

Enantioselective Intermolecular Benzylic C–H Amination under Chiral Paddle-Wheel Diruthenium Catalysis

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ABSTRACT: A catalytic asymmetric intermolecular benzylic C–H amination was achieved under paddle-wheel diruthenium catalysis. A chiral diruthenium catalyst incorporating (*S*)-TPPTTL (tetraphenylphthaloyl-(*S*)-*tert*-leucine) ligands exhibited notable enantioselectivity, and aminated products were obtained with up to 99% ee. Unique chemoselectivity of the chiral diruthenium catalyst was also found for allylbenzene and alkyl-naphthalene substrates, demonstrating the complementary synthetic utility of chiral paddle-wheel Ru(II)-Ru(III) catalysts to Rh(II) counterparts.

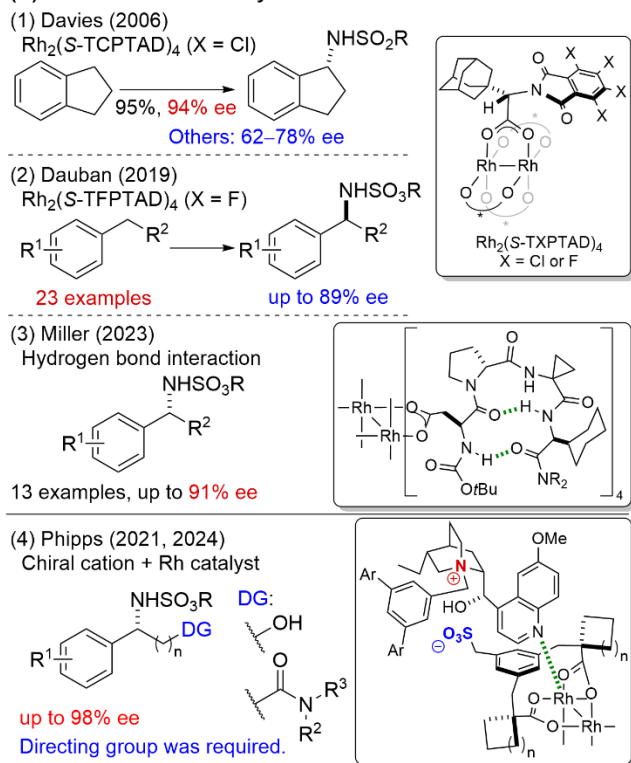
INTRODUCTION

Through continuous investigation over the past few decades, chiral paddle-wheel dinuclear Rh(II) complexes have emerged as invaluable catalysts in asymmetric transformations.¹ Carbenoid transfer reactions for intermolecular asymmetric C–H alkylation consistently deliver high yield and remarkable site-, diastereo- and enantioselectivity, as highlighted in the reports by Davies and others.^{1d} While the Rh-carbenoid chemistry for intermolecular C–H alkylation has reached an advanced stage of development, Rh-nitrenoid chemistry for intermolecular C–H amination has not progressed as rapidly, particularly in terms of enantioselectivity. C–H amination reactions utilizing Rh(II) catalysts have been explored by Müller, Du Bois, Lebel, Dauban, and others, resulting in significant advancements.² These methodologies have widespread applicability for the total synthesis of complex natural products and related complex molecules, mainly via either intramolecular asymmetric C–H amination or diastereoselective intermolecular C–H amination.^{2,3} On the other hand, catalytic asymmetric intermolecular C–H amination reactions still have room for improvement (Scheme 1A).^{4–6} The first example of asymmetric C–H amination under Rh(II) catalysis was reported by Müller et al. in 1996.^{4a} Subsequently, the Davies group achieved moderate to high enantioselectivity (94% ee for one example, 62–78% ee for others) using Rh₂(*S*-TCPTAD)₄ as the catalyst (Scheme 1A, eq 1).^{4b} Dauban's group successfully broadened the scope of enantioselective benzylic C–H amination using Rh₂(*S*-TFPTAD)₄ with up to 89% ee in 2019 (Scheme 1A, eq 2).^{4d} Further advancements were recently reported by Miller,^{4f} who introduced a rigid chiral environment created by peptide-type ligands and their hydrogen bond, thereby improving the enantioselectivity up to 91% ee (13 examples, eq 3). In a different approach, Phipps and co-workers introduced a sulfonate-pendant ligand and a chiral counter ion, achieving excellent enantioselectivity up to 98% ee, but the reaction was restricted to substrates bearing directing groups (DG), such as a hydroxy group or tertiary amides (eq 4).^{4e,g}

