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Enantioselective Photocatalytic [3 + 2] Cycloadditions of Aryl Cyclopropyl Ketones

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Supporting Information

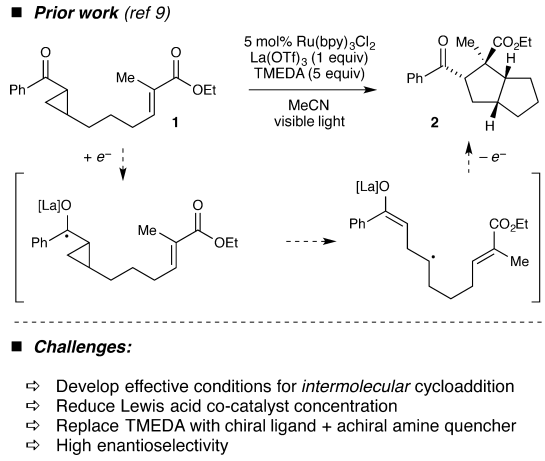
ABSTRACT: Control of stereochemistry in photocycloaddition reactions remains a substantial challenge; almost all successful catalytic examples to date have involved [2 + 2] photocycloadditions of enones. We report a method for the asymmetric [3 + 2] photocycloaddition of aryl cyclopropyl ketones that enables the enantiocontrolled construction of densely substituted cyclopentane structures not synthetically accessible using other catalytic methods. These results show that the dual-catalyst strategy developed in our laboratory broadens synthetic chemists' access to classes of photochemical cycloadditions that have not previously been feasible in enantioselective form.

Stereocontrolled cycloadditions are valued in synthetic chemistry both as methods to construct the ring systems that are ubiquitous in chiral bioactive compounds and as model reactions to evaluate new concepts in enantioselective synthesis.[1] Control over the absolute stereochemistry of photochemical cycloadditions, however, remains a substantial challenge without a general solution.[2] A relatively small number of highly enantioselective organocatalytic[3] and Lewis acid[4] catalyzed photocycloadditions have been described in the past several years, but these successful methods have been focused upon [2 + 2] cycloadditions of enones. No strategies for photocatalytic stereocontrol have emerged that appear to be broadly applicable to the asymmetric catalysis of other classes of photocycloaddition reactions.

Our laboratory recently reported a dual-catalyst system for enantioselective [2 + 2] photocycloaddition using a chiral Lewis acid in tandem with a transition metal photoredox catalyst.[5] The success of this strategy relies upon the ability to tune the structure of the stereocontrolling chiral catalyst for optimal selectivity without adversely affecting the performance of the photocatalyst. We speculated that this combination of catalytic strategies might successfully control the stereochemical behavior of many of the reactions now known to be amenable to photoredox catalysis.[6−8]

We became interested in designing an asymmetric version of the photocatalytic [3 + 2] cycloaddition between aryl cyclopropyl ketones and alkenes that our laboratory reported several years ago (Scheme 1).[9] Although enantioselective cycloadditions of highly activated "donor−acceptor" cyclopropanes are known,[10] no catalytic asymmetric [3 + 2] cycloadditions of less activated cyclopropyl ketones have yet been reported. Our photocatalytic process involves photoreduction of a Lewis acid activated aryl cyclopropyl ketone (**1**)

Scheme 1. Precedent and Project Objectives



to afford a ring-opened distonic radical anion that can react in an intramolecular fashion with a wide range of alkene partners. Although this methodology enables the facile synthesis of structurally diverse cyclopentane-containing polycyclic compounds (e.g., **2**), the reaction gives high yields only in an intramolecular context, requires stoichiometric $La(OTf)_3$ as a Lewis acid catalyst, and employs 5 equiv of TMEDA as both a ligand for La^{3+} and a reductive quencher of $Ru^*(bpy)_3^{2+}$, rendering the use of a chiral diamine ligand unattractive. We report here the development of an enantioselective photocatalytic [3 + 2] cycloaddition that successfully addresses all of these challenges.

