Dual Catalysis

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Asymmetric Synthesis of 1,4-Dicarbonyl Compounds from Aldehydes by Hydrogen Atom Transfer Photocatalysis and Chiral Lewis Acid Catalysis

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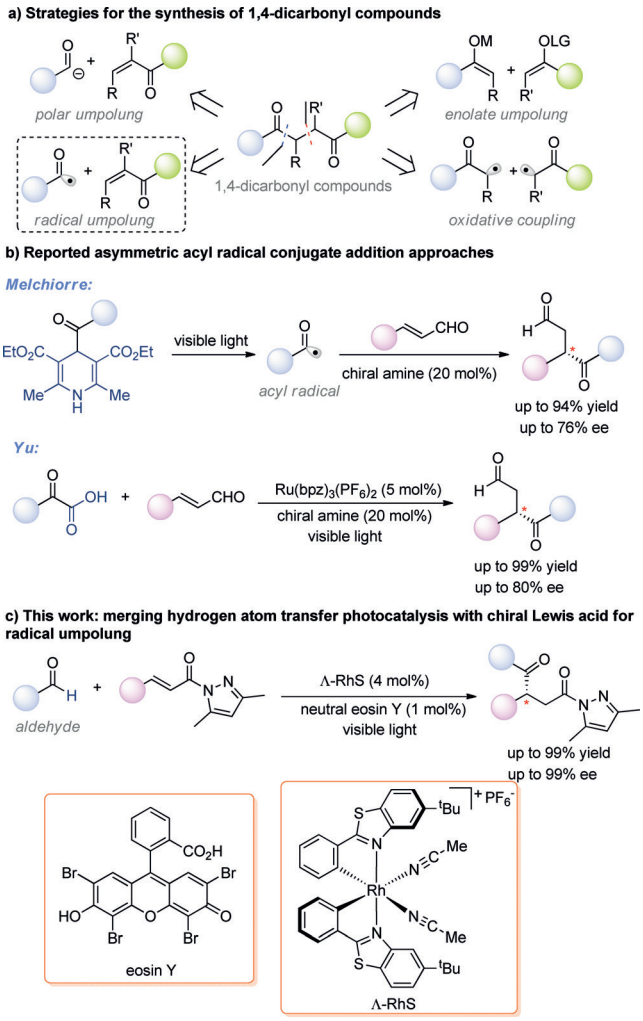
Abstract: *Enantioenriched 1,4-dicarbonyl compounds are versatile synthons in natural product and pharmaceutical drug synthesis. We herein report a mild pathway for the efficient enantioselective synthesis of these compounds directly from aldehydes through synergistic cooperation between a neutral eosin Y hydrogen atom transfer photocatalyst and a chiral rhodium Lewis acid catalyst. This method is distinguished by its operational simplicity, abundant feedstocks, atom economy, and ability to generate products in high yields (up to 99 %) and high enantioselectivity (up to 99 % ee).*

Enantioenriched 1,4-dicarbonyl compounds are prevalent structural motifs in drug scaffolds (e.g., ilomastat, batimastat, TAPI-1, and BMS-906024) and natural products (e.g., aspartic acid and (−)-bursehemin), and are versatile building blocks in pharmaceutical drug synthesis.[1] The synthesis of 1,4-dicarbonyl compounds is not straightforward and is generally achieved through oxidative coupling[1] or umpolung strategies[2] including enolate,[3] acyl anion,[4] and radical-based umpolung[5] processes (Scheme 1 a). The stereoselective synthesis of 1,4-dicarbonyl compounds normally relies on chiral auxiliaries,[6] while catalytic asymmetric variants are rare.[7] Elegant examples of intermolecular catalytic enantioselective Stetter reactions have been reported by Enders,[8] Rovis,[9] Glorius,[10] and Chi,[11] in which an electrophilic aldehyde is catalytically converted into an nucleophilic acyl anion equivalent.

