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Catalytic, Enantioselective Addition of Alkyl Radicals to Alkenes via Visible-Light-Activated Photoredox Catalysis with a Chiral Rhodium Complex

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Supporting Information

ABSTRACT: An efficient enantioselective addition of alkyl radicals, oxidatively generated from organotrifluoroborates, to acceptor-substituted alkenes is catalyzed by a bis-cyclometalated rhodium catalyst (4 mol %) under photoredox conditions. The practical method provides yields up to 97% with excellent enantioselectivities up to 99% ee and can be classified as a redox neutral, electron-transfer-catalyzed reaction.

The renaissance of single electron transfer activated chemistry has recently redirected some focus to the chemistry of the involved odd electron species such as organic radicals.[1−3] Although elementary reactions of organic radicals are well understood, controlling their stereoselective chemistry in a practical reaction setting is still a formidable challenge that needs to be addressed.[4] For example, although the addition of nucleophilic alkyl radicals to electron deficient alkenes is an established and much applied C−C bond formation reaction, efficient catalytic enantioselective versions are still limited, and this can be pinpointed to the high background (uncatalyzed) reactivity of the involved alkyl radicals.[5] Sibi and co-workers reported one of the most impressive examples of chiral Lewis acid catalysis in conjugate radical additions, namely using a magnesium bisoxazoline complex at 5 mol % loading for catalyzing the enantioselective conjugate isopropyl radical addition to an oxazolidinone cinnamate (Figure 1).[6] However, the reaction needs equimolar amounts of a toxic stannane and is executed at −78 °C to achieve such low catalyst loading. Recently, Yoon and co-workers reported a catalytic enantioselective addition of α-aminoalkyl radicals to α,β-unsaturated carbonyl compounds under photoredox conditions.[7,8] However, catalyst loadings of the employed chiral scandium complex are fairly high, and the system is limited to silanes with amines in α-position. Here we wish to report our progress into this direction, namely a very efficient and practical enantioselective addition of alkyl radicals, released from organotrifluoroborates, to acceptor-substituted alkenes via chiral rhodium catalysis under photoredox conditions.

Inspired by recent work of Molander and co-workers on using organotrifluoroborates as precursors for radicals under oxidative photoredox conditions,[9] we started our study by investigating the reaction of the α,β-unsaturated acyl imidazole **1a** with potassium benzyltrifluoroborate **2a** under photoredox conditions (Table 1). Disappointingly, in the presence of the previously developed dual function photoredox/chiral Lewis acid catalysts Λ-**IrO** or Λ-**IrS** under visible light irradiation,[10] no desired C−C bond formation product **3a** was detectable