Table 1 outlines optimization studies for a model asymmetric [3 + 2] cycloaddition between phenyl ketone **3** and styrene. We initially examined conditions based upon those we reported for the racemic intramolecular reaction, employing 2.5 mol % $Ru(bpy)_3^{2+}$ as the photocatalyst, 1 equiv of $La(OTf)_3^{2+}$ as a Lewis acid cocatalyst, and *i*-Pr_2NEt as a reductive quencher. Consistent with our prior observations, the intermolecular reaction was sluggish, and the addition of chiral ligands strongly inhibited the reaction (entries 1 and 2). A screen of other Lewis acidic metal triflate complexes revealed that Gd(III) pybox complexes[11] could provide somewhat better conversions and, gratifyingly, experimentally significant enantioselectivity, with a maximum ee of 59% using the *s*-Bu-substituted pybox ligand **L3** (entries 3−5).

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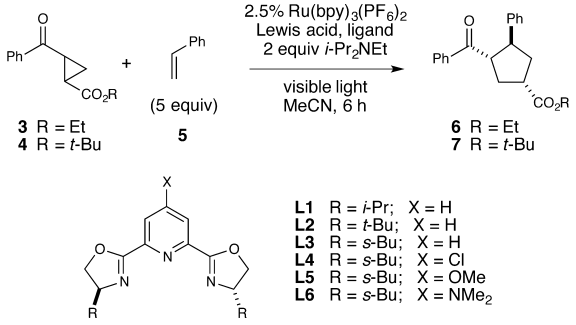
Table 1. Optimization Studies



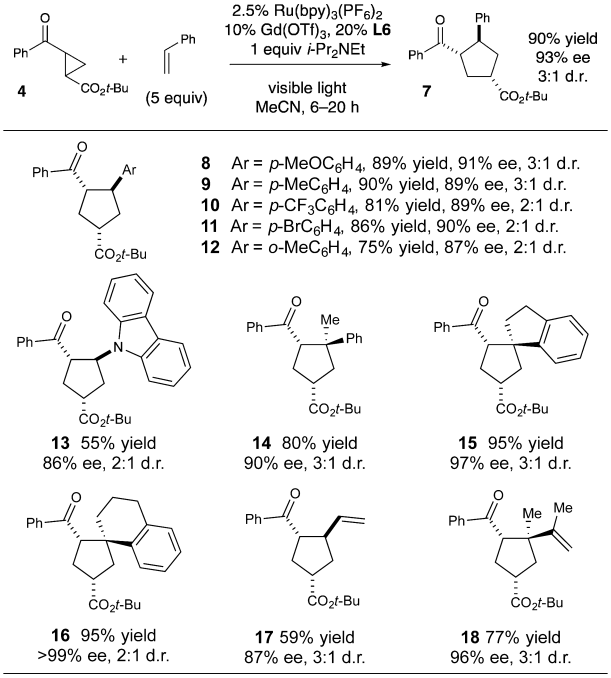
entry	conditions[a]	yield (%)[b]	dr; % ee
1	100% $La(OTf)_3$	25	14:1; n/a
2	100% $La(OTf)_3$, 100% **L2**	5	
3	100% $Gd(OTf)_3$, 100% **L1**	15	3:1; 38%
4	100% $Gd(OTf)_3$, 100% **L2**	96	3:1; 45%
5	100% $Gd(OTf)_3$, 100% **L3**	25	2:1; 59%
6	100% $Gd(OTf)_3$, 200% **L3**	36	3:1; 63%
7	100% $Gd(OTf)_3$, 200% **L4**	0	
8	100% $Gd(OTf)_3$, 200% **L5**	90	2:1; 64%
9	100% $Gd(OTf)_3$, 200% **L6**	89	2:1; 85%
10	10% $Gd(OTf)_3$, 20% **L6**	96	2:1; 79%
11	10% $Gd(OTf)_3$, 20% **L6**, 0 °C	80	3:1; 85%
12	10% $Gd(OTf)_3$, 20% **L6**, − 20 °C	41	3:1; 91%
13[c]	10% $Gd(OTf)_3$, 20% **L6**, 0 °C	86	3:1; 90%
14[c,d]	10% $Gd(OTf)_3$, 20% **L6**, 0 °C	95	3:1; 93%

[a]Reactions carried out on 0.045 mmol scale, irradiating with a 23 W CFL for 6 h. [b]Yields determined by ^{1}H NMR using phenanthrene as an internal standard. [c]Using **4** instead of **3**. [d]Using 1 equiv of *i*-Pr_2NEt.

