Asymmetric Catalysis

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Catalytic Asymmetric C_{sp^3}–H Functionalization under Photoredox Conditions by Radical Translocation and Stereocontrolled Alkene Addition

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Abstract: *This work demonstrates how photoredox-mediated C(sp^3)–H activation through radical translocation can be combined with asymmetric catalysis. Upon irradiation with visible light, α,β-unsaturated N-acylpyrazoles react with N-alkoxyphthalimides in the presence of a rhodium-based chiral Lewis acid catalyst and the photosensitizer fac-[Ir(ppy)$_3$] to provide a C–C bond-formation product with high enantioselectivity (up to 97% ee) and, where applicable, with some diastereoselectivity (3.0:1 d.r.). Mechanistically, the synthetic strategy exploits a radical translocation (1,5-hydrogen transfer) from an oxygen-centered to a carbon-centered radical with a subsequent stereocontrolled radical alkene addition.*

A range of powerful strategies have emerged for the functionalization of unactivated C–H bonds, including transition-metal-based C–H activation, metal carbenoid C–H insertion, and the direct oxidation of C–H bonds or functional groups at its α-position.[1] However, formidable challenges still remain with respect to substrate scope, reaction conditions, site selectivity, and the combination with asymmetric catalysis.

Free-radical processes have been among the oldest strategies for the controlled functionalization of unactivated C–H bonds, such as the Barton and Hofmann–Löffler–Freytag reactions,[2] and have attracted renewed attention, in part due to recently developed methods for the generation of reactive radicals in a mild and convenient fashion under photoredox conditions.[3] Recently, Chen and co-workers introduced a visible-light-induced release of alkoxy radicals from N-alkoxyphthalimides and applied it to selective C(sp^3)–H functionalization by exploiting 1,5-hydrogen atom transfer (1,5-HAT).[4–6] Radical translocation[7,8] has been used extensively for the functionalization of remote C(sp^3)–H bonds, but to our knowledge the combination with a catalytic asymmetric C–C bond formation remains elusive. We therefore envisioned merging this photoredox-mediated C–H activation with asymmetric catalysis, as shown in Figure 1, by trapping the intermediate (electron-rich) carbon-centered radical in a stereocontrolled fashion with an acceptor-substituted alkene catalyzed by a chiral Lewis acid.[9] Challenges include the compatibility of the individual steps with respect to the reactivity of the radical intermediates and the kinetics of the individual steps, as well as the ability to control the relative and absolute stereochemistry of the radical reaction in a catalytic fashion.[10–12]

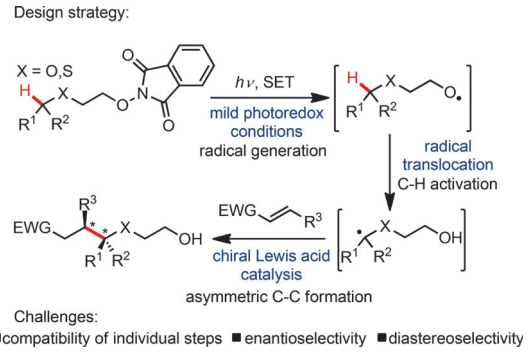

Figure 1. Design strategy for combining free-radical C(sp^3)–H activation with catalytic, asymmetric C–C bond formation. EWG = electron-withdrawing group, SET = single-electron transfer.