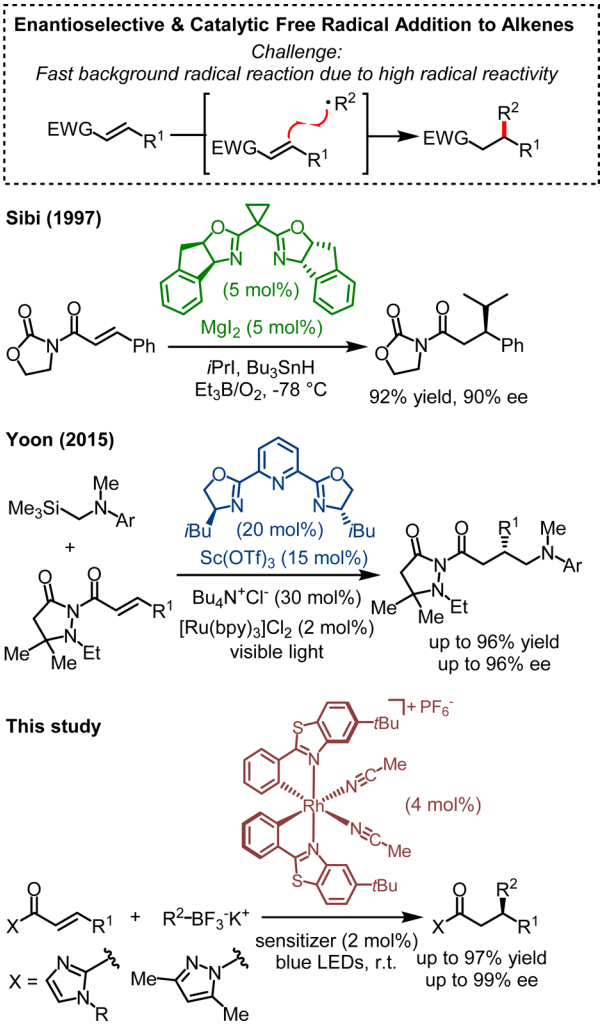

Figure 1. Previous work and this study on catalytic enantioselective radical additions to acceptor-substituted alkenes.

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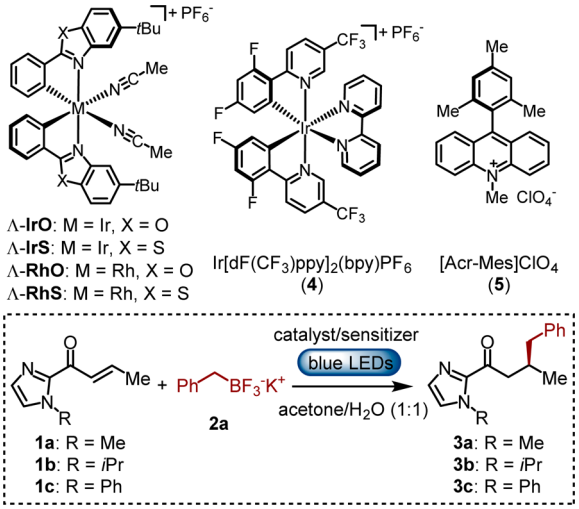
Table 1. Initial Experiments To Identify an Optimal Catalyst/Sensitizer Combination[a]



entry	catalyst	sensitizer	hν[b]	substrate	yield (%)[c]	ee (%)[d]
1	Λ-**IrO**	none	yes	**1a**	0	n.a.
2	Λ-**IrS**	none	yes	**1a**	0	n.a.
3	Λ-**IrS**	**4**	yes	**1a**	<5	n.d.
4	Λ-**RhO**	**4**	yes	**1a**	43	79
5	Λ-**RhS**	**4**	yes	**1a**	67	88
6	Λ-**RhS**	**4**	yes	**1b**	66	93
7	Λ-**RhS**	**4**	yes	**1c**	73	94
8	Λ-**RhS**	**5**	yes	**1c**	73	96
9	Λ-**RhS**	**4**	no	**1c**	0	n.a.
10	Λ-**RhS**	none	yes	**1c**	0	n.a.
11	none	**4**	yes	**1c**	29	0

[a]Conditions: **1a–c** and **2a** (1.5 equiv) with catalyst (none or 4 mol %), and photosensitizer (none or 2 mol %) in acetone/H_2O (1:1) at r.t. for 4–6 h under irradiation with visible light. [b]Light source: 24 W blue LEDs. [c]Isolated yields. [d]Enantioselectivities of **3a–c** determined by HPLC on chiral stationary phase. n.a. = not applicable; n.d. = not determined.

(Table 1, entries 1–2). The presence of an additional photosensitizer did not improve the result (Table 1, entry 3). Encouragingly, when the chiral Lewis acid Λ-**RhO**[11] in combination with the photosensitizer **4** was applied to this system, the reaction proceeded in 43% yield and with 79% ee.[12] The newly developed Lewis acid Λ-**RhS**,[13] which provides an increased steric hindrance due to long C–S bonds, afforded the product **3a** with an improved yield of 67% and 88% ee (Table 1, entry 5). An optimization of the imidazole auxiliary by replacing the *N*-methyl (**1a**) with an isopropyl (**1b**) or a phenyl (**1c**) substituent improved the enantioselectivity to 93% ee (**3b**) and 94% ee (**3c**), respectively (Table 1, entries 6 and 7). Use of the substrate **1c** in combination with the less expensive organic sensitizer **5**[14] provided the C–C formation product even with 96% ee (Table 1, entry 8). Meanwhile, control experiments verified that the photosensitizer and visible light are essential for product formation (Table 1, entries 9 and 10). However, in absence of the chiral Lewis acid Λ-**RhS**, the radical addition product **3c** was still generated in 29% yield, albeit as a racemic mixture (Table 1, entry 11).[15] This observation demonstrates that Λ-**RhS** must strongly accelerate the radical addition to overcome the prevailing racemic background reaction.

