C–H Activation

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Aerobic Asymmetric Dehydrogenative Cross-Coupling between Two C_{sp^3}–H Groups Catalyzed by a Chiral-at-Metal Rhodium Complex

Yuqi Tan, Wei Yuan, Lei Gong, and Eric Meggers**

Abstract: *A sustainable C–C bond formation is merged with the catalytic asymmetric generation of one or two stereocenters. The introduced catalytic asymmetric cross-coupling of two C_{sp^3}–H groups with molecular oxygen as the oxidant profits from the oxidative robustness of a chiral-at-metal rhodium(III) catalyst and exploits an autoxidation mechanism or visible-light photosensitized oxidation. In the latter case, the catalyst serves a dual function, namely as a chiral Lewis acid for catalyzing enantioselective enolate chemistry and at the same time as a visible-light-driven photoredox catalyst.*

The construction of C–C bonds from two C–H bonds under oxidative conditions has been identified as a highly attractive conversion from ecological and economical aspects as it avoids waste from the implementation and removal of reactive functional groups and therefore also reduces the number of reaction steps.[1] Despite great progress being made, key challenges remain. Firstly, current methods rely too often on oxidation reagents which produce undesired waste, whereas molecular oxygen as the ideal "green" oxidant suffers from poor reactivity.[2,3] Secondly, combining dehydrogenative cross-coupling with asymmetric catalysis remains a formidable challenge, but gains importance because of the increasing structural complexity of bioactive molecules resulting from one or multiple stereocenters.[4] In one of the most attractive scenarios, two C–H groups are coupled in a catalytic and asymmetric fashion by the formation of a new C–C bond, including at least one stereocenter, while molecular oxygen serves as the oxidant (Figure 1). Only very few studies report such a combination of dehydrogenative cross-coupling, asymmetric catalysis, and aerobic conditions.[5] With respect to the coupling of two C_{sp^3}–H groups, Cui, Jiao, and co-workers introduced the α-alkylation of aldehydes using combined enamine and acid catalysis (Figure 1a),[5a] Xu and co-workers disclosed the β-alkylation of aldehydes using combined oxidative enamine and palladium catalysis (Figure 1b),[5c] and Kim and co-workers reported the combination of oxidative enamine chemistry with an intramolecular 1,5-hydride shift (Figure 1c).[5d] All these methods rely on the use of an aldehyde substrate together with a chiral secondary amine catalyst at high loadings of 10–20 mol%.

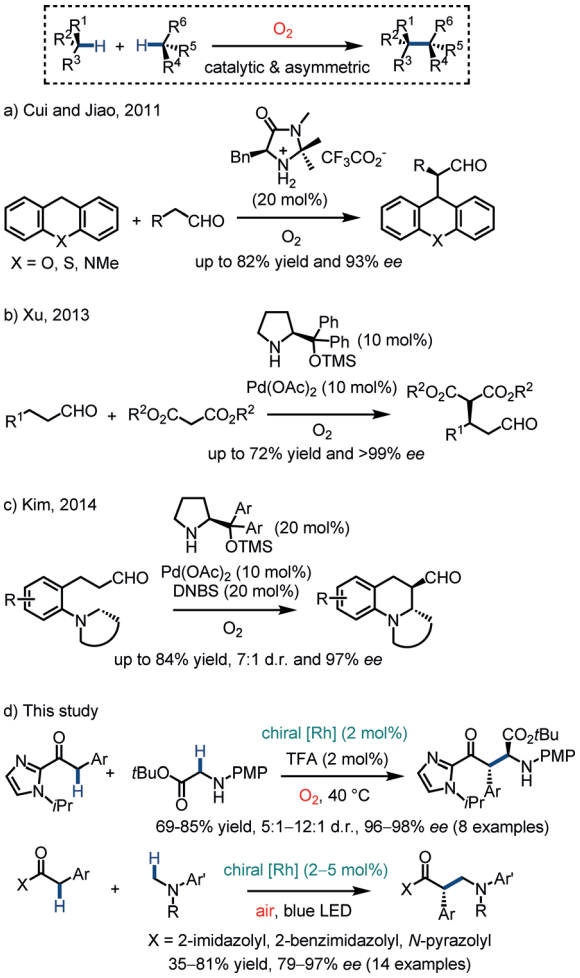

Figure 1. Previous work and this study on the areobic catalytic asymmetric cross-dehydrogenative cross-coupling of two C_{sp^3}–H groups. DNBS = 2,4-dinitrobenzenesulfonic acid, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