We started our study by investigating the reaction of the α,β-unsaturated N-acylpyrazole **1a** with the N-alkoxyphthalimide **2a** under photoredox conditions (Table 1). In the presence of the previously developed dual function photoredox/chiral Lewis acid catalyst Δ-IrS[13] (3 mol%), under irradiation with a 23 W compact fluorescent lamp (CFL), the desired C–C bond formation product **3a** was obtained in 85% yield after 20 hours, but to our disappointment, no enantioselectivity was observed (entry 1). Encouragingly, when the chiral Lewis acid Δ-RhO[14] (3 mol%), in combination with the photosensitizer *fac*-[Ir(ppy)$_3$] (1 mol%), was applied to this system, the reaction proceeded in 60% yield and 18% *ee* (entry 2).[15] The enantioselectivity was improved to 79% *ee* when Δ-RhS[16] (3 mol%) was used as the chiral Lewis acid (entry 3).[17] At a catalyst loading of 8 mol%, even 92% *ee* was reached (entry 6). Other photosensitizers, such as [Ir(ppy)$_2$(dtbbpy)]PF$_6$ and [Ru(bpy)$_3$](PF$_6$)$_2$, were inferior to *fac*-[Ir(ppy)$_3$] (entries 4 and 5). The reaction is sensitive to solvent effects (entries 7 and 8) and the light source, as blue LEDs provided a somewhat lower enantioselectivity (entry 9).[18] Control experiments verified that both visible light and Hantzsch ester are essential for product formation (entries 10 and 11). In the absence of the chiral Lewis acid Δ-RhS, **3a** was still formed (75% yield), albeit as a racemic mixture (entry 12). It is worth noting that in the absence of the photosensitizer *fac*-[Ir(ppy)$_3$] (entry 13) or both Δ-RhS and *fac*-[Ir(ppy)$_3$] (entry 14), **3a** was still generated but with significantly reduced efficiency. UV/Vis-absorbance spectra of the individual substrates and Hantzsch ester (see the

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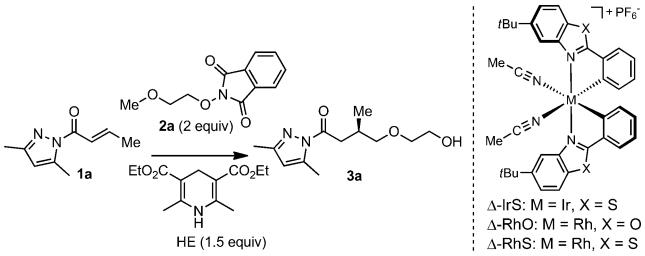
Table 1: Reaction development.[a]



Entry	Catalyst[b]	Sensitizer[b]	*hν*[c]	Sol.	*t* [h]	Yield [%][d]	*ee* [%][e]
1	Δ-IrS (3.0)	none	CFL	THF	20	85	0
2	Δ-RhO (3.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	THF	20	60	18
3	Δ-RhS (3.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	THF	20	61	79
4	Δ-RhS (3.0)	[Ir(ppy)$_2$(dtbbpy)]PF$_6$ (1.0)	CFL	THF	20	76	36
5	Δ-RhS (3.0)	[Ru(bpy)$_3$](PF$_6$)$_2$ (1.0)	CFL	THF	20	< 5	n.d.
6	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	THF	40	70	92
7	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	CH_2Cl_2	40	13	86
8	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	DMF	40	21	60
9	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	blue LEDs	THF	40	69	86
10	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	none	THF	40	0	n.a.
11[f]	Δ-RhS (8.0)	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	THF	40	0	n.a.
12	none	*fac*-[Ir(ppy)$_3$] (1.0)	CFL	THF	20	75	n.a.
13	Δ-RhS (8.0)	none	CFL	THF	40	33	92
14	none	none	CFL	THF	20	56	n.a.

[a] Reaction conditions: The N-acylpyrazole **1a** (0.4 mmol), the N-alkoxyphthalimide **2a** (0.2 mmol), and the Hantzsch ester (none or 0.3 mmol) with catalyst (none, 3.0, or 8.0 mol%) and sensitizer (none or 1.0 mol%) in solvent (1.0 mL) at RT for 20–40 h under an atmosphere of nitrogen. [b] Catalyst or sensitizer loading provided as mol% within parentheses. [c] 23 W compact fluorescent lamp (CFL) or 6 W blue LEDs. [d] Yield of isolated product. [e] Enantiomeric excess determined by HPLC on chiral stationary phase. [f] Control experiment without Hantzsch ester. n.a. = not applicable, n.d. = not determined, DMF = *N*,*N*-dimethylformamide, ppy = phenylpyridyl, THF = tetrahydrofuran.

