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A Dual-Catalysis Approach to Enantioselective [2+2] Photocycloadditions Using Visible Light

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Abstract

In contrast to the wealth of catalytic systems that are available to control the stereochemistry of thermally promoted cycloadditions, few similarly effective methods exist for the stereocontrol of photochemical cycloadditions. A major unsolved challenge in the design of enantioselective catalytic photocycloaddition reactions has been the difficulty of controlling racemic background reactions that occur by direct photoexcitation of substrates while unbound to catalyst. Here we describe a strategy for eliminating the racemic background reaction in asymmetric [2+2] photocycloadditions of α,β-unsaturated ketones to the corresponding cyclobutanes by employing a dual-catalyst system consisting of a visible light-absorbing transition metal photocatalyst and a stereocontrolling Lewis acid co-catalyst. The independence of these two catalysts enables broader scope, greater stereochemical flexibility, and better efficiency than previously reported methods for enantioselective photochemical cycloadditions.

Modern stereoselective synthesis enables the construction of a vast array of organic molecules with precise control over their three-dimensional structure (1, 2), which is important in a variety of fields ranging from drug discovery to materials engineering. Photochemical reactions could have a substantial impact on these fields by affording direct access to certain structural motifs that are otherwise difficult to construct (3, 4). For example, the most straightforward methods for the construction of cyclobutanes and other strained four-membered rings are photochemical [2+2] cycloaddition reactions. The stereochemical control of photocycloadditions, however, remains much more challenging than the stereocontrol of analogous non-photochemical reactions (5, 6) despite the chemistry community's sustained interest in photochemical stereoinduction over the last century (7, 8).

Although many strategies using covalent chiral auxiliaries (9, 10) or non-covalent chiral controllers (11, 12) have been used to dictate absolute stereochemistry in photochemical cycloaddition reactions, the development of methods that utilize sub-stoichiometric stereodifferentiating chiral catalysts has proven a more formidable challenge. This is in large part due to the difficulty of controlling uncatalyzed background photochemical processes (Figure 1A, *path i*). The direct photoexcitation of an unbound achiral substrate, free from the influence of a chiral catalyst, necessarily results in racemic products; thus, regardless of how

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enantioselective the catalyzed reaction might be (Figure 1A, *path ii*), the net enantiomeric excess (ee) of the product will be low unless the rate of the uncatalyzed racemic background cycloaddition can be diminished. Bach, whose laboratory has reported the only highly enantioselective catalytic photocycloadditions to date, has approached this problem by designing elegant reactions where the catalyst-substrate complex absorbs light at longer wavelengths than the free substrate. This has been accomplished either by using a chiral hydrogen-bonding xanthone-based photosensitizer (13–15) or by using a chiral Lewis acid catalyst capable of inducing a bathochromic shift in the bound substrate (16, 17). In both cases, Bach has been able to achieve impressive enantioselectivities with substoichiometric chiral controllers. However, effective stereocontrol requires careful irradiation with a monochromatic light source that selectively excites the catalyst-substrate complex at a wavelength where absorption by the free substrate is minimized. The contribution of background reaction, though lessened in these systems, nevertheless remains significant and results in a dependence of the ee on catalyst concentration; optimal selectivities are obtained only at high catalyst loadings (typically ~50 mol%) at which the catalyzed process can outcompete the racemic background cycloaddition. Thus, the lack of a general strategy for completely eliminating uncatalyzed background photochemistry continues to be a fundamental impediment to the discovery of efficient enantioselective catalytic photocycloadditions.