We started our study on this topic by investigating an asymmetric Mannich reaction between 2-acyl imidazoles and imino esters, thus considering it as the first step towards an asymmetric cross-dehydrogenative coupling. In previous work we demonstrated that the chiral-at-rhodium complex Λ-**Rh** (for structure see Table 1) is capable of catalyzing the α-amination of 2-acyl imidazoles through the formation of a coordinated rhodium enolate.[6] Trapping such chiral metal

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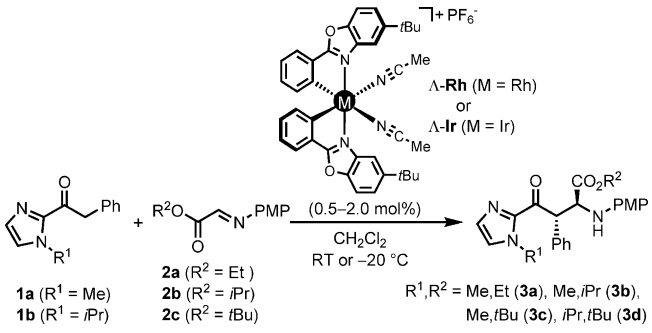
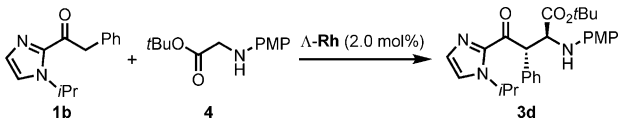
Table 1: Initial experiments and optimization of an asymmetric Mannich reaction.[a]



Entry	R^1	R^2	Catalyst[b]	*T* [°C]	*t* [h]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	Me	Et	Λ-**Rh** (2.0 mol%)	RT	1	97	2:1	99.2
2	Me	Et	Λ-**Rh** (2.0 mol%)	−20	10	96	4:1	99.6
3	Me	*i*Pr	Λ-**Rh** (2.0 mol%)	−20	10	97	9:1	99.5
4	Me	*t*Bu	Λ-**Rh** (2.0 mol%)	−20	10	96	24:1	99.5
5	*iPr*	*tBu*	*Λ-**Rh** (2.0 mol%)*	*−20*	*10*	*98*	*27:1*	*99.6*
6	*iPr*	*tBu*	*Λ-**Rh** (0.5 mol%)*	*−20*	*52*	*95*	*21:1*	*98.6*
7	*i*Pr	*t*Bu	Λ-**Ir** (2.0 mol%)	RT	25	84	1:1.7	69
8	*i*Pr	*t*Bu	Λ-**Ir** (2.0 mol%)	−20	30	< 5[f]	n.d.	n.d.

[a] Reaction conditions: 1.5 equiv of iminoester. See the Supporting Information for details. [b] Catalyst loading given in brackets. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis using a chiral stationary phase. [f] Conversion determined by ^{1}H NMR spectroscopy.

Table 2: Optimization of the reaction conditions for the tandem autoxidation/Mannich reaction.[a]



Entry	Ox.	Additive	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	air	none	CH_2Cl_2	RT	30	26	12:1	99
2	O_2	none	CH_2Cl_2	RT	30	31	12:1	99
3	O_2	none	NMP	RT	30	35	12:1	99
4	O_2	none	NMP	30	30	56	14:1	98
5	O_2	none	NMP	35	30	62	14:1	98
6	O_2	none	NMP	40	48	66	7:1	96
7	O_2	TFA (0.2 equiv)	NMP	40	19	84	10:1	95
8	*O_2*	*TFA (0.02 equiv)*	*NMP*	*40*	*36*	*85*	*12:1*	*98*

[a] Reaction conditions: 5.0 equiv of **4** and 2 mol% of Λ-**Rh**. See the Supporting Information for details. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phase. NMP = *N*-methylpyrrolidine.