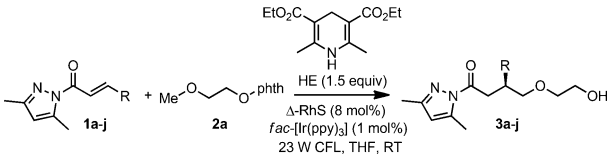
Supporting Information) suggest that this must be due to the direct photoexcitation of the Hantzsch ester.[19]

After the optimized reaction conditions were established, we next tested the substrate scope of the asymmetric photoinduced C(sp^3)–H functionalization. Table 2 shows that the reaction of a variety of 2-acyl pyrazoles (**1a–j**) with **2a** in the presence of Δ-RhS, *fac*-[Ir(ppy)$_3$], and the Hantzsch ester, while under illumination with visible light, provided the expected C–C formation products **3a–j** in 51–80% yields and 82–97% *ee*. The reaction was tolerant of aliphatic substituents (**3a–f**) and aromatic moieties with electron-rich groups (**3i,j**). Notably, the ethoxy- and benzyloxy-substituted **1g** and **1h**, respectively, are favorable here, thus affording the corresponding products **3g** and **3h** in good yields and high stereoselectivities. To further expand the scope, a wide range of tertiary N-alkoxyphthalimides were applied to the reaction (Figure 2), thus affording the adducts in yields of 57–85% and with 86–97% *ee* (**3k–s**). Secondary N-alkoxyphthalimides with aromatic substitutents were also suitable for the reaction and afforded the corresponding products (**3t–u**) with diastereoselectivities of up to 3:1 and enantioselectivities of up to 97% *ee*. Notably, this α-heteroatom activation is not limited by oxygen, as α-sulfur-activated C–H bonds also work well under standard reaction conditions (**3v,w**).

A plausible mechanism is shown in Figure 3 and starts with the photoactivation of *fac*-[Ir(ppy)$_3$], whose excited state [Ir(ppy)$_3$]* is reductively quenched by the Hantzsch ester.[20] Thereby generated *fac*-[Ir(ppy)$_3$]$^-$ serves as a strong reducing agent and transfers a single electron to N-alkoxyphthalimide (redox handle) under formation of an N-alkoxyphthalimide radical anion, which is subsequently protonated by the oxidized Hantzsch ester (radical cation), and then undergoes a homolytic N–O cleavage under formation of an alkoxy radical. This alkoxy radical now engages in an intramolecular HAT to yield a carbon-centered radical,[21,22] which adds to a N,O-rhodium-coordinated N-acylpyrazole substrate (**Rh-I**; see Figure 4a for a crystal structure), thereby generating the secondary radical intermediate **Rh-II**. This radical intermediate is further trapped by the Hantzsch ester radical to provide the rhodium-bound product **Rh-III**. The observed high enantioselectivity in this new process demonstrates that the chiral Lewis acid Δ-RhS strongly accelerates the radical addition so that it is capable of outcompeting the prevailing racemic background reaction.[9,17]

Several experiments support this mechanism. First, the expected byproducts isoindoline-1,3-dione and diethyl 2,6-dimethylpyridine-3,5-dicarboxylate could be isolated (see the Supporting Information for more details).[23] Second, Stern–Volmer plots (Figure 4b) reveal that the luminescence emission of *fac*-[Ir(ppy)$_3$] is quenched effi-

Table 2: Substrate scope with respect to α,β-unsaturated N-acylpyrazoles.[a]



Entry	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me (**1a**)	40	70 (**3a**)	92
2	Et (**1b**)	48	67 (**3b**)	93
3	*n*Pr (**1c**)	50	65 (**3c**)	92
4	*i*Pr (**1d**)	50	62 (**3d**)	94
5	*i*Bu (**1e**)	48	62 (**3e**)	91
6	cyclohexyl (**1f**)	65	74 (**3f**)	91
7	OEt (**1g**)	48	80 (**3g**)	97
8	OBn (**1h**)	48	78 (**3h**)	97
9	2,4-dimethylphenyl (**1i**)	60	51 (**3i**)	91
10	4-methoxyphenyl (**1j**)	48	57 (**3j**)	82

[a] Reaction conditions: N-Acylpyrazole (**1a–j**; 0.4 mmol), **2a** (0.2 mmol), and Hantzsch ester (0.3 mmol) with catalyst (8.0 mol%) and sensitizer (1.0 mol%) in THF (1.0 mL) at RT for 40–65 h under an atmosphere of nitrogen. [b] Yield of isolated product. [c] Enantiomeric excess determined by HPLC using a chiral stationary phase. phth = N-phthalimide.