Next, we evaluated the scope of the visible-light-induced enantioselective addition of trifluoroborate **2a** to electron-deficient alkenes **1c–k**, providing the C–C bond formation products **3c–k** with 40–90% yields and 83–96% ee (Figure 2).

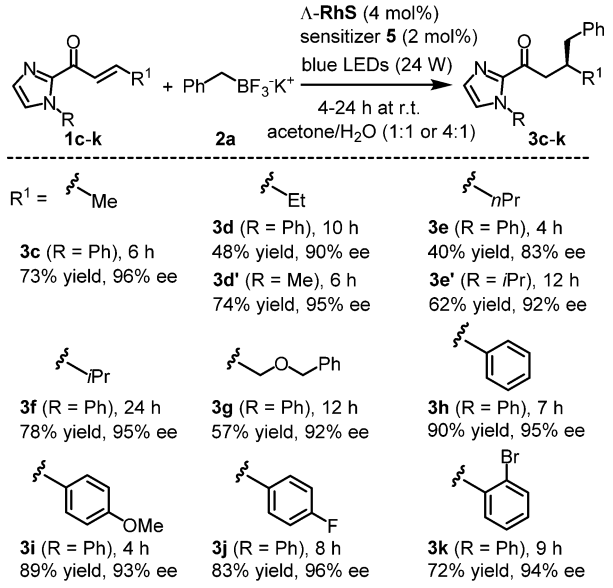


Figure 2. Substrate scope with different 2-acyl imidazoles.

Figure 2 summarizes the effect of various alkene substituents. The reaction is tolerant of aliphatic substituents (**3c–f**), an ether (**3g**), and aromatic moieties with electron-rich or electron-deficient groups (**3h–k**). It is noteworthy that depending on the particular alkene, different *N*-imidazole substituents provide the best results as can be seen by the comparison of **3d** with **3d′** (Me favored) and **3e** with **3e′** (*i*Pr favored), which allow for an individual optimization of yields and enantioselectivities.

The scope of this reaction with respect to organotrifluoroborates is outlined in Figure 3. A wide range of trifluoroborates (**2b–p**), ranging from benzyltrifluoroborates with electron withdrawing and electron donating substituents, various alkoxylmethyltrifluoroborates, and secondary alkyltrifluoroborates, to tertiary alkyltrifluoroborates, can be used in this reaction providing the products **3l–z** in yields of 61–97% and with 77–99% ee.

Next, to improve the practical utility of this reaction, we were seeking a synthetically more versatile class of alkene substrates, and we found that *α,β*-unsaturated *N*-acyl-3,5-dimethylpyrazoles (**6a–e**) react readily with benzyltrifluoroborates (**2a–e**) under our developed reaction conditions to provide the C–C bond formation products **7a–g** in yields of 54–75% and with 83–97% ee (Figure 4).