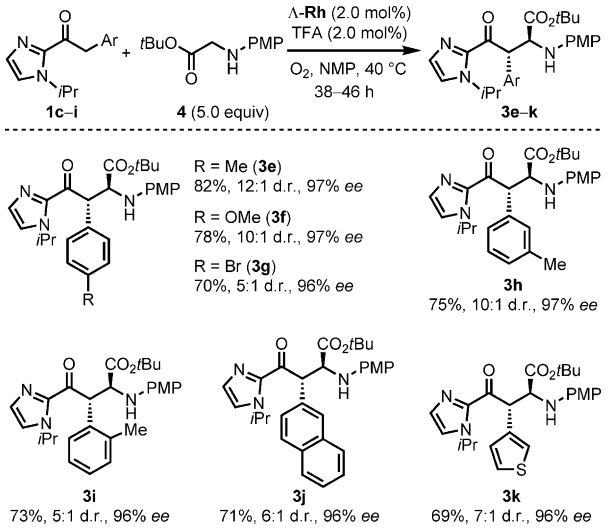


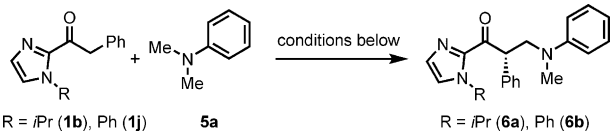
Figure 2. Scope for the tandem autoxidation/Mannich reaction catalyzed by Λ-**Rh**.

enolate intermediates with electrophilic imino esters would provide two stereocenters, possibly in a stereocontrolled fashion. Indeed, when we reacted the 2-acyl imidazole **1a** with the *p*-methoxyphenyl (PMP)-protected imino ester **2a** in the presence of 2 mol% Λ-**Rh**, we obtained the Mannich product **3a** in high yield (97%) and almost perfect enantioselectivity (99.2% *ee*), but with poor diastereoselectivity of 2:1 d.r. (entry 1). Reducing the temperature to −20 °C (entry 2), and replacing the ethyl ester with either an *i*Pr ester (**2b**; entry 3) or a *t*Bu ester (**2c**; entry 4) improved the diastereoselectivity. Finally, when we used **2c** in combination with a 2-acyl imidazole in which the *N*-methyl group was replaced with a more bulky *i*Pr group (**1b**), the best results were obtained, thus providing a 27:1 d.r. with an excellent *ee* value of 99.6% (entry 5). It also allowed a reduced catalyst loading of 0.5 mol% (entry 6). It is noteworthy that the analogous iridium catalyst[7] did not provide satisfactory results (entries 7 and 8).

Since imino esters related to **2a–c** were recently reported to be accessible by autoxidation of the corresponding glycine esters,[8,9] we were envisioning the merging of both processes, namely the developed asymmetric Mannich reaction and the described autoxidation of glycine esters, into a single asymmetric catalytic cross-dehydrogenative coupling.[10] Indeed, when we reacted the acyl imidazole **1b** with the PMP-protected glycine ester **4** in the presence of air at room temperature for 30 hours, we obtained the desired C–C bond formation product **3d** with an excellent *ee* value of 99% and 12:1 d.r., albeit with a low yield of 26% (Table 2, entry 1). However, the yield could be improved by using an atmosphere of oxygen instead of air (entry 2), switching to *N*-methylpyrrolidine (NMP) as the solvent (entry 3), and raising the temperature to 40 °C (entries 4–6). Finally, adding catalytic amounts of trifluoroacetic acid (TFA; entries 7 and 8), presumably to eliminate H_2O_2 from a hydroperoxide intermediate,[9,11] further improved the results. Thus, when executed in NMP with 2 mol% TFA under an atmosphere of oxygen at 40 °C, the reaction of **1b** with **4** provided the cross-dehydrogenative coupling product **3d** in 85% yield with a satisfactory 12:1 d.r. and excellent *ee* value of 98% (entry 8). The substrate scope is shown in Figure 2 and demonstrates the generality of this straightforward methodology.