The dramatic developments in photocatalysis over the past decade have allowed acyl radical conjugate additions to be achieved in a mild and green manner.[5] To the best of our knowledge, however, there have only been two recent reports on asymmetric acyl radical conjugate additions targeting the synthesis of enantioenriched 1,4-dicarbonyl compounds. Melchiorre et al. reported the first direct access to chiral 1,4-dicarbonyl compound using a proline-based secondary amine organocatalyst. In this reaction, acyl radicals were generated from 4-acyl-1,4-dihydropyridines upon visible-light irradiation without an external photocatalyst (Scheme 1 b).[12] Yu et al. subsequently demonstrated an asymmetric transformation using the same chiral amine organocatalyst in the presence of the photocatalyst $Ru(bpz)_3(PF_6)_2$, with ketoacids as the starting materials (Scheme 1 b).[13] Despite the effectiveness of these reactions, the enantioselectivity achieved was generally moderate, and a redox auxiliary was required in the starting substrates to promote the generation of acyl radicals through a redox process. A method that can deliver 1,4-dicarbonyl compounds with excellent enantioselectivity



Scheme 1. Synthesis of 1,4-dicarbonyl compounds through asymmetric acyl radical conjugate addition.

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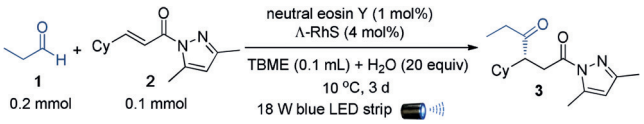
directly from aldehydes, which are naturally abundant, widely available, and inexpensive feedstocks, would therefore be highly attractive.

We recently disclosed unique properties of neutral eosin Y, which can function as an ideal direct hydrogen atom transfer (HAT) photocatalyst due to its absorption of visible light, and is also metal-free, readily available, and inexpensive.[14] It was capable of providing access to acyl radicals directly from aldehydes to achieve umpolung reactivity for the production of 1,4-diketones upon reaction with unsaturated ketones.[14] We therefore anticipated that this photocatalytic HAT approach could be extended to the synthesis of enantioenriched 1,4-dicarbonyl compounds through combination with a suitable chiral Lewis acid.[15,16] We herein report that by combining neutral eosin Y with a chiral-at-metal bis-cyclometalated rhodium(III) complex (Λ-RhS or Δ-RhS), aldehydes can be directly used as acyl radical precursors to undergo catalytic enantioselective addition to α,β-unsaturated *N*-acyl-3,5-dimethylpyrazoles with high enantioselectivity (Scheme 1 c).

The bis-cyclometalated rhodium(III) complex RhS was chosen to validate the hypothesis due to its versatile asymmetric induction under photocatalysis[17] and its successful application in enantioselective addition of alkyl radicals to acceptor substituted alkenes (Table 1).[18] Notably, different from α,β-unsaturated ketones,[14] eosin Y alone cannot promote the coupling of aldehydes with α,β-unsaturated amides, and only a negligible amount of product was detected (entry 1).[19] This provides the opportunity to achieve highly selective asymmetric synthesis, considering that the racemic

Table 1: Investigation of reaction parameters.[a]



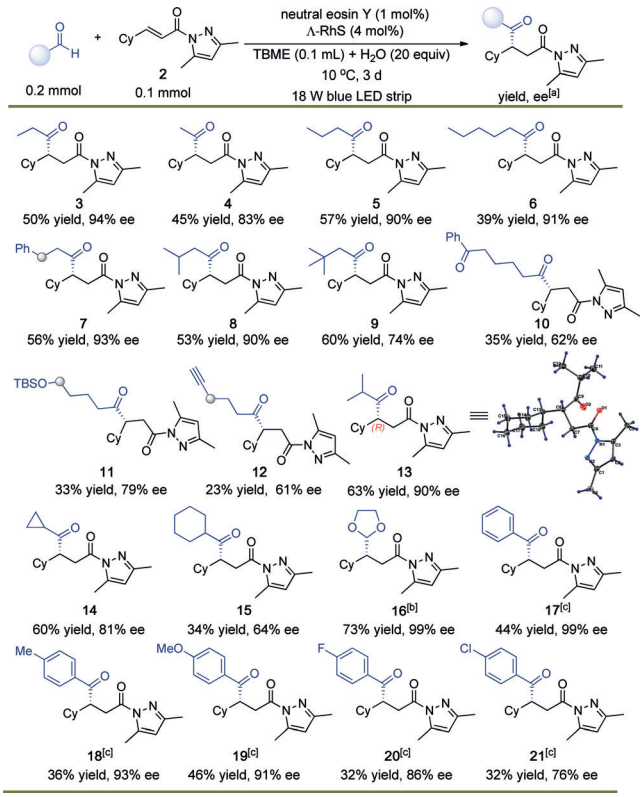
Entry	Deviation from standard conditions[a]	Yield [%][b]	*ee* [%][c]
1	without Λ-Rh	< 5	racemic
2	without neutral eosin Y	< 5	87
3	none	52 (50)[d]	94
4	no H_2O	6	27
5[e]	eosin Y-Na_2 instead of neutral eosin Y	< 5	38
6	$[Ru(bpy)_3]^{2+}Cl_2$ instead of eosin Y	0	–
7	$[Ru(phen)_3]^{2+}Cl_2$ instead of eosin Y	0	–
8	fluorescein instead of eosin Y	11	89
9	30 °C instead of 10 °C	42	76
10	acetone instead of TBME	13	88
11	benzene instead of TBME	29	82
12	without light	0	–
13	Δ-RhS instead of Λ-Rh	52 (49)[d]	92[f]