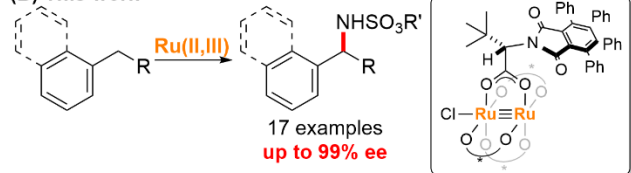
Thus far, the improvement in chiral paddle-wheel Rh(II)-catalyzed intermolecular C–H amination reactions has been due mainly to the development of innovative novel chiral ligands and their corresponding efficacy. As an alternative approach for advancing chiral paddle-wheel dinuclear catalysis, we are focusing on modifications of central metals using the privileged chiral ligands

Scheme 1. Asymmetric intermolecular C–H amination using chiral paddle-wheel dinuclear catalysts.

(A) Previous results of asymmetric intermolecular C–H amination



(B) This work



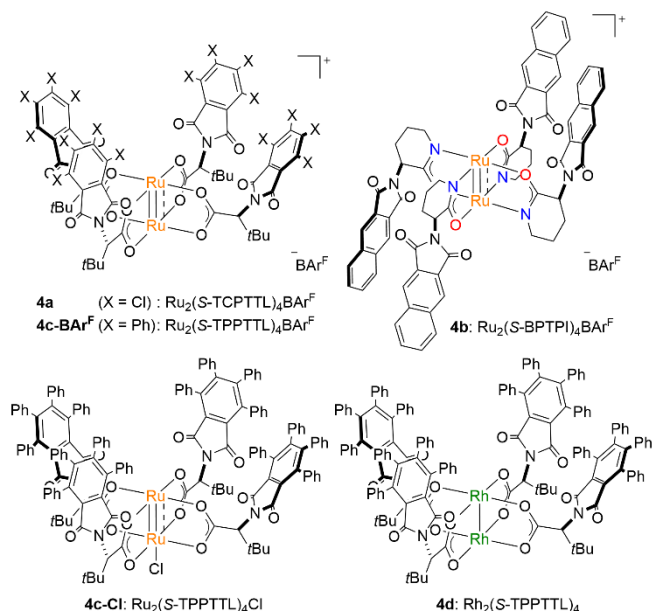
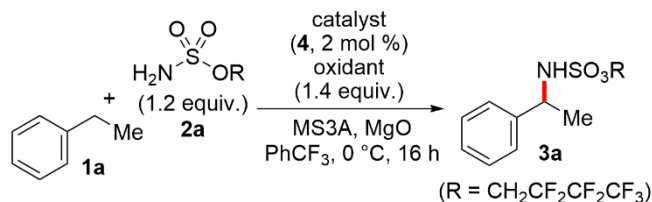


Figure 1. Structures of chiral paddle-wheel Ru(II)-Ru(III) complexes used in this study.

Table 1. Effects of catalysts and reaction conditions for enantioselective benzylic C–H amination.^a



entry	catalyst	oxidant	% yield ^b	% ee ^c
1	Ru, 4a	PIFA	66	15
2	Ru, 4b	PIFA	9	49
3	Ru, 4c-BAR ^F	PIFA	40	89
4	Ru, 4c-Cl	PIFA	42	93
5	Ru, 4c-Cl	HTIB	70	95
6 ^d	Ru, 4c-Cl	HTIB	44	96
7 ^{d,e}	Ru, 4c-Cl	HTIB	64(61)	94
8 ^{d,e,f}	Ru, 4c-Cl	HTIB	81(71)	95
9 ^{d,e,f}	Rh, 4d	HTIB	66(67)	86

^aReaction conditions (unless otherwise noted): **1a** (0.050 mmol), MS3A (18 mg), MgO (0.15 mmol), catalyst (1.0 μmol, 2 mol %), **2a** (0.060 mmol), and oxidant (0.070 mmol) in PhCF₃ (0.50 mL) at 0 °C for 16 h. ^bDetermined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. The isolated yield of analytically pure **3a** after silica gel column chromatography is shown in parentheses. ^cDetermined by chiral HPLC analysis. ^d0.20 mmol of **1a**. ^eat 5 °C ^f**2a** (2.0 equiv.), cat. **4** (3 mol %), PhI(OH)OTs (2.2 equiv.), MgO (5.0 equiv.). PIFA: PhI(OCOCF₃)₂. HTIB: PhI(OH)OTs.