Finally, the conversion of two typical products, one imidazole and one pyrazole, to useful synthetic building blocks is illustrated in Figure 5. Cleavage of the pyrazole auxiliary in **7e** under reductive conditions afforded the alcohol **7e′** quantitatively and with unchanged ee.[16] On the other hand, the removal of the imidazole moiety of **3w** smoothly proceeded to provide ethyl ester **3w′** in 90% yield and with unchanged ee.[17]

The proposed mechanism is shown in Figure 6. The reaction is initiated by the now well-established photosensitized oxidative conversion of organotrifluoroborates to carbon-

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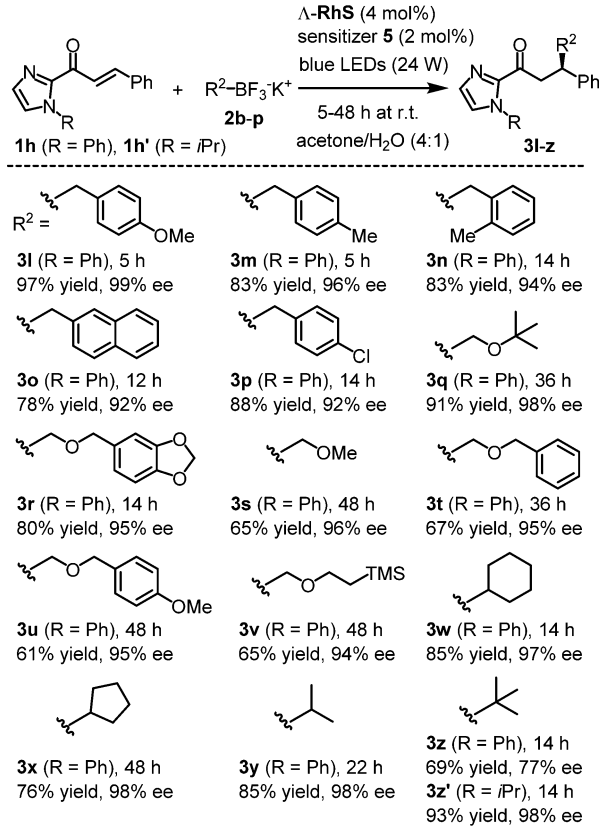
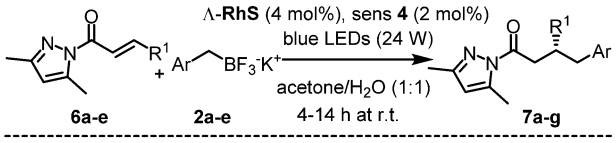


Figure 3. Substrate scope regarding organotrifluoroborates.



	R^1	Ar	t (h)	yield	ee
7a	Me	Ph	6	62%	96%
7b	Me	2-MePh	12	61%	95%
7c	Me	2-Naph	12	68%	96%
7d	Et	4-MePh	14	54%	96%
7e	*n*Pr	4-MeOPh	14	75%	97%
7f	*n*Pentyl	4-MeOPh	14	61%	90%
7g	Ph	4-MeOPh	4	73%	83%

Figure 4. 2-Acyl pyrazoles as substrates.

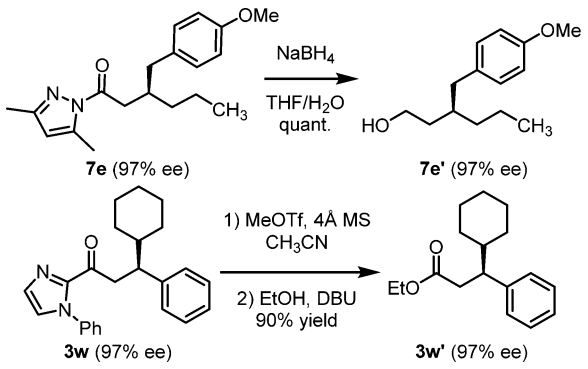


Figure 5. Transformation of selected products.