Given these considerations, we speculated that the visible light induced (18) photocatalytic [2+2] cycloaddition (19, 20) recently reported in our lab (Figure 1B) might be an ideal platform for the development of a highly enantioselective catalytic photocycloaddition that is free of racemic background reaction. The crucial activation step in this cycloaddition involves the one-electron reduction of a Lewis acid-activated aryl enone by a Ru(I) complex generated by visible light irradiation of $Ru(bpy)_3^{2+}$ in the presence of an amine donor. There are two distinct features of this process that work together to prevent uncatalyzed background reactions. First, $Ru(bpy)_3^{2+}$ is activated by visible light (λ_{max} = 450 nm) at wavelengths where the enone substrates do not absorb (21); direct photoexcitation of the enone does not occur using the household white light sources utilized in our studies. Second, a Lewis acid ($LiBF_4$) is an essential additive for cycloaddition to proceed; the Li^+ cation presumably activates the enone substrate toward one-electron reduction and stabilizes the resulting radical anion species (22). We hypothesized, therefore, that a dual-catalyst system consisting of $Ru(bpy)_3^{2+}$ and an appropriate chiral Lewis acid co-catalyst would be able to promote highly enantioselective [2+2] cycloadditions without the complications arising from uncatalyzed background photoreactions.

In our initial screen of Lewis acids, we found that trivalent lanthanide salts such as $Gd(OTf)_3$ were particularly effective co-catalysts for the production of [2+2] cycloadducts **2** and **3** (Figure 1C, entry 1). This observation is consistent with the high kinetic lability of lanthanides (23), which may aid catalyst turnover by facilitating displacement of the bidentate product by a monodentate enone substrate. Next, we evaluated a series of Gd complexes bearing chiral ligands that we hoped would influence the stereochemistry of the [2+2] cycloaddition. Unfortunately, several ligand classes (e.g., **4–6**) that have been effective in previously reported Lewis acid-catalyzed enantioselective transformations (24)

provided negligible ee's in this reaction (entries 2–4). On the other hand, Schiff base dipeptide ligand **7**, originally reported by Hoveyda for Cu-catalyzed asymmetric allylic alkylation (25), provided [2+2] cycloadduct **2** with promising ee (entry 5). To the best of our knowledge, this class of ligand has not previously been used in lanthanide-catalyzed asymmetric reactions; however, its modular structure (26) facilitated the rapid synthesis and evaluation of a small library of ligands composed of various salicylaldehyde and amino acid units. A Lewis acid co-catalyst composed of the optimal ligand (**8**) and $Gd(OTf)_3$ afforded cyclobutane **2** in 56% ee (entry 6). Further optimization studies revealed that by replacing the Gd salt with $Eu(OTf)_3$ and by performing the reaction at lower temperatures, the ee of **2** could be increased to 92% (entries 7–9).

The optimized conditions call for 5 mol% $Ru(bpy)_3Cl_2$ as a visible light photocatalyst and 10 mol% of a Lewis acid complex composed of a 1:2 ratio of $Eu(OTf)_3$ and chiral ligand **8**. A series of control experiments verify the necessity of each reaction component (Figure 2A). In the absence of light, photocatalyst, or Lewis acid catalyst, either singularly or in combination, no product is formed and enone substrate **1** can be recovered in good yield. On the other hand, although the rate of cycloaddition is dependent on the concentration of Lewis acid catalyst, there is no noticeable impact on the ee of the product. Catalyst loadings varying from 2.5 to 20 mol% produced cycloadduct **2** with the same ee in each case (Figure 2B). These experiments indicate that all of the [2+2] cycloadduct is being formed via a pathway involving the chiral Lewis acid, and that there is no contribution from a competitive racemic background process, consistent with our design plan.

Previous approaches towards asymmetric catalytic photocycloaddition reactions have exhibited rather limited scope. Minor modifications to the substrate can result in substantial spectral changes that impact the ability to selectively photoexcite the catalyst-bound substrate (15). In contrast, the results summarized in Figure 3 demonstrate that our dual-catalytic system tolerates wide-ranging structural variation (27). Successful substrates include aryl enones bearing electron-donating and –withdrawing substituents, heteroaryl enones, and γ-substituted enones (Figure 3). The enantioselectivity remains high for all of these cycloadducts regardless of the UV absorptivity of the substrates (28). For example, the phenyl and naphthyl enones leading to cyclobutanes **2a** and **2g** both provide high ee even though the UV absorption of the latter extends to considerably longer wavelengths (Figure S1). Consistent with our studies of racemic crossed enone cycloadditions (20), we observe the formation of readily separable byproducts arising from competitive reductive coupling and aryl enone homodimerization processes. The use of a five-fold excess of the aliphatic enone increases the overall rate of formation of [2+2] cycloadducts and minimizes the formation of homocoupling products. Overall, these results represent a substantial improvement in the structural variety of enantioenriched [2+2] cycloadducts available by catalysis. Each of the previous reports of asymmetric catalytic photocycloadditions has involved intramolecular reactions of cyclic enone substrates and thus furnished bicyclic products. Our intermolecular cycloaddition of acyclic enones is capable of producing a diverse range of simple monocyclic cyclobutane products in good ee.