previously developed for Rh(II).⁷⁻⁹ In 2020, we reported the utility of chiral Ru(II)-Ru(III) complexes for the first time in asymmetric cyclopropanation, the hetero-Diels Alder reaction, and intramolecular C–H amination.^{9a,10} While diruthenium complexes exhibit paddle-wheel-type frameworks similar to those of rhodium complexes, their X-ray crystallographic structures reveal differences in the bond

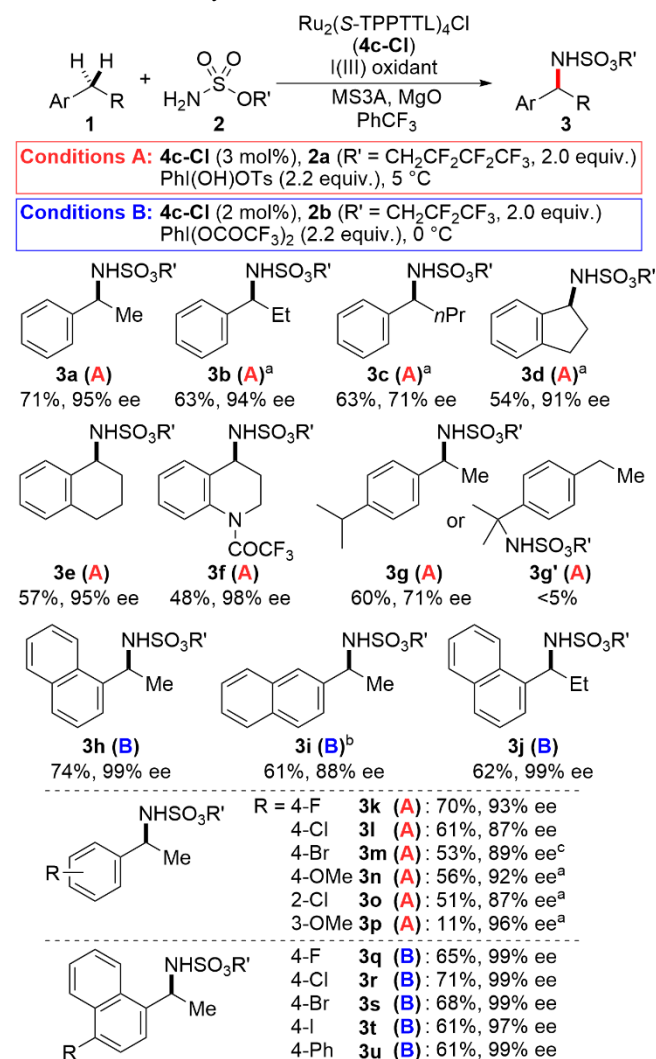
distances between the central metals and ligands depending on the metal used. Thus, we envisioned that differences in the chiral environment of Ru(II)-Ru(III) catalysts would lead to an improved stereoselectivity and/or substrate scope, complementary to Rh(II) catalysts with the same chiral ligands.^{9b} Herein, we report the utility of chiral paddle-wheel diruthenium catalysis in intermolecular benzylic C–H amination. A diruthenium catalyst incorporating (*S*)-TPPTTL (tetraphenylphthaloyl-*S*-*tert*-leucine) ligands afforded aminated products with up to 99% ee (Scheme 1B).