Analysis of reaction progress revealed that $Gd(OTf)_3$ and *i*-Pr_2NEt slowly formed an inactive Lewis acid−base complex over several hours, which coincided with a concomitant decrease in the rate of product formation. We increased the ligand-to-metal ratio in an attempt to slow formation of a deactivated complex, albeit with little beneficial effect (entry 6). As an alternative strategy, we wondered if we might stabilize the active Gd-pybox complex by increasing the coordinating ability of the chiral ligand.[12] Indeed, although chloride-substituted ligand **L4** resulted in no product formation, electron-rich methoxy-substituted ligand **L5** provided **6** in excellent yield (entry 8). Dimethylamino-substituted ligand **L6** provided optimal rate and stereoselectivity (entry 9); with this ligand, the Lewis acid loading could be decreased to 10 mol % with little effect on ee (entry 10). Lowering temperature to 0 °C resulted in an increase in the enantioselectivity to 85% ee (entry 11). The ee was further improved at −20 °C, but we observed an increased proportion of an undesired reductive ring-opening product (entry 12). Increasing the bulk of the ester substituent provided somewhat higher ee at 0 °C (entry 13), and the occurrence of the reductive ring-opening side-product could be minimized by lowering the concentration of *i*-Pr_2NEt (entry 14). Under these optimized conditions, cycloadduct **7** was obtained in 95% yield, 93% ee, and 3:1 d.r..[13]

We next conducted an exploration of the scope of the enantioselective cycloaddition under these conditions. Table 2 outlines the effect of varying the structure of the alkene reaction partner.[14] We have proposed a stepwise cycloaddition initiated by radical addition of a ring-opened distonic radical anion to an alkene. Consistent with this proposal, simple aliphatic alkenes are not reactive. However, a variety of electronically modified

Table 2. Alkene Substrate Scope[a]



[a]Reactions irradiated with a 23 W CFL for 6−20 h. Yields reported are the combined isolated yields of all diastereomers. Major diastereomer shown.

styrenes react smoothly and with good ee (**8**−**10**). Potentially reactive aryl halides are well-tolerated (**11**), providing a handle for derivatization of the enantioenriched cycloadducts. The enantioselectivity is relatively insensitive to the position of substituents on the aryl ring (**12**). Although heterocycles containing Lewis basic heteroatoms resulted in a loss in stereoselectivity, alkenes bearing less basic heterocycles such as carbazoles react smoothly with good ee (**13**). Internal olefins, unfortunately, were unreactive under these reaction conditions; however, 1,1-disubstituted styrenes react smoothly and provide excellent ee (**14**−**16**). Finally, dienes are also competent reaction partners, affording vinyl cyclopentane products in good ee (**17** and **18**).

The scope of this reaction with respect to the aryl ketone component is summarized in Table 3. The aryl moiety tolerates significant electronic perturbation: Both electron-rich and -deficient substituents provided the corresponding cyclopentanes in good yield and excellent ee (**19**−**22**). Heteroaryl cyclopropyl ketones are also tolerated (**23**), although the ee suffers if the heterocycle is positioned to provide an alternate site for Lewis acid chelation. Arene substituents at the 3-position have minimal impact on the selectivity of the reaction (**24**). However, 2- substituents have a large deleterious effect, which would be expected if the ketone were coordinated to the chiral Lewis acid in the enantioselectivity-determining step. The ester moiety can be replaced by a ketone with minimal impact on the stereoselectivity (**25**), but a methyl-substituted cyclopropane provides poor ee (**26**). However, cyclopropyl ketones bearing geminal β-dialkyl substituents afford excellent ee, although higher Lewis acid concentrations were required for optimal rate (**27**, **28**).

