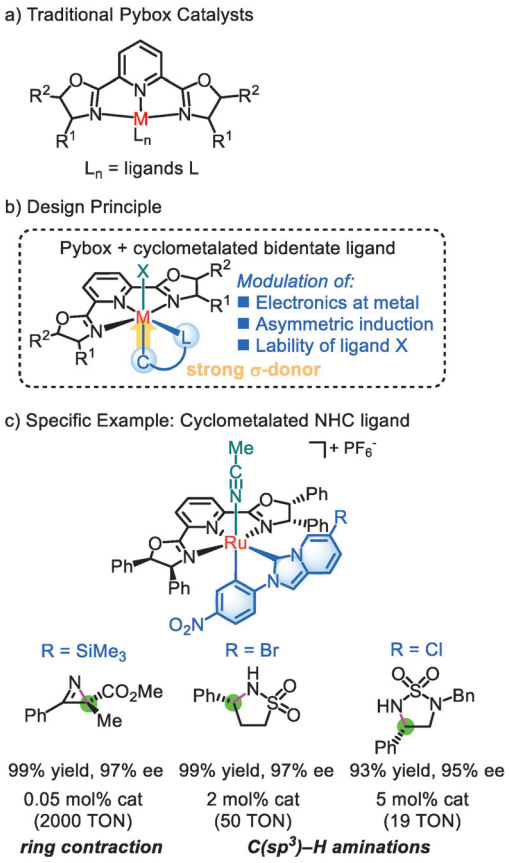
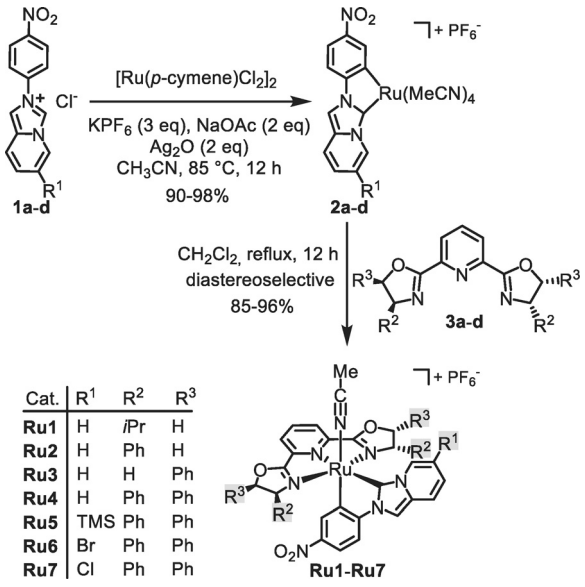


Figure 1. Chiral pybox metal complexes: Standard complexes, design principle of this study, and realization.

[*] Dr. L. Li,[+] F. Han,[+] X. Nie,[+] Y. Hong, Dr. S. Ivlev, Prof. Dr. E. Meggers
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Straße 4, 35043 Marburg (Germany)
E-mail: meggers@chemie.uni-marburg.de
[+] 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.202004988.

We commenced our study with the objective to design novel chiral ruthenium catalysts by complementing the established pybox ligand with a strongly electron-donating bidentate ligand. Ruthenium has been proven to show highly versatile catalytic properties in many complexes but is significantly less expensive than other platinum-group members.[5] Furthermore, important for this study, many synthetic methods exist for a controlled stepwise incorporation of ligands into the coordination sphere of ruthenium complexes. Thus, we started with the ruthenium precursor complex $[Ru(p\text{-cymene})Cl_2]_2$ and reacted it with the imidazolium salts **1a–d** to obtain the Ru complexes **2a–d** in 90–98% yield, in which ruthenium is cyclometalated with an *N*-(4-nitrophenyl)imidazo[1,5-*a*]pyridine ligand together with four labile acetonitrile ligands (Scheme 1).[6] Since cyclometalated ligands with ruthenium tend to be unstable, we incorporated a nitro group into the phenyl moiety. Reaction of **2a–d** with pybox ligands **3a–d** provided the ruthenium pybox complexes **Ru1**–**Ru7** as single diastereomers and single enantiomers in 85–96% yield (see the Supporting Information for more details). In these complexes, ruthenium coordinates to pybox in a meridional tridentate fashion, is additionally cyclometalated to an imidazo[1,5-*a*]pyridine ligand, and contains one acetonitrile ligand. The cyclometalated NHC ligand is highly electron-donating and should change the electronic properties of the metal center significantly. Furthermore, the phenyl moiety with its strong σ-donating ability is oriented *trans* to the acetonitrile ligand and should lead to a significant labilization due to the kinetic *trans* effect. A crystal structure of **Ru4** is shown in Figure 2 and confirms this *trans* effect[7] with an elongated Ru–N bond to the coordinated acetonitrile (Ru2–N8 = 2.165 Å).