RESULTS AND DISCUSSION

Optimization of the ruthenium-catalyzed asymmetric intermolecular benzylic C–H amination reaction of ethylbenzene **1a** with sulfamate **2a** is summarized in Table 1. Ru₂(S-TCPTTL)₄BAR^F **4a** and Ru₂(S-BPTPI)₄BAR^F **4b** (Figure 1), previously used for intramolecular C–H amination,^{9a} afforded **3a** with unsatisfactory enantioselectivity (entry 1, 15% ee; entry 2, 49% ee). In our continuing efforts to diversify the repertoire of chiral diruthenium complexes,^{9a,11} we turned our attention to incorporating an (*S*)-TPPTTL ligand, which has been intensively investigated for dirhodium catalysis by Davies et al.¹² We anticipated that the 16 phenyl rings in the 4 (*S*)-TPPTTL ligands would create a more confined chiral environment.¹³ To our delight, Ru₂(S-TPPTTL)₄BAR^F (**4c-BAR^F**) improved the enantioselectivity to 89% ee (entry 3). The counter anion also exhibited some influence; Ru₂(S-TPPTTL)₄Cl (**4c-Cl**) further improved the enantioselectivity (93% ee, entry 4). We assume that the chloride anion acts as an axial ligand and shields one of the Ru metal center, thereby suppressing the less stereoselective reaction pathway. Among the hypervalent iodine oxidants screened, PhI(OH)OTs (Koser's reagent) was optimum, giving **3a** with 95% ee (entry 5). When the reaction was performed in a semi-preparative scale (0.20 mmol), however, the yield of **3a** diminished to 44% (entry 6); thus, further modifications of the reaction conditions were required. Changing the reaction temperature from 0 °C to 5 °C improved the yield with a minimal decrease in the enantioselectivity (entry 7). Finally, by increasing the amount of the Ru catalyst **4c-Cl** (3 mol %), sulfamate **2a** (2.0 equiv), PhI(OH)OTs (2.2 equiv), and MgO (5.0 equiv), we obtained product **3a** in 71% isolated yield with 95% ee (entry 8). As a control experiment, the Rh(II) counterpart, Rh₂(S-TPPTTL)₄ (**4d**), was used as the catalyst in place of **4c-Cl**. Under the identical reaction conditions, Rh₂(S-TPPTTL)₄ (**4d**) gave **3a** in 67% yield but the enantioselectivity was lower than that when using the Ru catalyst (entry 9, 86% ee). The enantioselectivity with **4d** was similar to the selectivity reported by Dauban and coworkers using other Rh(II) catalysts.^{4d}

With the optimized reaction conditions in hand, we investigated the substrate scope and limitations of benzylic C–H amination (Scheme 2). We began by applying substrates possessing varied alkyl chains (**1b–1e**). The amination of propylbenzene (**1b**) and butylbenzene (**1c**) proceeded with slightly decreased yields (63% yield for both **3b** and **3c**). While the enantioselectivity with propylbenzene (**1b**) was retained (**3b**: 94% ee), butylbenzene (**1c**) gave product **3c** in decreased enantioselectivity (71% ee). A substrate with branched alkyl chain, however, resulted in a much lower yield.¹⁴ Cyclic alkylarenes (**1d**, **1e**) were applicable, and aminated products **3d**, **3e** were obtained with 91% ee and 95% ee, respectively, albeit in modest yield. A substrate with a polar functional group exhibited lower reactivity, while high enantioselectivity was observed (**3f**: 48%, 98% ee). When substrate **1g** containing both secondary and tertiary benzylic C(sp³)–H bonds was used, the amination selectively proceeded at the secondary C–H bond, giving **3g** in 60% yield along with trace **3g'** (<5% yield). Enantioselectivity of **3g** was moderate, possibly due to steric hindrance with *i*-Pr substituent. The amination of 1-ethynaphthalene (**1h**) proceeded in good yield

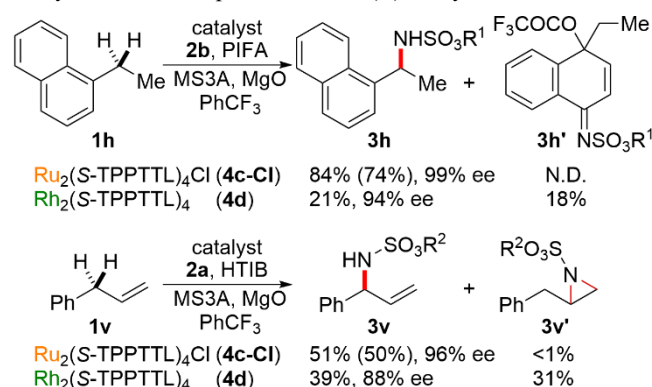
Scheme 2. Substrate scope of the benzylic C–H amination using chiral diruthenium catalyst.



Reaction conditions (unless otherwise noted), Conditions A: **1** (0.20 mmol), MS3A (70 mg), MgO (1.0 mmol), **4c-Cl** (6.0 μmol, 3 mol %), **2a** (0.40 mmol), and PhI(OH)OTs (0.44 mmol) in PhCF₃ (2.0 mL) at 5 °C for 16 h. Conditions B: **1** (0.20 mmol), MS3A (70 mg), MgO (1.0 mmol), **4c-Cl** (4.0 μmol, 2 mol %), **2b** (0.40 mmol), and PhI(OCOCF₃)₂ (0.44 mmol) in PhCF₃ (2.0 mL) at 0 °C for 16 h. See Supporting Information for details. ^a**4c-Cl** (5 mol %). ^bat 10 °C. ^c**2a** (0.24 mmol) and PhI(OH)OTs (0.28 mmol) at 10 °C.

