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

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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(sp³)–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. 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.”

Pyridine-2,6-bis(oxazolines) (pybox), first reported by Nishiyama in 1989, constitute a highly popular class of chiral ligands for asymmetric transition metal catalysis. 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 C₂ 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. This is demonstrated for the enantioselective isomerization of isoxazoles to chiral 2H-azirines with up to 97% ee and up to 2000 TON and for two enantioselective C(sp³)–H amination reactions with up to 97% ee and 50 TON.
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-cymene)Cl]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). 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 η-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 2H-azirines.[8] Starting with Ru1 (1 mol%), in which the oxazolines bear an isopropyl group at the 4-position in a S-configuration, isoxazole 1 was smoothly converted into 2H-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 2H-azirines.

The transition metal catalyzed enantioselective ring contraction of isoxazoles to chiral 2H-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(sp2)–H bonds.[10,11] Indeed, we found that catalyst Ru5 smoothly cyclizes the sulfamyl azide 6 to provide the corresponding cyclic sulfonamidate (R)-7 in 99% yield and with 90% ee.[12] Ru5 can also catalyze the C(sp2)–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
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)/C0H amination to the cyclic sulfamide (99% yield, 97% ee), and a chlorine (Ru7) provides the best yield and enantioselectivity for the C(sp^3)/C0H amination of the cyclic sulfamide (93% yield, 95% ee).[14] The enantioselective C(sp^3)/C0H 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)/C0H 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 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-

### Table 1: Initial experiments and optimization of reaction conditions.[4]

| Entry | Cat. | Loading [mol%] | Conc. [mol L^{-1}] | T [°C] | T [h] | Yield [%] | ee [%] |
|-------|------|----------------|--------------------|--------|-------|-----------|--------|
| 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 CHCl₃ (0.05–0.4 mL) with Ru5 (0.01–1 mol%) was stirred at the indicated temperature and time under an atmosphere of air. [b] ^1H NMR yields using 1,2,3-trimethoxybenzene as internal standard. [c] ee values determined by HPLC on a chiral stationary phase.

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

Figure 4. Reaction matrix for three different reactions and three catalyst derivatives. Conditions for reaction 1: 0.1 mol% cat., CHCl₃, 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.
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Conflict of interest

The authors declare no conflict of interest.

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[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. Bormann, 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. Dhondthreedi, 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. Meeggers, 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. Nanyo, A. Eguchi, K. Ohie, 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. Nocqet, P. Compain, Org. Chem. Front. 2017, 4, 2500–2521; c) Y. Park, Y. Kim, S. Chang, Chem. Rev. 2017, 117, 9247–9301.
[11] a) S.-B. Park, H. Nishiyama, Y. Itoh, K. Itoh, J. Am. Chem. Soc. 1994, 116, 1315–1316; b) C.-G. Hiroshi, I. Yoshiki, S. Yui, M. Hideo, A. Katsuaki, 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. Dobler, M. Beller, Tetrahedron Lett. 2003, 44, 7479–7483; f) S. Bhor, M. K. Tse, M. Klawonn, C. Dobler, W. Mayerle, 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. Dobler, S. Bhor, M. Klawonn, W. Mayerle, 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. Dobler, A. Spannenberg, W. Mayerle, H. Hugl, M. Beller, Chem. Eur. J. 2006, 12, 1855–1874; j) E. Mileczek, N. Boudet, S. Blayke, Angew. Chem. Int. Ed. 2008, 47, 6825–6828; Angew. Chem. 2008, 120, 6031–6034; k) E. Menéndez-Pedregal, M. Vaquero, E. Lastra, P. Gamasa, A. Pizzano, Chem. Eur. J. 2015, 21, 549–553; l) F. Zhong, A. Poóth, 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.
[12] a) I. S. Kim, M.-Y. Nam, 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.
[13] This should not be confused with the concept of a “pseudo-asymmetric carbon atoms” within organic meso compounds.
[14] For a recent example of a cyclometalated ruthenium catalyst, see: M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, Chem. Eur. J. 2018, 24, 724–731.
[15] 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, 6090–6095.
[16] CCDC 1991204 (rac-Ru4) contains the supplementary crystallographic data for this paper. These data are provided free of charge from Cambridge Crystallographic Data Centre.