One important advantage of this dual-catalytic system is the functional independence of the photocatalyst and the chiral Lewis acid catalyst (29). Extensive variations can be made to

the structure of the chiral Lewis acid without any deleterious impact on the photochemical properties of the $Ru(bpy)_3^{2+}$ chromophore. This feature facilitates both the optimization of the enantioselectivity as well as the discovery of complementary reactivity. For example, reduction of Schiff base ligand **8** with $NaBH_4$ afforded secondary amine ligand **9**, the $Eu(OTf)_3$ complex of which was also a highly enantioselective Lewis acid co-catalyst for [2+2] cycloaddition. These conditions, however, favored the formation of 1,2-*cis* diastereomer **3** in good ee (Figure 4A) (30). The scope of the cycloaddition using **9** exhibits the same general breadth as reactions conducted with ligand **8** (Figure 4B), but with complementary diastereoselectivity (31).

These studies demonstrate that transition metal photocatalysts are compatible with a variety of structurally diverse chiral Lewis acid catalysts. The factors governing the success of chiral Lewis acids in asymmetric catalysis have been studied for decades and are now well-understood (32). The ability to combine the power and versatility of chiral Lewis acids with the unique reactivity of photocatalytically generated intermediates has the potential to be a valuable platform for the development of a wide range of broadly useful stereocontrolled reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Brian Dolinar and Ilia Guzei for determining absolute stereochemistry by X-ray crystallography. Metrical parameters for the structures of **3c** and **S3** are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-988977 and 988978, respectively. Funding for this work was provided by the NIH in the form of a research grant (GM095666) and postdoctoral fellowship to DMS (GM105149).