Scheme 2 depicts our working model for the mechanism of this reaction. Photoexcitation of $Ru(bpy)_3^{2+}$ and reductive quenching by *i*-Pr_2NEt affords $Ru(bpy)_3^{+}$. Subsequent electron

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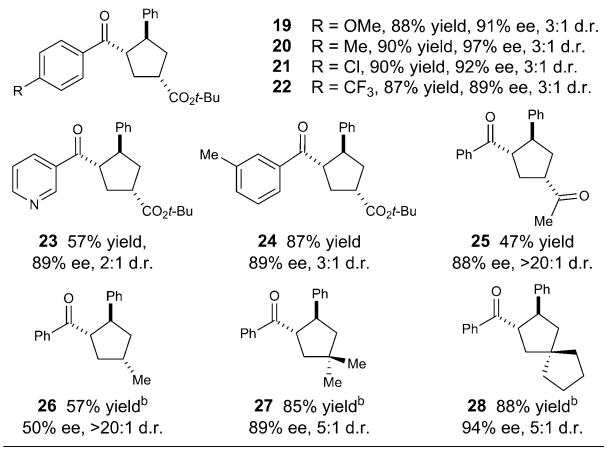
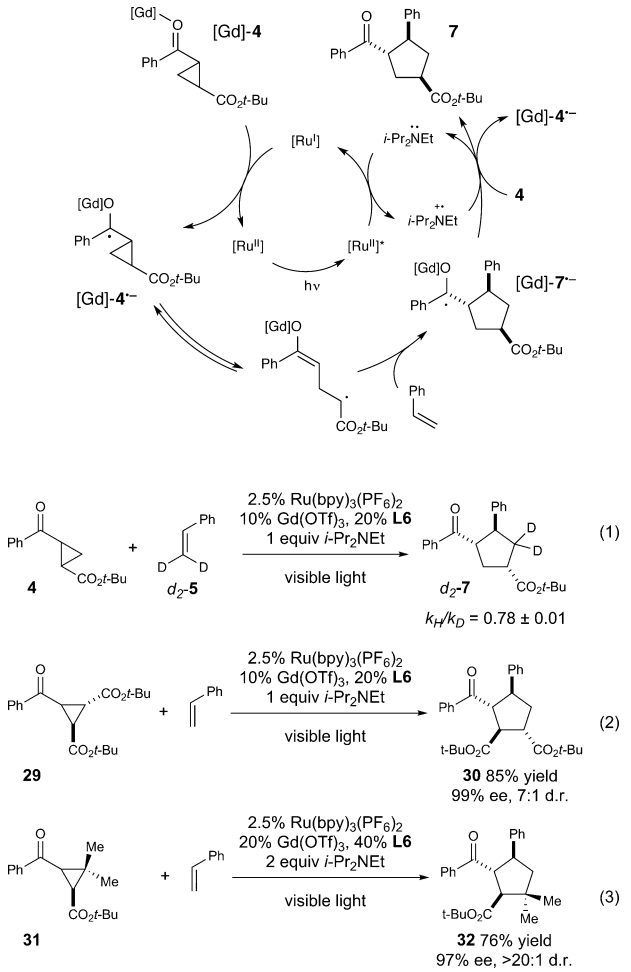
Table 3. Cyclopropane Substrate Scope[a]



[a]Yields reported are the combined isolated yields of all diastereomers. Major diastereomer shown. [b]Reaction conducted using 20 mol % $Gd(OTf)_3$ and 30 mol % **L6** at −20 °C for 48 h.

