

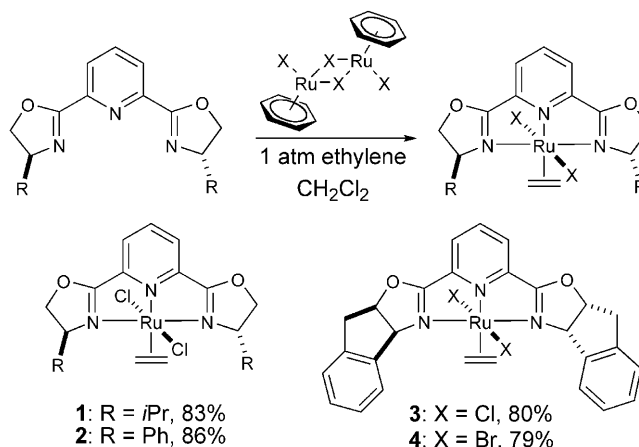
Enantioselective C–H Amination Using Cationic Ruthenium(II)–pybox Catalysts**

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C–H bond amination has emerged as a powerful tool for the synthesis of complex nitrogen-containing molecules. Following the early discoveries by Breslow and Gellman,^[1] Du Bois and co-workers revolutionized this area of chemistry by developing protocols for practical, efficient, and predictable reactions for oxidative C–H amination.^[2] Dirhodium(II) tetracarboxylate catalysts were shown to be particularly effective. Manganese- and ruthenium-porphyrin complexes,^[3] silver complexes,^[4] and preoxidized nitrogen sources have also been developed as catalysts to carry out this important reaction.^[5]

Despite these recent advances, general methods for both enantioselective and intermolecular C–H amination remain elusive. Although chiral dirhodium(II) complexes have been developed as catalysts for highly enantioselective metal-carbene reactions,^[6] their application to C–H amination chemistry is yet to produce the same spectacular results.^[7] To date, the most effective protocol for asymmetric C–H amination requires the combination of enantioenriched sulfoxamines as chiral auxiliaries and a chiral dirhodium(II) catalyst.^[8] To address the challenge of catalytic asymmetric C–H amination, we chose to study ruthenium(II)–pybox (pybox = pyridine bisoxazoline) complexes (Scheme 1). Despite reports that show complex **1** exhibited limited reactivity and selectivity in C–H amination reactions,^[3f] we felt that the modular nature of the ligand, and the fact that the anionic ligands were independent of the chiral pybox ligand, offered us an opportunity which had not been possible by using either dirhodium(II)- or porphyrin-based catalyst systems.

Ruthenium(II)–pybox complexes **1–4** were readily prepared by using the method developed by Nishiyama et al. (Scheme 1).^[9] In our initial study, the challenging test substrate sulfamate ester **5**^[10] was treated with 1.1 equivalents of the oxidant bis(acetoxy)iodobenzene and 5 mol % catalyst **2** to give the desired product of C–H insertion **6**, albeit in modest yield and enantiomeric excess (Table 1, entries 1–3).



Scheme 1. Synthesis of ruthenium(II)–pybox complexes.

Based on the study by Fiori and Du Bois, which demonstrates that rhodium-catalyzed C–H amination involves formation of an electrophilic metallonitrene and a build up of positive charge on the carbon center during the insertion process, we rationalized that a cationic catalyst would be more reactive than its neutral analogue.^[2e] Halide abstraction from the

Table 1: Reaction optimization studies.

Entry	Solvent	Additive ^[a]	Catalyst	Yield [%] ^[b]	ee [%] ^[b]
1	CH ₂ Cl ₂	–	2	50	24
2	C ₆ H ₆	–	2	47	26
3	Et ₂ O	–	2	33	43
4	CH ₂ Cl ₂	AgOTf	2	61	53
5	C ₆ H ₆	AgOTf	2	49	70
6	Et ₂ O	AgOTf	2	42	77
7	CH ₂ Cl ₂	AgOTf	3	94	69
8	C ₆ H ₆	AgOTf	3	45	84
9	Et ₂ O	AgOTf	3	40	84
10 ^[c,d]	CH ₂ Cl ₂	AgOTf	3	98	61
11 ^[c,d]	C ₆ H ₆	AgOTf	3	84	76
12 ^[c,d]	Et ₂ O	AgOTf	3	58	81
13 ^[c,d]	C ₆ H ₆	AgOTf	4	93	80
14 ^[c,e]	C ₆ H ₆	AgOTf	4	84	84

[a] 5 mol % additive used; Tf = trifluoromethanesulfonyl. [b] The yields and ee values were determined by HPLC on a chiral stationary phase. [c] PhI(O₂CtBu)₂ was used in place of PhI(OAc)₂. [d] Reaction conducted at 22 °C. [e] Reaction conducted at 4 °C.