Next, we wondered whether this rhodium-catalyzed asymmetric C–H cross-coupling with oxygen as the oxidant could be extended to amine substrates which are not activated

Table 3: Initial experiments and optimization of photoinduced asymmetric dehydrogenative C–C bond formation.[a]



R = *i*Pr (**1b**), Ph (**1j**) **5a** R = *i*Pr (**6a**), Ph (**6b**)

Entry	Catalyst	R	Reaction conditions[b]	Solvent	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	Λ-**Rh** (2.0 mol%)	*i*Pr	O_2, TFA (2 mol%)	NMP	40	48	6	98
2	Λ-**Rh** (2.0 mol%)	*i*Pr	O_2, TFA (2 mol%)	NMP	60	48	8	95
3	Λ-**Rh** (2.0 mol%)	*i*Pr	O_2, white light	NMP	22–23	48	16	98
4	Λ-**Rh** (2.0 mol%)	*i*Pr	air, white light	NMP	22–23	48	18	98
5	Λ-**Rh** (2.0 mol%)	*i*Pr	air, white light	DMSO	22–23	48	34	98
6	Λ-**Rh** (2.0 mol%)	Ph	air, white light	DMSO	22–23	48	66	94
7	Λ-**Rh** (2.0 mol%)	Ph	air, UV light	DMSO	22–23	36	45	95
8	*Λ-**Rh** (2.0 mol%)*	*Ph*	*air, blue LED*	*DMSO*	*22–23*	*22*	*80*	*96*
9	none	Ph	air, blue LED	DMSO	22–23	24	0	n.d.
10	Λ-**Rh** (2.0 mol%)	Ph	argon, blue LED	DMSO	22–23	24	0	n.d.
11	Λ-**Ir** (2.0 mol%)	Ph	air, blue LED	DMSO	22–23	36	3	n.d.

[a] Reaction conditions: 3.0 equiv of **5a** under the shown conditions. [b] 24 W compact fluorescence light bulb, 24 W blue LED, or 16 W UV light (365 nm). [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. n.d. = not determined.

by a carboxylic ester in the α-position. Thus we started to investigate the reaction of the acyl imidazole **1b** with *N*,*N*-dimethylaniline (**5a**; Table 3). When reacted under the optimized reaction conditions (see Table 2), less than 10% of the C–C coupling product was identified, and increasing the temperature to 60 °C did not improve the yield significantly (Table 3, entries 1 and 2). However, in the presence of white light instead of heating, the C–C coupling product **6a** was obtained in 16% yield and 98% *ee* (entry 3). The observation of a diketone oxidation side-product led us use an air atmosphere instead of oxygen, and thus afforded **6a** in 18% yield and 98% *ee* (entry 4). Optimization of the reaction conditions by switching to the solvent DMSO (entry 5), and using the substrate **1j** bearing a phenyl instead of isopropyl substituent at the imidazole (entry 6) increased the yield to 66% with 94% *ee* (product **6b**). Using UV-light instead of white light did not improve the results significantly (entry 7). However, under illumination with blue light, optimal reaction conditions were obtained: Just using air as the oxidant at room temperature in the presence of 2 mol% of Λ-**Rh** afforded the C–C coupling product in 80% yield and with 96% *ee* (entry 8). Control experiments verified that the reaction requires the combined presence of the rhodium catalyst and air (entries 9 and 10). The related iridium catalyst Λ-**Ir** did not give satisfactory results, and is a catalyst which was recently demonstrated to activate α-silyl amines, but apparently was not capable of converting synthetically much more attractive non-functionalized, non-activated amines (entry 11).[7c] Figure 3 demonstrates that a variety of 2-acyl imidazoles (**6b–f**) and anilines (**6g–m**) serve as substrates.[12] The imidazole moiety can also be replaced by pyrazole (**6n**) or benzimidazole (**6o**), although the yields and enantioselectivities are somewhat diminished.

The putative mechanism for both the reported catalytic asymmetric cross-dehydrogenative couplings involves a rhodium coordination of the acyl imidazole substrate followed by deprotonation (Figure 4). The hereby generated intermediate nucleophilic enolate complex then reacts in a stereocontrolled fashion with the in situ, oxidatively generated carbon electrophiles, which can either be an imine that is formed through autoxidation of the corresponding glycine ester[9,10] or an iminium ion formed by photosensitized oxidation of the corresponding *N*,*N*-dialkylaniline.[13] In the latter case, the rhodium complex does not only serve as a catalyst for the enantioselective enolate chemistry, but also functions as a visible-light-activated photoredox catalyst.[14,15] Accordingly, a photoactivated rhodium sensitizer removes an electron from the *N*,*N*-dialkylaniline, thus leading to a radical cation which undergoes rapid α-deprotonation to afford an α-aminoradical which is subsequently oxidized by air to its electrophilic iminium ion.[13] Such photosensitized oxidation of tertiary amines is well established for a variety of transition-metal photoredox sensitizers, particularly ruthenium(II) and iridium(III), but has not been reported for rhodium(III)