with excellent enantioselectivity using PhI(OCOCF₃)₂ as an oxidant (74% yield, 99% ee; conditions B: See, Supporting Information for optimization details), whereas 2-ethylnaphthalene (**1i**) resulted in lower enantioselectivity (**3i**, 88% ee). Excellent enantioselectivity was also observed for 1-naphthyl substrate with an elongated alkyl chain (**3j**, 62%, 99% ee). We next investigated the effects of the substituents on the phenyl and naphthyl rings. Aminated products with a halogen group at the *para*-position on the phenyl ring (**3k**–**3m**) were obtained with good enantioselectivity. The presence of the methoxy group at the *para*-position (**3n**) decreased the reactivity and 5 mol% of **4c-Cl** was required. Substitution with 2-Cl in **3o** resulted in a moderate yield and enantioselectivity, even with 5 mol% catalyst loading.¹⁴ The reactivity of 3-OMe substituted substrate **1p** decreased significantly (**3p**: 11%), which might be due to the mismatch issue of the chiral environment with *S*-TPPTTL

Scheme 3. Unique chemoselectivity of paddle-wheel Ru(II)-Ru(III) catalyst **4c-Cl** in comparison with Rh(II) catalyst **4d**.^a



^aSee section 3-4 of Supporting Information for details. The isolated yield of **3h** and **3v** are shown in parentheses.

ligands towards *meta*-substituents (see, Supporting Information for details on limitations). 1-Ethynaphthalenes substituted with a halogen- or phenyl-group at the 4-position (**1q**–**1u**) gave products **3q**–**3u** with high enantioselectivity (97–99% ee). On the other hand, substrates substituted with the methoxy group on the naphthalene ring prohibited the amination reaction.¹⁴ The absolute configuration of **3a** was determined by comparing the optical rotation of the Boc-protected α -methyl benzyl amine. Deprotection of sulfamate smoothly proceeded according to the reported procedure (See, Supporting Information).^{5c} The absolute configuration of **3r** was also unambiguously determined by X-ray diffraction analysis (See, Supporting Information).

Unique chemoselectivity of the Ru(II)-Ru(III) catalysis over the paddle-wheel Rh(II)-catalysis is summarized in Scheme 3. Control experiments on ethylnaphthalene (**1h**) and allylbenzene (**1v**) using Rh₂(S-TPPTTL)₄ (**4d**) catalyst resulted in much less satisfactory results. For ethylnaphthalene (**1h**), the Rh catalyst **4d** gave **3h** in only 24% yield with 94% ee as byproduct **3h'** was obtained in a similar yield (18%).¹⁵ **3h'** was obtained possibly via aromatic electrophilic substitution reaction with nitrenium ion as reported previously under Rh(II) catalysis,^{2i,16} followed by further oxidation with PIFA.¹⁷ Thus, aromatic C–H amination competed with the desired benzylic C–H amination with Rh catalyst **4d**. Notably, the Ru-catalyzed amination of allylbenzene (**1v**) also proceeded chemoselectively without forming aziridine **3v'**, giving **3v** in 50% isolated yield and 96% ee. On the other hand, the Rh catalyst **4d** afforded a mixture of desired product **3v** (39%, 88% ee) and aziridine **3v'** (31%). On the basis of previous reports on achiral Ru(II)-Ru(III) catalysis,^{10a} we assume that the observed unique chemoselectivity of the chiral Ru₂(S-TPPTTL)₄Cl catalyst in Scheme 3 is likely due to radical-like property of a Ru-nitrene active species.

CONCLUSION

In summary, we demonstrated the utility of a chiral paddle-wheel diruthenium catalyst, Ru₂(S-TPPTTL)₄Cl, in intermolecular benzylic C–H amination. The diruthenium catalyst achieved remarkable enantioselectivity up to 95% ee with alkylbenzenes and up to 99% ee with alkynaphthalenes. Unique chemoselectivity of the chiral diruthenium catalyst was also found for allylbenzene and alkyl-naphthalene substrates, demonstrating the complementary synthetic utility of chiral paddle-wheel Ru(II)-Ru(III) catalysts to Rh(II) counterparts. Further studies to expand the scope of chiral paddle-wheel diruthenium catalysts are ongoing in our group.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization of the synthesized compounds, and NMR spectra (PDF). These materials are available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Substrate limitations are summarized in Supporting Information (Section 2-3)

(15) The amination reaction of 1-ethyl-4-phenyl-naphthalene (**1u**) using $\text{Rh}_2(\text{S-TPPTTL})_4$ (**4d**) gave the aminated product **3u** in poor yield (21%)

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