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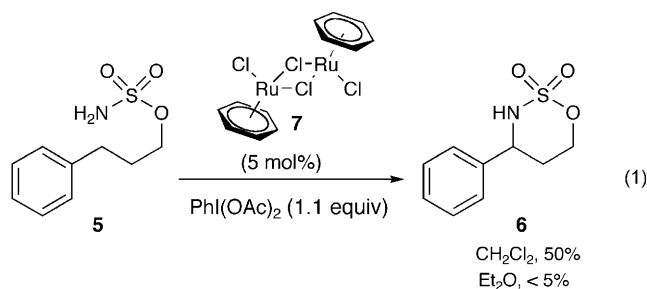
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parent ruthenium(II)–pybox complex **2** using AgOTf gave improved yields and selectivities in the solvents studied (Table 1, entries 4–6). Other silver salts with noncoordinating counterions (AgBF₄, AgSbF₆, AgPF₆, AgBARF₄) all gave similar results. However, silver salts with coordinating counterions (AgOAc and AgOCOCF₃) were not effective.

The rigid indenyl-pybox ligand provided catalyst **3** which showed improved conversion (94 % yield in CH₂Cl₂; Table 1, entry 7) and selectivity (84 % *ee*; Table 1, entries 8 and 9). By employing a more soluble oxidant (PhI(O₂CtBu)₂) the reaction could be conducted at room temperature and the yields of the amination product improved (Table 1, entries 10–12). However, despite the lower reaction temperature, a small decrease in enantioselectivity was observed. The tunability of the [RuX₂L(pybox)] catalyst framework is demonstrated by the effects of replacing the chloride ligands (**3**) with bromide (**4**). This change increased both the turnover and selectivity, as well as allowing the reaction temperature to be lowered to 4 °C, thus producing the desired C–H amination product in good yield (84 %) and enantioselectivity (84 % *ee*; Table 1, entry 14).

Several trends were observed in the optimization studies. Reactions conducted in CH₂Cl₂ had the highest yields but the lowest enantioselectivities, while reactions conducted in Et₂O had the best enantioselectivities but the lowest yields. A control experiment revealed that the Ru^{II} complex **7** was a competent catalyst for the C–H amination reaction in CH₂Cl₂ but was not effective in Et₂O [Eq. (1)]. This observation led



us to speculate that the poor enantioselectivities in CH₂Cl₂ may arise from a catalytically active ruthenium species that is released from the chiral pybox ligand. However, attempts to improve the enantioselectivities in CH₂Cl₂ by conducting the reaction in the presence of excess ligand led only to lower yields. No improvement in the selectivity was observed.

The optimized reaction conditions allow asymmetric C–H amination of substrates with benzylic and allylic C–H bonds (Table 2). Both electron-donating and electron-withdrawing substituents are tolerated on the aryl ring, and the products are obtained with good yields and excellent enantioselectivities (88–92 % *ee*; Table 2, entries 1–5). Notably, the catalyst performs well on the *ortho*-substituted substrate **8**, with the C–H insertion reaction proceeding in 71 % yield and 88 % *ee* (Table 2, entry 2). This observation is in stark contrast to the significant drop in reactivity seen when these substrates are exposed to porphyrin-based Ru^{II} catalysts.^[11] Additionally, excellent enantioselectivity is observed for the insertion

Table 2: Asymmetric amination of benzylic and allylic C–H bonds.

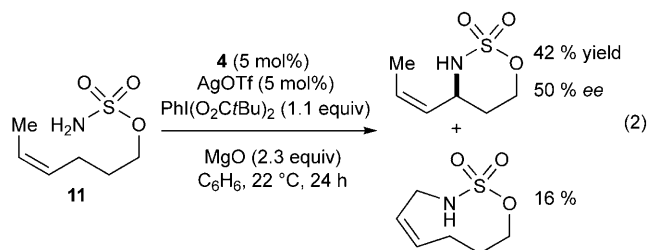
<div>4 (5 mol%), AgOTf (5 mol%) PhI(O₂CtBu)₂ (1.1 equiv) MgO (2.3 equiv) C₆H₆, 22 °C, 24 h</div>				
Entry	Substrate	Product	Yield [%] ^[a]	ee [%] ^[b]
1 ^[c]			68	90
2			71	88
3 ^[c]			60	88 ^[d]
4 ^[e]			56	80
5			58	92
6			60	89
7			42	75
8			14	n.d.