[a] Standard conditions: **1** (0.2 mmol), **2** (0.1 mmol), neutral eosin Y (0.001 mmol, 1 mol%), Λ-RhS (0.004 mmol, 4 mol%), and water (2 mmol) in *tert*-butyl methyl ether (TBME) (0.1 mL), irradiated under an 18 W blue LED strip at 10 °C for 3 days. [b] Yields were determined by ^{1}H-NMR spectra of the crude product mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] *ee* values were determined by HPLC analysis over a commercial chiral column (chiralcel ID). [d] Yields of isolated products. [e] 13% yield and 84% *ee* of product was obtained when the reaction was conducted with an 18 W white LED strip. [f] The other enantiomer was obtained. LED = light-emitting diode.

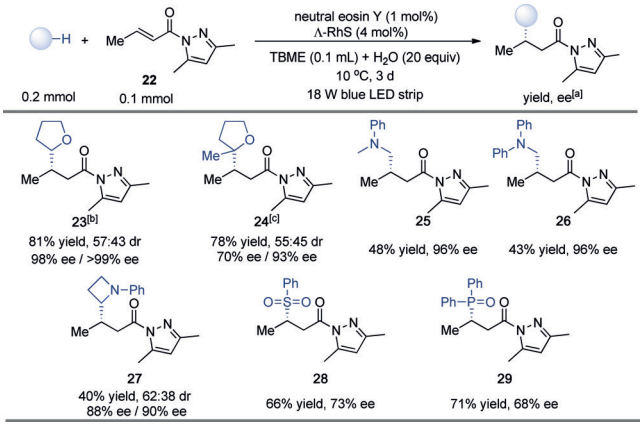
transformation is diminished in the absence of a Lewis acid catalyst.[16i,20] In the absence of eosin Y, Λ-RhS was ineffective too (entry 2). In stark contrast, a significantly higher yield (50%) of product **3** was obtained with high enantioselectivity (94% *ee*) through the combination of eosin Y (1 mol%) and Λ-RhS (4 mol%) (entry 3). This indicates a strong rate acceleration effect on the acyl radical addition induced by substrate coordination with the rhodium complex.[18] The major side product detected originated from hydrolysis of the amide, but water was essential for this transformation and could not be avoided (entry 4). Replacing water with other additives resulted in a significant decline in either reactivity or enantioselectivity (Table S1 in the Supporting Information).[21] The reaction was retarded with the commercial dianionic form of eosin Y as the photocatalyst (entry 5), which is consistent with our earlier recognition of neutral eosin Y as the active HAT photocatalyst.[14] Other photocatalysts bearing a redox potential similar to that of eosin Y ($E^{S*/S^-} = +0.83$ V vs. saturated calomel electrode (SCE)), such as $Ru(bpy)_3^{2+}$ ($E^{Ru^{II}*/Ru^{I}} = +0.77$ V vs. SCE, entry 6), $Ru(phen)_3^{2+}$ ($E^{Ru^{II}*/Ru^{I}} = +0.82$ V vs. SCE, entry 7), and fluorescein ($E^{S*/S^-} = +0.78$ V vs. SCE, entry 8), were not effective for this transformation, which further excludes a redox-induced process. A low temperature (10 °C) was essential to achieve products with high enantioselectivity (entry 9). Among the solvents evaluated, TBME was optimal (entries 10 and 11). No product was formed in the absence of light irradiation (entry 12). Importantly, the other enantiomer of the 1,4-dicarbonyl product could be obtained with equally good yield and enantioselectivity simply by using Δ-RhS (entry 13), thus demonstrating the versatility of this method.