Next, we investigated the catalytic properties of these new types of ruthenium pybox complexes and found that they are excellent catalysts for the ring contraction of isoxazoles to chiral 2*H*-azirines.[8] Starting with **Ru1** (1 mol%), in which the oxazolines bear an isopropyl group at the 4-position in a *S*-



Cat.	R^1	R^2	R^3
Ru1	H	*i*Pr	H
Ru2	H	Ph	H
Ru3	H	H	Ph
Ru4	H	Ph	Ph
Ru5	TMS	Ph	Ph
Ru6	Br	Ph	Ph
Ru7	Cl	Ph	Ph

Scheme 1. Catalyst synthesis.

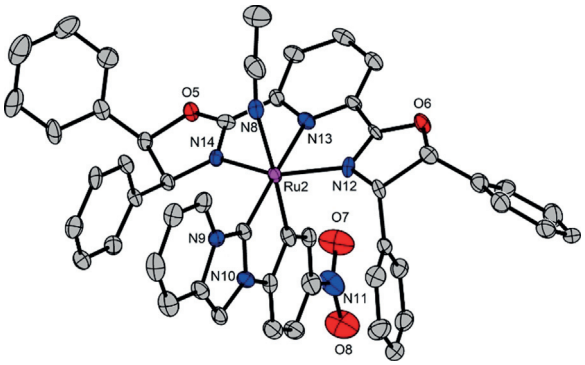
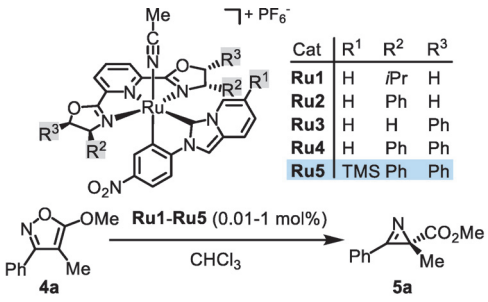


Figure 2. X-ray crystal structure of *rac*-**Ru4**. Only one enantiomer is shown.[21] The hexafluorophosphate anion is omitted for clarity.

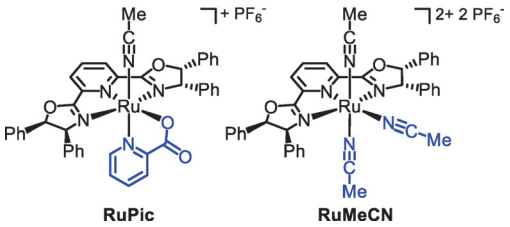
configuration, isoxazole **1** was smoothly converted into 2*H*-azirine **2** within 15 min in 95% yield as determined by NMR analysis, but with a low enantioselectivity of 32% *ee* (Table 1, entry 1). Replacing the isopropyl with a phenyl group (**Ru2**) resulted in an improved 58% *ee*. Moving the phenyl moiety to the 5-position (**Ru3**) resulted in a reduced *ee* of 33%. However, **Ru4** bearing phenyl moieties in both the 4- and 5-position provided an increased 74% *ee*. Gratifyingly, when we further added a trimethylsilyl (TMS) group at the 3-position of the imidazo[1,5-*a*]pyridine ligand, the *ee* value improved to excellent 97% (entry 5). Reducing the catalyst loading to 0.5 mol% did not affect the enantioselectivity (entry 6). A further reduction to 0.1 mol% also resulted in an unchanged 97% *ee* when the concentration was increased and the temperature raised to 30 °C in order to speed up the reaction (entry 7). Even at 0.05 mol% **Ru5** full conversion was achieved within 3 hours with 97% *ee* (entry 8). However, at a further reduced catalyst loading of 0.01 mol%, the reaction proceeds sluggishly with a reduced yield of 73% (7300 TON) but still respectable 90% *ee* (entry 9). For comparison, catalysts bearing a picolinate[9] (**RuPic**, entry 10) or two acetonitriles (**RuMeCN**, entry 11) instead of the cyclometalated NHC displayed only very low catalytic activity with no enantioselectivity, thus demonstrating the crucial role of the cyclometalated NHC ligand for both catalytic activity and asymmetric induction. A substrate scope is shown in Figure 3 and demonstrates the excellent suitability of **Ru5** for the catalytic enantioselective ring contraction to chiral 2*H*-azirines.