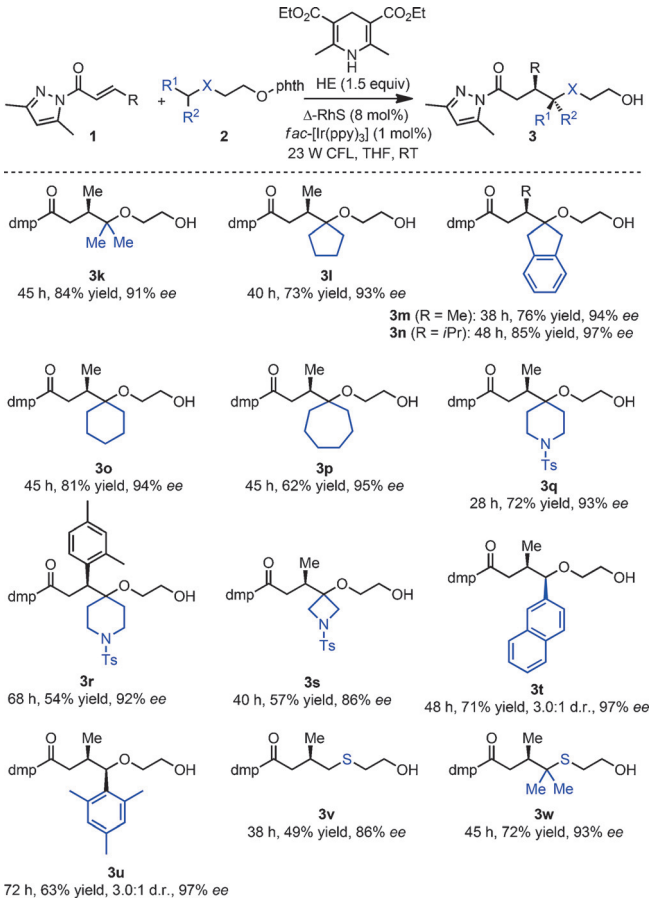


Figure 2. Substrate scope with respect to N-alkoxyphthalimides. An X-ray crystal structure[25] of **3r** was obtained to assign the absolute configuration of the products (see the Supporting Information). dmp = 3,5-Dimethylpyrazole, phth = *N*-phthalimide.

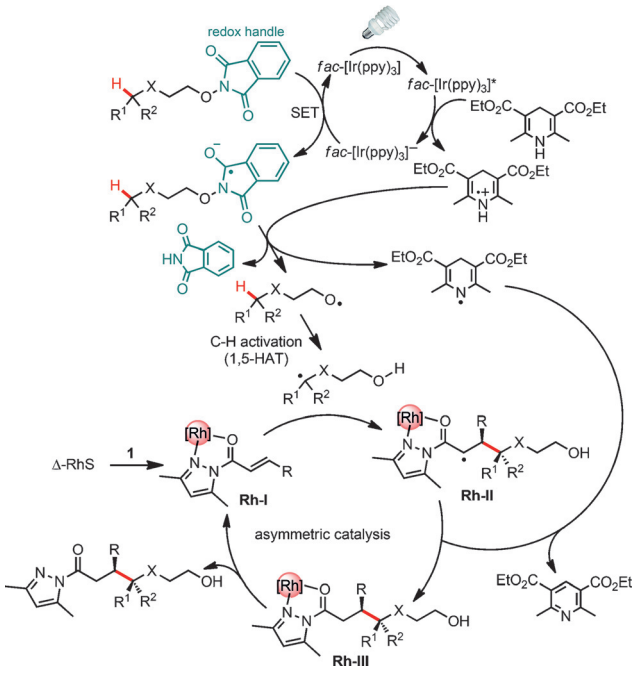


Figure 3. Proposed mechanism which is consistent with the observed product formation and the mechanistic experiments.