With the optimal conditions in hand, the generality of this asymmetric Giese-type addition with respect to the aldehyde component was evaluated. As shown in Scheme 2, a variety of primary aliphatic aldehydes participated smoothly in the dual catalytic reaction, delivering products **3**–**12** in generally moderate yields of isolated product (23–60%) and moderate to very good enantioselectivity (61–94% *ee*). Functionalities including arenes, ketones, silylethers, and alkynes were well-tolerated. Notably, the eosin Y based HAT approach demonstrated excellent selectivity for activating the aldehyde in the presence of other activated hydridic C–H bonds such as benzylic (**7**), α-oxy (**11**), and propargylic (**12**) C–H bonds. Secondary alkyl aldehydes, either acyclic (**13**) or cyclic (**14**, **15**), were viable coupling partners. Compound **16**, a masked aldehyde, was synthesized in good yield (73%) with excellent enantioselectivity (98%) by using readily available 1,3-dioxolane as the solvent.[22] Aryl aldehydes were less reactive than aliphatic aldehydes and the reactions had to be conducted at 30 °C to achieve synthetically useful conversions (**17**–**21**). However, all electron-neutral (**17**), electron-rich (**18**, **19**), and electron-deficient (**20**, **21**) aryl aldehydes proceeded to afford the desired products in moderate yields (32–46%) with good to excellent enantioselectivity (76–99% *ee*). The absolute configuration of **13** identified by X-ray structural analysis as *R*.[23]

To expand the utility of this dual catalytic asymmetric Giese-type addition, other HAT precursors were investigated (Scheme 3). Cyclic ethers such as tetrahydrofuran (THF) and



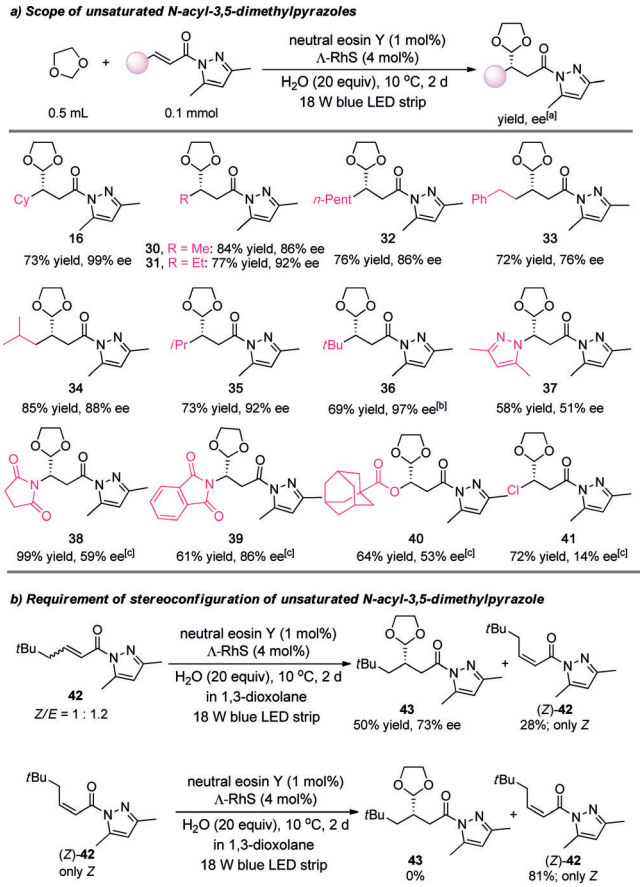
Scheme 2. Aldehyde scope of the asymmetric Giese-type addition. [a] Yields of isolated products. *ee* values were determined by HPLC over the chiral stationary phase. [b] Reaction was conducted in 0.5 mL 1,3-dioxolane. [c] Reaction was conducted at 30 °C for 3 days. The small grey spheres represent other activated hydridic C–H bonds which may undergo HAT.