[a] Yield of isolated product. [b] The *ee* values were determined by HPLC on a chiral stationary phase. [c] Reaction conducted at 4 °C. [d] The absolute configuration determined by X-ray crystallography; other configurations assigned by analogy. [e] After 16 h, additional catalyst (5 mol %), AgOTf (5 mol %), and PhI(O₂CtBu)₂ were added. Boc = *tert*-butoxycarbonyl, n.d. = not determined.

reaction of indole **9** (92 % *ee*; Table 2, entry 5) as well as in the allylic amination of **10** (89 % *ee*; Table 2, entry 6).

The allylic amination reaction proceeds with complete selectivity for the C–H insertion product. Under our reaction conditions, we have not observed the competing aziridination product, which is commonly generated when dirhodium(II)

tetracarboxylate catalysts are used.^[12] The preference for C–H insertion exhibited by the cationic ruthenium(II)–pybox system is further highlighted by the reaction of *cis*-olefin **11** [Eq. (2)]. Under the standard reaction conditions, six- and



nine-membered-ring products (resulting from C–H insertion reactions) are produced, but no aziridination product was observed. Although this substrate highlights the remarkable chemoselectivity profile of this catalyst, the *cis* substituent on the double bond disrupts the transition state and leads to significantly lower enantioselectivity (50% *ee*).

The standard reaction conditions are capable of promoting C–H insertion reactions to form five-membered rings (Table 2, entry 7), but they are ineffective for the amination of straight-chain aliphatic substrates (Table 2, entry 8).

In considering the mechanism of this reaction, we note that the five-coordinate [RuCl₂(indenyl-pybox)] complex, which lacks the ethylene ligand, leads to a lower yield and selectivity with the test substrate **5** (32%, 59% *ee*; compare with Table 3, entry 5). This observation suggests that the ethylene group in catalyst **4** might remain bound to the ruthenium center during the amination reaction, and therefore prompted us to further examine the role of this ancillary ligand.^[13]

Unfortunately, our attempts to replace the ethylene ligand in catalyst **4** with alternative olefins, such as *trans*-2-butene or *trans*-cyclooctene, were not successful, presumably because of the steric hindrance imparted by both the indenyl-pybox and bromide ligands.^[14] However, we were able to synthesize complexes **12** and **13** in which the olefin was replaced by carbon monoxide and triphenylphosphine, respectively (Table 3). When these new catalysts were tested under the optimized reaction conditions we observed that the ancillary ligand had an impact on the catalyst turnover number (TON); however, the enantioselectivities were identical (within error; Table 3, entries 1–3). These data indicate that while the nature of the ancillary ligand is important for accessing the active catalyst, in all likelihood the ancillary ligand dissociates before C–H amination takes place and therefore the active aminating species is identical for all three catalysts.

Based on these data that indicates the necessity of removing a halide ion from the Ru^{II} complex to achieve good TON and selectivity as well as the studies of Che and co-workers that show that the active aminating species in ruthenium porphyrin complexes are bisimido–ruthenium(VI) compounds,^[3b,e] we propose that a C₂-symmetric cationic bisimido–ruthenium(VI) complex (**14**) is the active species for the reaction conditions outlined in this study (Figure 1).

Table 3: Effect of the ancillary ligand on catalyst performance.

4: L = C₂H₄
12: L = CO
13: L = PPh₃

Entry	Catalyst	Yield [%] ^[a]	<i>ee</i> [%] ^[a]
1	4	84	84
2	12	62	83
3	13	80	82

[a] The yields and *ee* values were determined by HPLC on a chiral stationary phase.

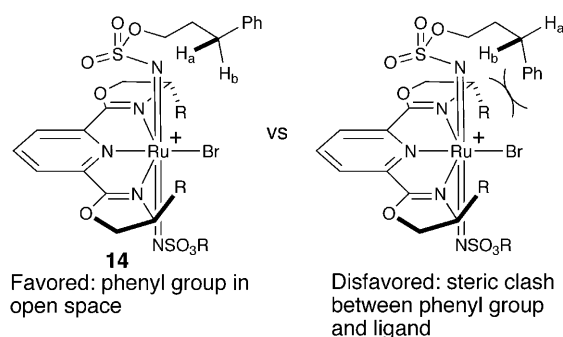


Figure 1. Stereochemical model for the cationic ruthenium(II)–pybox-catalyzed C–H amination reaction.