The transition metal catalyzed enantioselective ring contraction of isoxazoles to chiral 2*H*-azirines is reported to proceed through a transition metal nitrenoid intermediate.[7] We therefore wondered whether our cyclometalated ruthenium pybox catalyst system is applicable to other nitrenoid chemistry. Of particular current interest are enantioselective aminations of $C(sp^3)$–H bonds.[10,11] Indeed, we found that catalyst **Ru5** smoothly cyclizes the sulfonyl azide **6** to provide the corresponding cyclic sulfonylamide (*R*)-**7** in 99% yield and with 90% *ee*.[12] **Ru5** can also catalyze the $C(sp^3)$–H amination of the sulfamyl azide **8** to provide the cyclic sulfamide (*S*)-**9**, a useful precursor for chiral 1,2-diamines,[13] but only in 75% yield and with merely 70% *ee*. However, Figure 4 demonstrates that the catalytic performance can be

Table 1: Initial experiments and optimization of reaction conditions.[a]



Catalysts for Comparison:



Entry	Cat.	Loading [mol%]	Conc. [mol L^{-1}]	*T* [°C]	*T* [h]	Yield [%][b]	*ee* [%][c]
1	**Ru1**	1.0	0.05	r.t.	0.25	95	32
2	**Ru2**	1.0	0.05	r.t.	0.25	99	58
3	**Ru3**	1.0	0.05	r.t.	0.25	99	33
4	**Ru4**	1.0	0.05	r.t.	0.25	99	74
5	**Ru5**	1.0	0.05	r.t.	0.5	99	97
6	**Ru5**	0.5	0.05	r.t.	4	99	97
7	**Ru5**	0.1	1.0	30	3	99	97
8	**Ru5**	0.05	1.0	30	3	99	97
9	**Ru5**	0.01	4.0	40	3	73	90
10	**RuPic**	1.0	0.05	50	24	30	0
11	**RuMeCN**	1.0	0.05	50	24	20	0

[a] Reaction conditions: Substrate **4a** (0.1 mmol) in $CHCl_3$ (0.05–04 M) with **Ru5** (0.01–1 mol%) was stirred at the indicated temperature and time under an atmosphere of air. [b] ^{1}H NMR yields using 1,2,3-trimethoxybenzene as internal standard. [c] *ee* values determined by HPLC on a chiral stationary phase.

adjusted simply by changing the substituent at the 3-position of the imidazo[1,5-*a*]pyridine ligand. Accordingly, whereas a TMS group (**Ru5**) affords the best result for the ring contraction, a bromine (**Ru6**) provides a superior result for the C(sp^3)–H amination to the cyclic sulfonylamide (99% yield, 97% *ee*), and a chlorine (**Ru7**) provides the best yield and enantioselectivity for the C(sp^3)–H amination of the cyclic sulfamide (93% yield, 95% *ee*).[14] The enantioselective C(sp^3)–H amination of sulfonyl azides and sulfamyl azides was recently reported by Zhang and co-workers but relied on a synthetically complicated chiral cobalt porphyrin system.[12,13,15] In contrast, the cyclometalated ruthenium pybox catalyst system is easy to synthesize and can be modulated in its catalytic properties in a straightforward fashion. There is no precedent for using chiral Ru-pybox catalysts for enantioselective C(sp^3)–H aminations of organic azides.[16]