Scheme 3. Other C–H or X-H substrates for the asymmetric Giese-type addition. [a] Yields of isolated products. *ee* values were determined by HPLC over the chiral stationary phase. [b] THF (0.5 mL) was used as solvent. [c] 2-Me-THF (0.5 mL) was used as solvent.

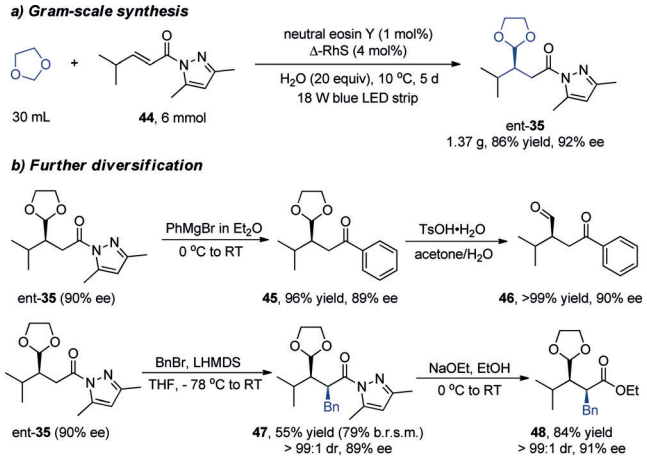
2-methyl tetrahydrofuran delivered products **23** and **24** with excellent enantioselectivity. Both acyclic and cyclic tertiary amines were good candidates for this asymmetric transformation, which provided effective and convenient method direct access to chiral γ-aminoacid skeletons (**25**–**27**). A chiral sulfone (**28**) and phosphine oxide (**29**) were generated smoothly from sulfinic acid and hydrophosphine oxide, respectively, in good yields and with moderate enantioselectivity.

The scope of this asymmetric reaction with respect to α,β-unsaturated *N*-acyl-3,5-dimethylpyrazoles was evaluated using 1,3-dioxolane as the C–H partner. Scheme 4 a summarizes the effect of various alkene substituents. The transformation proceeded well with a range of aliphatic substituents (primary, secondary, and tertiary) in good yields and good to excellent enantioselectivity (**30**–**36**), with bulkier substituents delivering higher selectivity. More pharmaceutically interesting heteroatom-substituted unsaturated amides were also tolerated. While the nitrogen- and oxygen-substituted alkenes afforded products **37**–**40**, derivatives of aspartic acid or malic acid, with moderate to good enantioselectivity, the chlorine-substituted compound gave only poor selectivity (**41**). It is worth noting that when a mixture of *Z*/*E* isomers of α,β-unsaturated *N*-acyl-3,5-dimethylpyrazole (**42**) was employed, only the *E* stereoisomer participated in the radical addition, while the *Z* isomer was fully recovered (Scheme 4 b). No reaction was observed with the *Z* isomer as the only starting alkene. This can be explained by its diminished coordination to the rhodium catalyst due to steric hindrance.



Scheme 4. Scope with respect to unsaturated *N*-acyl-3,5-dimethylpyrazoles. [a] Yields of isolated products. *ee* was determined by HPLC over chiral stationary phase. [b] Reaction conducted for 3 days. [c] Using 8 mol% Λ-RhS.