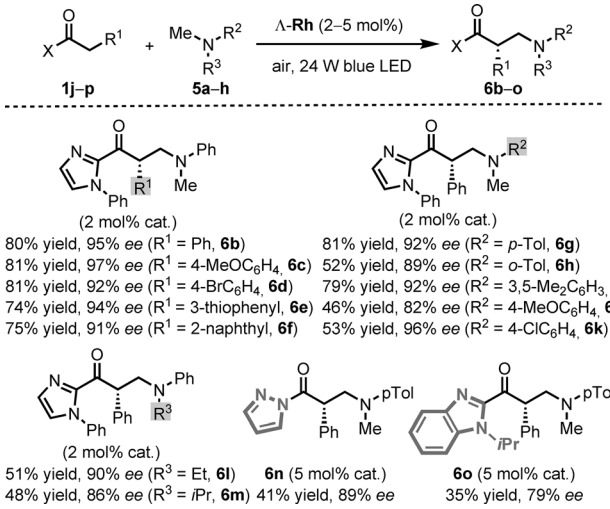


Figure 3. Substrate scope for the photoinduced asymmetric C–C bond formation catalyzed by Λ-**Rh**.

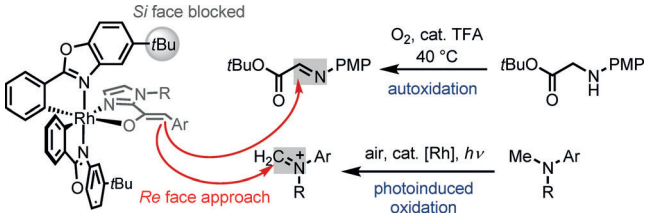


Figure 4. Putative mechanism for the catalytic asymmetric cross-dehydrogenative couplings with molecular oxygen.

complexes (see the Supporting Information for UV/Vis absorption spectra and cyclovoltammetry).[16]

In conclusion, we have introduced a new methodology for the catalytic asymmetric cross-coupling of two C_{sp^3}–H groups with molecular oxygen as the terminal oxidant, and it addresses several aspects of sustainable chemistry: the C–C bond formation under the asymmetric formation of one or two new stereocenters does not rely on the wasteful removal of functional groups, it uses abundant oxygen as the stoichiometric oxidant, and employs visible light as an economical source of energy for the activation of *N*,*N*-dialkylanilines. Furthermore, to our knowledge, this work marks the first example of an asymmetric photoredox reaction catalyzed by a chiral rhodium complex.[17] This study contributes to the development of sustainable methods for the generation of nonracemic chiral compounds.

Acknowledgements

Y.T. and W.Y. contributed equally. This work was supported by the National Natural Science Foundation of P. R. China (grant nos. 21272192, 21201143, and 21472154), the Program for Changjiang Scholars and Innovative Research Team of P. R. China (PCSIRT), the National Thousand Talents Program of P. R. China, and the 985 Program of the Chemistry and Chemical Engineering disciplines of Xiamen University.

Keywords: asymmetric catalysis · C–H activation · green chemistry · oxygen · rhodium

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Communications

C–H Activation

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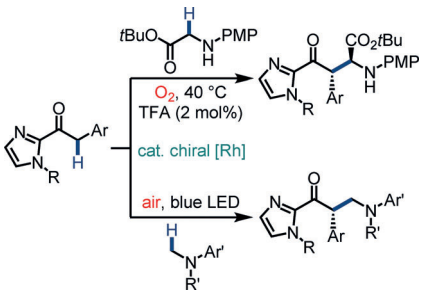
Aerobic Asymmetric Dehydrogenative Cross-Coupling between Two C_{sp^3}–H Groups Catalyzed by a Chiral-at-Metal Rhodium Complex



Green stuff: A sustainable C–C bond formation is merged with the catalytic asymmetric generation of one or two stereocenters by combining asymmetric enolate chemistry with either autoxidation or visible-light photosensitized oxidation. The robustness of a chiral-at-metal rhodium(III) catalyst serves to facilitate the reaction. PMP = *para*-methoxyphenyl, TFA = trifluoroacetic acid.