The strategy presented here to complement the widely used pybox ligand with an electron-donating cyclometalated ligand should be applicable to other privileged chiral ligands.[2] In fact, Krische recently introduced a novel chiral

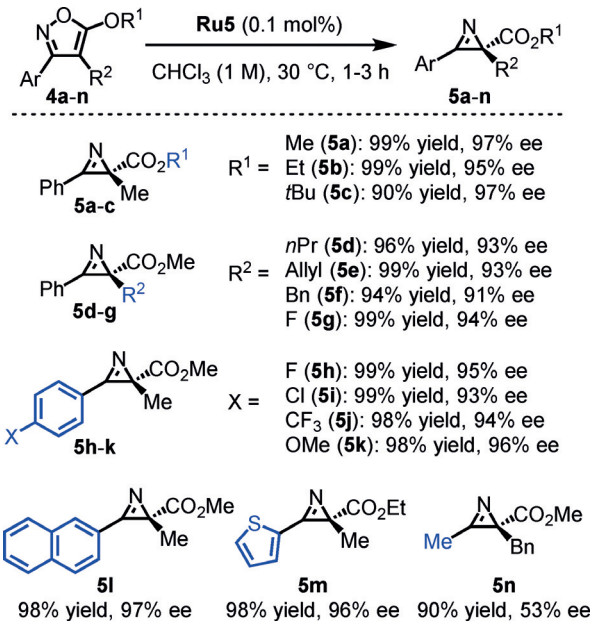


Figure 3. Substrate scope for the enantioselective ring contraction of isoxazoles to give chiral 2*H*-azirines.

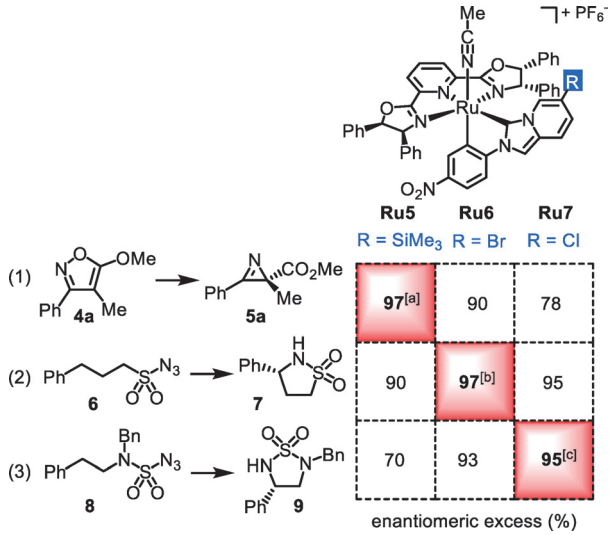


Figure 4. Reaction matrix for three different reactions and three catalyst derivatives. Conditions for reaction 1: 0.1 mol% cat., $CHCl_3$, 30°C, 1 h. Conditions for reaction 2: 2 mol% cat., DCE, 40°C, 20 h. Conditions for reaction 3: 5 mol% cat., DCE, 50°C, 48 h. [a] 99% yield. [b] 99% yield. [c] 93% yield.

iridium catalyst scaffold in which the axially chiral BINAP ligand or one of its derivatives is complemented with an *ortho*-cyclometalated C,O-benzoate ligand to provide uniquely effective catalytic activity for a variety of asymmetric C–C bond formations via hydrogen transfer processes.[17]

It is also worthwhile to take a closer look at the stereochemical environment around the central ruthenium atom. Formally the ruthenium is not a stereogenic center due to the identical absolute configurations of the two oxazoline moieties. However, due to the fixed conformations of the two oxazoline moieties within the meridional tridentate coordination, the ruthenium center is in fact equivalent to a stereo-

genic center and one might call it a "pseudo-stereogenic metal center".[18]