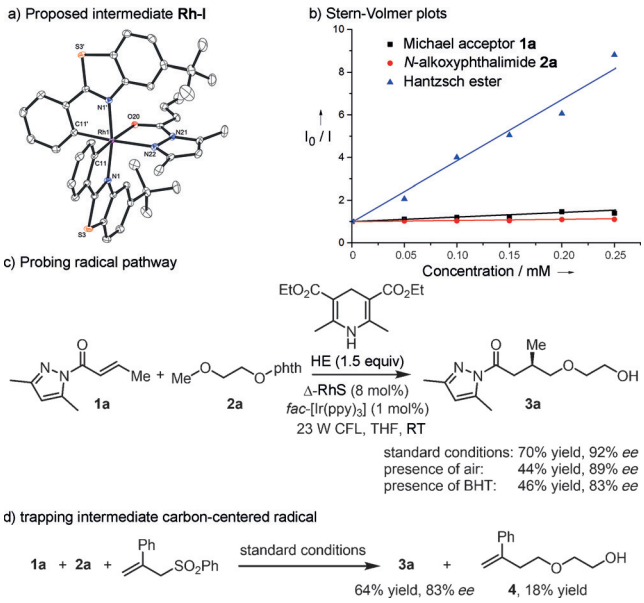


Figure 4. Mechanistic experiments. BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene.

ciently by the Hantzsch ester, in contrast to either substrate **1a** or **2a**, and supports the proposed catalytic mechanism in which electron transfer from the Hantzsch ester to the excited state *fac*-$[Ir(ppy)_3]^*$ occurs and is at the center of the redox process. Third, the presence of air or the radical inhibitor BHT (5 equiv) results in a reduced yield and enantioselectivity of the C–C-formation product **3a**, which provides evidence for a radical pathway (Figure 4c). The proposed intermediate carbon-centered radical was verified by a trapping experiment with a competing electron-deficient alkene (Figure 4d). Finally, we determined a quantum yield of 0.05 for the reaction **1a**+**2a**→**3a** which is consistent with the proposed absence of a chain process.[24]

In summary, we here demonstrated how C(sp^3)–H bond functionalization through radical translocation can be merged with a catalytic asymmetric C–C bond formation by combining visible-light-activated photoredox catalysis with chiral Lewis acid catalysis. We believe that this method is of significant practical value since it makes use of the functionalization of unactivated C(sp^3)–H bonds, and at the same time introduces two stereocenters. It employs simple activating groups, namely N-alkoxyphthalimides as recently developed redox-active radical precursors,[4] as well as N-acylpyrazoles as Lewis-acid-activatable functional groups. It is worth noting that N-acylpyrazoles are highly useful precursors for mild conversion into other carbonyl functionalities with high yields, as shown for the representative conversion into an amide (**3q**→**3q′**) and a diol (**3q**→**3q″**; Figure 5). The extension of this methodology to the activation of other remote C(sp^3)–H groups is underway in our laboratory.

Acknowledgments

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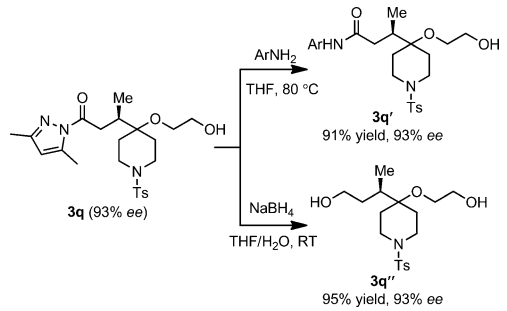

Figure 5. Exemplary transformations starting with the N-acylpyrazole **3q**. Ar = *p*-MeC$_6$H$_4$, Ts = 4-toluenesulfonyl.

Keywords: asymmetric catalysis · C–H activation · photochemistry · radicals · rhodium

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[23] For the relatively sluggish conversion **1a** + **2h** → **3s** (Figure 2) we were able to isolate 2-((1-tosylazetidin-3-yl)oxy)ethanol as a side product. This furthermore supports our proposed mechanism and can be explained by a competing undesired reduction of the initial oxygen- or carbon-centered radicals. See the Supporting Information for more details.

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[25] CCDC 1492579 (**3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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