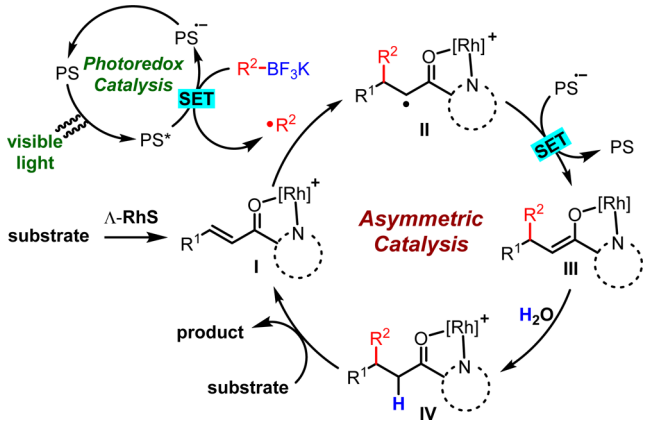


Figure 6. Proposed simplified mechanism without indicating possible chain transfer. SET = single electron transfer; PS = photosensitizer.

centered radicals,[9,18] which in turn add to *N*,*O*-rhodium-coordinated 2-acyl imidazole or *N*-acyl pyrazole substrate (intermediate **I**, see Supporting Information for a crystal structure with an *N*-acyl pyrazole substrate), thereby generating the secondary radical intermediate **II**, which is subsequently reduced by single electron transfer (SET) to a rhodium enolate (intermediate **III**), which upon protonation by water provides rhodium-bound product (intermediate **IV**).

A number of control experiments back this mechanism. First, visible light and photosensitizer are required for product formation (Table 1, entries 9 and 10). Second, Stern–Volmer plots and TEMPO trapping experiments support the intermediate generation of alkyl radicals from organotrifluoroborates induced by SET from the photoexcited sensitizer. Third, product deuteration upon performing the reaction in acetone/D_2O is consistent with the proposed SET/protonation sequence as opposed to an alternative H-abstraction from acetone. Finally, quantum yield measurements under consideration of competing light absorption and quenching effects from rhodium complexes, and other deactivation pathways, suggest that radical intermediate **II** not only accepts a single electron from the reduced photosensitizer, but also alternatively from an organotrifluoroborate substrate molecule, thereby leading to a chain process (see Supporting Information for more details).[19]

According to the described mechanism, it is unusual that with catalyst loadings of just 4 mol %, enantioselectivities of up to 99% ee can be obtained, and all this even at room temperature. Apparently, the radical addition to the double bond of free substrate (background reaction) cannot compete with the radical addition to rhodium-coordinated substrate (Lewis acid catalyzed reaction). This is counterintuitive considering the high reactivity of alkyl radicals toward acceptor-substituted alkenes combined with the fact that at the beginning of the reaction free substrate is in large excess (25-fold) over rhodium-coordinated substrate. The rhodium-based Lewis acid must therefore provide a strong acceleration of the radical addition. This is indeed the case as determined by competition experiments shown in Figure 7: rhodium coordination increases the radical addition rate by at least a factor of 3×10^4. This acceleration is obviously the reason for the ability to perform the developed enantioselective radical reaction with low loadings of the chiral Lewis acid.

In conclusion, we have developed a very efficient and practical catalytic enantioselective addition of organotrifluor-

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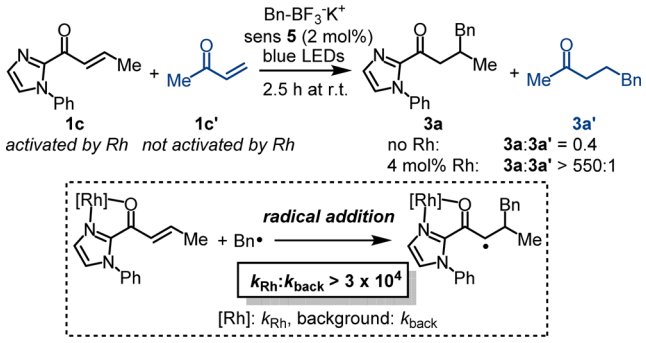

Figure 7. Evaluating the acceleration of the radical addition step by rhodium coordination.

oborates to acceptor-substituted alkenes under photoredox conditions. A key feature is a rhodium-based Lewis acid, which not only provides an excellent stereocontrol, but also accelerates the involved key radical addition step by at least 4−5 orders of magnitude, thereby laying the foundation for the low catalyst loadings for this radical reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03399.

Experimental details; chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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