In conclusion, we have introduced a very simple but highly effective strategy to design new chiral transition metal catalysts by adding a cyclometalated *N*-(4-nitrophenyl)-imidazo[1,5-*a*]pyridine ligand to a C_2-symmetric chiral ruthenium pyridine-2,6-bis(oxazoline) complex.[19,20] The cyclometalated ligand strongly modulates the catalytic activity of the ruthenium center and at the same time plays an important role in the asymmetric induction. This was demonstrated for a ring contraction to provide chiral 2*H*-azirines (up to 97% *ee* with 2000 TON) and for enantioselective C(sp^3)–H aminations of a sulfonyl and sulfamyl azide (up to 97% *ee* with 50 TON). We are currently exploring other applications of cyclometalated Ru-pybox catalysts.

Acknowledgements

Funding from the Deutsche Forschungsgemeinschaft is gratefully acknowledged (ME 1805/15-1).

Conflict of interest

The authors declare no conflict of interest.

Keywords: 2*H*-azirines · asymmetric catalysis · C(sp^3)–H amination · cyclometalations · pybox · ruthenium

[1] P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, Sausalito, California, **2009**.
[2] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691 – 1693.
[3] H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846 – 848.
[4] G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119 – 3154.
[5] "Ruthenium in Catalysis": in *Top. Organomet. Chem.*, *Vol. 48* (Eds.: P. H. Dixneuf, C. Bruneau), Springer, Berlin, Heidelberg, **2014**, pp. 1 – 401.
[6] For examples of ruthenium complexes with cyclometalated NHC ligands, see: a) C. Zhang, Y. Zhao, B. Li, H. Song, S. Xu, B. Wang, *Dalton Trans.* **2009**, 5182 – 5189; b) C. Zhang, B. Li, H. Song, S. Xu, B. Wang, *Organometallics* **2011**, *30*, 3029 – 3036; c) S. Aghazada, I. Zimmermann, V. Scutelnic, M. K. Nazeeruddin, *Organometallics* **2017**, *36*, 2397 – 2403; d) D. Schleicher, H. Leopold, H. Borrmann, T. Strassner, *Inorg. Chem.* **2017**, *56*, 7217 – 7229; e) D. Schleicher, H. Leopold, T. Strassner, *J. Organomet. Chem.* **2017**, *829*, 101 – 107; f) S. Bauri, S. N. R. Donthireddy, P. M. Illam, A. Rit, *Inorg. Chem.* **2018**, *57*, 14582 – 14593; g) Z.-Q. Wang, X.-S. Tang, Z.-Q. Yang, B.-Y. Yu, H.-J. Wang, W. Sang, Y. Yuan, C. Chen, F. Verpoort, *Chem. Commun.* **2019**, *55*, 8591 – 8594; h) Z. Zhou, S. Chen, Y. Hong, E. Winterling, Y. Tan, M. Hemming, K. Harms, K. N. Houk, E. Meggers, *J. Am. Chem. Soc.* **2019**, *141*, 19048 – 19057.
[7] J. B. Coe, S. J. Glenwright, *Coord. Chem. Rev.* **2000**, *203*, 5 – 80.
[8] K. Okamoto, A. Nanya, A. Eguchi, K. Ohe, *Angew. Chem. Int. Ed.* **2018**, *57*, 1039 – 1043; *Angew. Chem.* **2018**, *130*, 1051 – 1055.
[9] M. K. Tse, H. Jiao, G. Anilkumar, B. Bitterlich, F. G. Gelalcha, M. Beller, *J. Organomet. Chem.* **2006**, *691*, 4419 – 4433.
[10] a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061 – 5074; b) D. Hazelard, P.-A. Nocquet, P. Compain, *Org. Chem. Front.* **2017**, *4*, 2500 – 2521; c) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247 – 9301.
[11] For pioneering work on ruthenium–nitrenoid mediated C–H aminations, see: a) S.-M. Au, S.-B. Zhang, W.-H. Fung, W.-Y. Yu, C.-M. Che, K.-K. Cheung, *Chem. Commun.* **1998**, 2677 – 2678; b) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung, C.-M. Che, *J. Am. Chem. Soc.* **1999**, *121*, 9120 – 9132; c) X.-G. Zhou, X.-Q. Yu, J.-S. Huang, C.-M. Che, *Chem. Commun.* **1999**, 2377 – 2378.