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27. Consistent with our prior studies, crossed [2+2] cycloadditions can be achieved using one aryl enone that can easily be reduced to the corresponding radical anion and a second b-unsubstituted alkyl enone that possesses a more negative redox potential but is a less sterically encumbered Michael acceptor.
28. The absolute configuration of **2c** was determined by X-ray crystallographic analysis of the corresponding 2,4-dinitrophenylhydrazone (**S3**) using anomalous dispersion. See Supplementary Material for details. The configurations of other 1,2-*trans* cycloadducts were assigned by analogy.
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30. Reactions conducted using ligand **9** at −20 °C proceeded at prohibitively slow rates and offered little improvement in ee.
31. The absolute configuration of **3c** was determined by X-ray crystallographic analysis using anomalous dispersion. See Supplementary Material for details. The configurations of other 1,2-*cis* cycloadducts were assigned by analogy.
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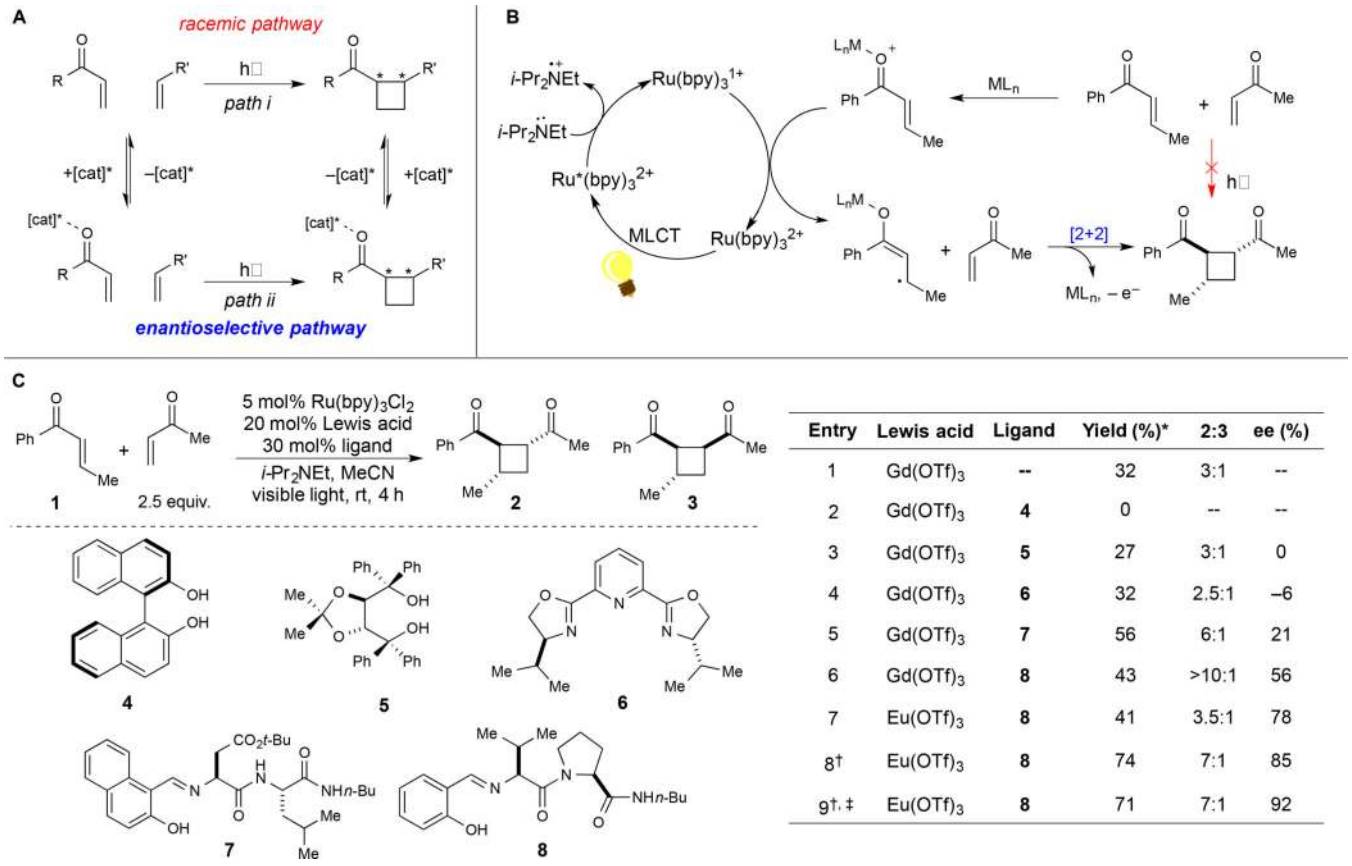
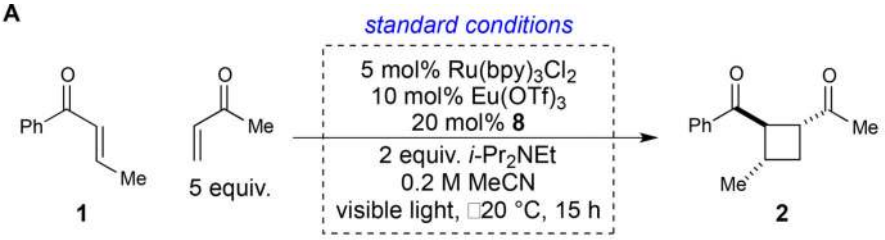