To further demonstrate the synthetic utility of this method, the asymmetric synthesis was scaled up to gram quantities by prolonging the reaction time to five days (Scheme 5a). Moreover, the pyrazole moiety of product ent-**35** could be converted into an aryl ketone simply through



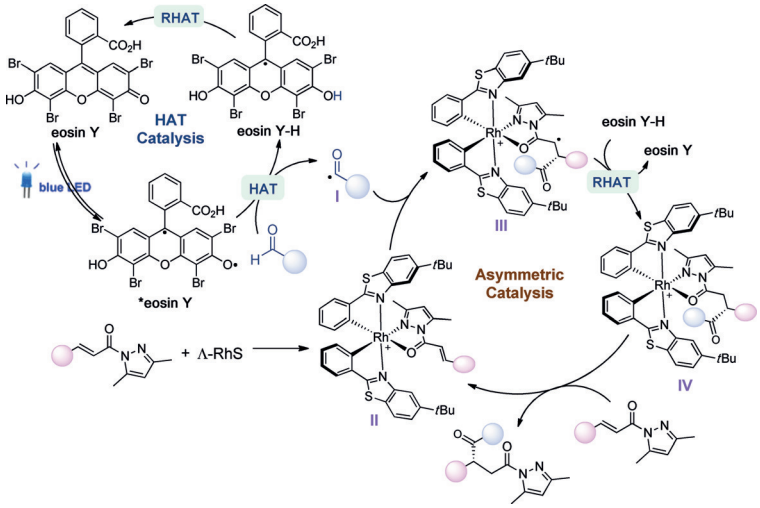
Scheme 5. Gram-scale synthesis and further synthetic diversification.

treatment with an equal amount of Grignard reagents. Deprotection of the 1,3-dioxolane **45** under acidic conditions afforded the aldehyde **46** with no loss of *ee*. Importantly, alkylation of chiral product ent-**35** via enolate formation resulted in the *syn* adduct **47** as a single diastereomer.[24] Subsequent removal of the pyrazole moiety proceeded smoothly to provide ester **48** with unchanged dr and *ee* values. The stereoselective synthesis of 2,3-disubstituted 1,4-dicarbonyl compounds is highly valuable, considering that many natural products and drug molecules contain this chiral motif.[1]

Control experiments were performed to gain further insight into the nature of this dual catalysis. Reaction monitoring by UV/Vis spectroscopy (Figure S9) illustrated that the neutral eosin Y species was the active photocatalyst in the presence of RhS during the reaction process.[14] Based on the redox potentials, excited neutral eosin Y ($E^{S*/S^-} = +0.83$ V vs. SCE in CH_3CN/H_2O)[25] is unable to oxidize an aldehyde to an acyl radical.[5b,26] The reaction was suppressed in the presence of radical scavenger TEMPO. Analysis of the GC-MS results indicated the presence of transient aldehyde radicals (Figure S3). ^{1}H NMR experiments were conducted to elucidate whether water plays a role to facilitate RhS catalyst turnover. As demonstrated in Figures S5–S7, starting amide **2** could displace product **3** from the pre-coordinated complex [RhS + **3**] in the absence of water, to deliver product **3** while regenerating the required complex [RhS + **2**]. However, the exact reason for the positive effect of the water additive is still not clear at this stage, and requires further mechanistic study.

Taking into account the experimental data, a plausible mechanism is proposed (Scheme 6). The acyl radical **I** is generated smoothly by a polarity-matched HAT[27] between photo-activated *eosin Y and an aldehyde. Radical **I** in turn adds to *N,O*-rhodium-coordinated N-acyl pyrazole substrate **II** to produce the secondary radical intermediate **III**, which subsequently undergoes reverse HAT with eosin Y-H to turn over the HAT catalytic cycle. Ligand exchange between intermediate **IV** and the starting unsaturated amide delivers the chiral product and regenerates the active complex **II**.

In conclusion, we have demonstrated that neutral eosin Y based HAT photocatalysis provides a convenient and green approach for the generation of acyl radicals from aldehydes, and can be merged with chiral rhodium based Lewis acid catalysis to deliver useful 1,4-dicarbonyl compounds in good yields and good enantioselectivity. The rhodium catalyst not only provides excellent stereocontrol, but also promotes the key radical addition step. Moreover, the substrate scope can be extended to other types of C–H bonds. This method can be easily scaled up and the product can be converted into a 2,3-disubsituted 1,4-dicarbonyl compound as a single isomer. It thus holds promise to find wide applications in the synthesis of natural products and pharmaceutical compounds.



Scheme 6. Proposed reaction mechanism for the merged HAT photocatalysis and asymmetric Lewis acid catalysis. RHAT = reverse hydrogen atom transfer.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · hydrogen atom transfer · eosin Y · radical umpolung · rhodium

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