[12] Y. Hu, K. Lang, C. Li, J. B. Gill, I. Kim, H. Lu, K. B. Fields, M. Marshall, Q. Cheng, X. Cui, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 18160 – 18169.
[13] K. Lang, S. Torker, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 12388 – 12396.
[14] It is worth noting that the catalysts **RuPic** and **RuMeCN** provide the C–H amination products **7** and **9** only in low yields of < 20% and without any enantioselectivity. See the Supporting Information for more details.
[15] For pioneering work, see also: M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 9884 – 9887; *Angew. Chem.* **2011**, *123*, 10058 – 10061.
[16] a) S.-B. Park, H. Nishiyama, Y. Itoh, K. Itoh, *J. Chem. Soc. Chem. Commun.* **1994**, 1315 – 1316; b) N. Hisao, I. Yoshiki, S. Yuji, M. Hideki, A. Katsuyuki, I. Kenji, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247 – 1262; c) S.-B. Park, N. Sakata, H. Nishiyama, *Chem. Eur. J.* **1996**, *2*, 303 – 306; d) H. Nishiyama, Y. Motoyama, *Chem. Commun.* **1997**, 1863 – 1864; e) M. K. Tse, S. Bhor, M. Klawonn, C. Döbler, M. Beller, *Tetrahedron Lett.* **2003**, *44*, 7479 – 7483; f) S. Bhor, M. K. Tse, M. Klawonn, C. Döbler, W. Mägerlein, M. Beller, *Adv. Synth. Catal.* **2004**, *346*, 263 – 267; g) D. Cuervo, M. P. Gamasa, J. Gimeno, *Chem. Eur. J.* **2004**, *10*, 425 – 432; h) M. K. Tse, C. Döbler, S. Bhor, M. Klawonn, W. Mägerlein, H. Hugl, M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 5255 – 5260; *Angew. Chem.* **2004**, *116*, 5367 – 5372; i) M. K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, C. Döbler, A. Spannenberg, W. Mägerlein, H. Hugl, M. Beller, *Chem. Eur. J.* **2006**, *12*, 1855 – 1874; j) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem. Int. Ed.* **2008**, *47*, 6825 – 6828; *Angew. Chem.* **2008**, *120*, 6931 – 6934; k) E. Menéndez-Pedregal, M. Vaquero, E. Lastra, P. Gamasa, A. Pizzano, *Chem. Eur. J.* **2015**, *21*, 549 – 553; l) F. Zhong, A. Pöthig, T. Bach, *Chem. Eur. J.* **2015**, *21*, 10310 – 10313; m) E. de Julián, E. Menéndez-Pedregal, M. Claros, M. Vaquero, J. Díez, E. Lastra, P. Gamasa, A. Pizzano, *Org. Chem. Front.* **2018**, *5*, 841 – 849.
[17] a) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891 – 14899; b) S. W. Kim, W. Zhang, M. J. Krische, *Acc. Chem. Res.* **2017**, *50*, 2371 – 2380.
[18] This should not be confused with the concept of a "pseudo-asymmetric carbon atoms" within organic *meso* compounds.
[19] For a recent example of a cyclometalated ruthenium catalyst, see: M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nat. Chem.* **2018**, *10*, 724 – 731.
[20] For a recently reported cyclometalated ruthenium pincer complexes as a new class of catalysts for the α-alkylation of ketones with alcohols, see: P. Piehl, R. Amuso, E. Alberico, H. Junge, B. Gabriele, H. Neumann, M. Beller, *Chem. Eur. J.* **2020**, *26*, 6050 – 6055.
[21] CCDC 1991204 (*rac*-**Ru4**) contains the supplementary crystallographic data for this paper. These data are provided free of charge from Cambridge Crystallographic Data Centre.

Manuscript received: March 23, 2020
Accepted manuscript online: May 12, 2020
Version of record online: June 5, 2020