Scheme 2. Proposed Mechanism for Enantioselective [3 + 2] Cycloaddition

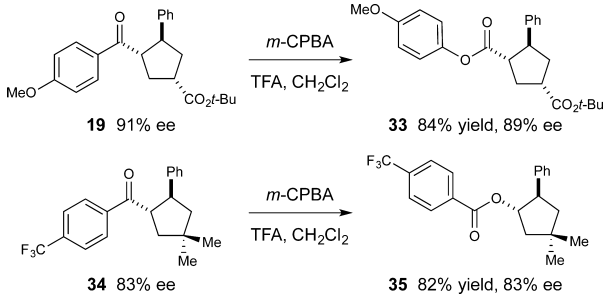


transfer to phenyl ketone **4** occurs only upon activation with the chiral Gd(III) Lewis acid; the resulting ketyl radical ([Gd]-$4^{\bullet-}$) undergoes reversible ring-opening followed by slow stepwise cycloaddition with styrene to afford product ketyl radical [Gd]-$7^{\bullet-}$. Formation of neutral product **7** could occur either by chain-propagating electron transfer to another equivalent of substrate or by chain-terminating reduction of the photogenerated amine radical cation.

The mechanism proposed in Scheme 2 is supported by several lines of evidence. First, a reaction with deuterium-labeled styrene d_2-**5** gives an inverse secondary kinetic isotope effect (k_H/k_D = 0.78) consistent with a rate-limiting intermolecular C−C-bond-forming step (Scheme 2, eq 1).[15] Second, Tanko has reported that the ring-opening of similar cyclopropyl ketyl radicals is reversible and endergonic.[16] To validate this expectation, we monitored a reaction starting with the cis isomer of **4** and found that cyclopropane was completely isomerized to the trans isomer within 1 h, well before the reaction was complete. This reversible cleavage is consistent with the observation that racemic β,β'-disubstituted cyclopropane **29** undergoes stereoconvergent cycloaddition to cyclopentyl ketone **30** in good diastereoselectivity and excellent ee (Scheme 2, eq 2).[17] The cycloaddition of unsymmetrically substituted cyclopropyl ketone **31** also provides excellent stereoselectivity and exclusive chemoselectivity for the formation of enantioenriched cyclopentane **32** and not its constitutional isomer (Scheme 2, eq 3).

Although the scope of this new asymmetric [3 + 2] cycloaddition is complementary to the established enantioselective reactions of donor−acceptor cyclopropanes, the aryl ketone moiety required for the initial one-electron reduction process imposes an undesirable limitation on scope. Thus, we wondered if the aryl ketone could be removed with retention of stereochemistry through a Baeyer−Villiger cleavage. Indeed, *p*-methoxyphenyl ketone cycloadduct **19** undergoes completely regioselective oxidation to afford **33** in good yield, the activated ester of which is poised for further manipulation into diverse carboxylic acid derivatives. Under identical conditions, *p*-trifluoromethylphenyl ketone **34** undergoes regiocomplementary oxidation to afford benzoate ester **35**. Thus, the applicability of this [3 + 2] photocycloaddition method to reactions of electronically varied aryl ketones provides a flexible strategy for the conversion of the enantioenriched products to a diverse array of five-membered carbocyclic derivatives.

Scheme 3. Cleavage of the Aryl Ketone Moiety



These studies have several important implications. From a practical perspective, this method provides an asymmetric catalytic method to assemble structurally complex five-membered carbocycles, which are a class of compounds that remain challenging to prepare in enantioenriched form. More broadly, these results demonstrate that the combination of chiral Lewis acid and photoredox catalysis offers a robust and potentially general approach to photochemical stereocontrol that is broadly applicable to the increasing number of powerful transformations achievable using photoredox catalysis.

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■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and compound characterization data. (PDF)

X-ray crystallographic data for **11**. (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The d.r. reflects the ratio of the major diastereomer shown and an epimer at the ester-bearing carbon. Only a trace of a presumed third diastereomer was observable by ^{1}H NMR analysis of the unpurified reaction mixture and could not be isolated for identification.

(14) The absolute configuration of **11** was determined by X-ray crystallographic analysis; the configuration of other cycloadducts were assigned by analogy.

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(17) The minor diastereomer of **31** can be isolated and resubjected to the reaction conditions with no loss of stereochemical integrity. Thus, the diastereoselectivity does not reflect an equilibrium ratio.

■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, an uncorrected version of the paper was published online on March 29, 2016. The fully corrected version was reposted on March 30, 2016.

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