Halide abstraction from catalyst **4** provides a vacant coordination site *cis* to the pyridine ring of the pybox ligand to enable metallonitrene formation.^[15] Subsequent ethylene dissociation and bromide isomerization provides a second vacant coordination site *cis* to the pyridine ring, and a second oxidation provides the active Ru^{VI} species. In the transition state, the sulfamate ester wraps around into the vacant quadrant created by the pybox ligand and the bulky aromatic group points away from the ligand, thus resulting in one of the two enantiotopic hydrogen atoms (H_a) pointing directly at the reactive metallonitrene species. The reaction of this hydrogen atom gives rise to products with the same absolute configuration as observed in the C–H amination protocol. Also, the geometry of this transition state is consistent with an H[•] abstraction/radical rebound mechanism, which has been observed for other ruthenium-catalyzed C–H amination processes.^[3b]

In conclusion, we have developed an effective protocol for the catalytic asymmetric amination of benzylic and allylic C–H bonds through the rational design of a cationic ruthenium(II)–pybox catalyst. Studies to fully understand the role of the ancillary ligands and to confirm the nature of the

amination process (H^\bullet abstraction vs concerted insertion) remain a focus of our research.

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- [1] a) R. Breslow, S. H. Gellman, *J. Chem. Soc. Chem. Commun.* **1982**, 1400; b) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728.
- [2] a) C. G. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618; *Angew. Chem. Int. Ed.* **2001**, *40*, 598; b) C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc.* **2001**, *123*, 6935; c) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378; d) M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett.* **2006**, *8*, 1073; e) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562.
- [3] a) S. M. Au, S. B. Zhang, W. H. Fung, W. Y. Yu, C. M. Che, K. K. Cheung, *Chem. Commun.* **1998**, 2677; b) S. M. Au, J. S. Huang, W. Y. Yu, W. H. Fung, C. M. Che, *J. Am. Chem. Soc.* **1999**, *121*, 9120; c) X.-G. Zhou, X.-Q. Yu, J.-S. Huang, C.-M. Che, *Chem. Commun.* **1999**, 2377; d) S. M. Au, J. S. Huang, C. M. Che, W. Y. Yu, *J. Org. Chem.* **2000**, *65*, 7858; e) X. Q. Yu, J. S. Huang, X. G. Zhou, C. M. Che, *Org. Lett.* **2000**, *2*, 2233; f) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem.* **2002**, *114*, 3615; *Angew. Chem. Int. Ed.* **2002**, *41*, 3465; g) S. K. Y. Leung, W. M. Tsui, J. S. Huang, C. M. Che, J. L. Liang, N. Y. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16629.
- [4] a) Y. Cui, C. He, *Angew. Chem.* **2004**, *116*, 4306; *Angew. Chem. Int. Ed.* **2004**, *43*, 4210; b) Z. Li, D. A. Capretto, R. Rahaman, C. He, *Angew. Chem.* **2007**, *119*, 5276; *Angew. Chem. Int. Ed.* **2007**, *46*, 5184.
- [5] H. Lebel, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198.
- [6] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861.
- [7] a) M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 9561; b) C. Fruit, P. Muller, *Helv. Chem. Acta* **2004**, *87*, 1607; c) R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013; for other catalysts see Ref. [2] and d) Y. Kohmura, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3339; e) K. Omura, M. Murakami, T. Uchida, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 354.
- [8] a) C. Liang, F. Robert-Peillard, C. Fruit, P. Mueller, R. H. Dodd, P. Dauban, *Angew. Chem.* **2006**, *118*, 4757; *Angew. Chem. Int. Ed.* **2006**, *45*, 4641; b) C. Liang, F. Collet, F. Robert-Peillard, P. Mueller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343.
- [9] H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223.
- [10] At the time of this investigation, the best reported results for the enantioselective cyclization of this substrate were 84% *ee*, 48% yield; see Ref. [3].
- [11] J. L. Liang, S. X. Yuan, J. S. Huang, C. M. Che, *J. Org. Chem.* **2004**, *69*, 3610.
- [12] K. Guthikonda, P. M. When, B. J. Caliendo, J. Du Bois, *Tetrahedron* **2006**, *62*, 11331.
- [13] For a recent review on the use of olefins as ligands in transition-metal-catalyzed reactions, see: J. B. Johnson, T. Rovis, *Angew. Chem.* **2008**, *120*, 852; *Angew. Chem. Int. Ed.* **2008**, *47*, 840.
- [14] *trans*-Cyclooctene has been used as a ligand in an analogous but less sterically encumbered ruthenium(II)–pybox complex: H. Nishiyama, T. Naitoh, Y. Motoyama, K. Aoki, *Chem. Eur. J.* **1999**, *5*, 3509.
- [15] For a similar model in the context of Ru-catalyzed cyclopropanation, see: H. Nishiyama, Y. Itoh, Y. Sugiwarra, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247.