Entry	Lewis acid	Ligand	Yield (%)*	2:3	ee (%)
1	$Gd(OTf)_3$	--	32	3:1	--
2	$Gd(OTf)_3$	4	0	--	--
3	$Gd(OTf)_3$	5	27	3:1	0
4	$Gd(OTf)_3$	6	32	2.5:1	–6
5	$Gd(OTf)_3$	7	56	6:1	21
6	$Gd(OTf)_3$	8	43	>10:1	56
7	$Eu(OTf)_3$	8	41	3.5:1	78
8†	$Eu(OTf)_3$	8	74	7:1	85
9†,‡	$Eu(OTf)_3$	8	71	7:1	92

Fig. 1. Design plan for enantioselective catalytic [2+2] cycloaddition reactions

(A) Competing enantioselective and racemic pathways in asymmetric photocycloadditions. **(B)** $Ru(bpy)_3^{2+}$-catalyzed [2+2] cycloaddition reaction using visible light. bpy = 2,2'-bipyridine, MLCT = metal-to-ligand charge transfer. **(C)** Survey of chiral Lewis acid co-catalysts. OTf = trifluoromethanesulfonate. *Yields determined by ^{1}H NMR analysis using an internal standard. †Optimized conditions: 5 equiv. methyl vinyl ketone, 5 mol% $Ru(bpy)_3Cl_2$, 10 mol% Lewis acid, 20 mol% ligand, 0.2 M MeCN, 2 h. ‡Reaction conducted at −20 °C for 15 h.

A



Entry	Variation from standard conditions	Yield (%)
1	none	71
2	no light	0
3	no $Ru(bpy)_3Cl_2$	0
4	no $Eu(OTf)_3$	0
5	no *i*-Pr_2NEt	0

B

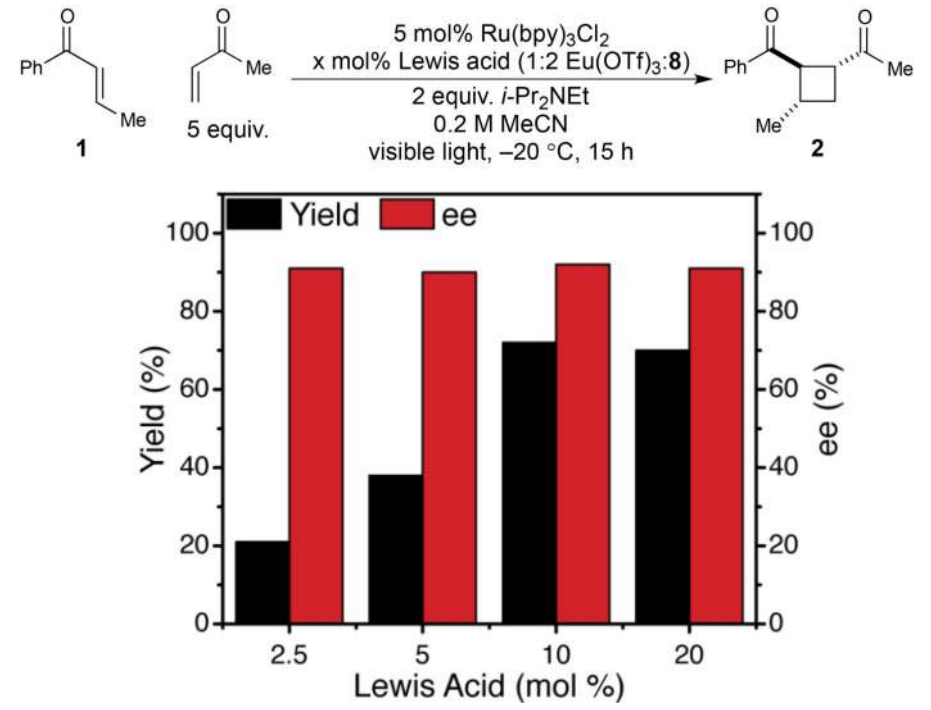


Fig. 2. Control experiments for the asymmetric visible light photocatalyzed [2+2] cycloaddition

(**A**) Omission of any reaction component results in no [2+2] cycloaddition. (**B**) Enantioselectivity of the photocatalyzed [2+2] cycloaddition is not affected by the concentration of chiral Lewis acid catalyst.

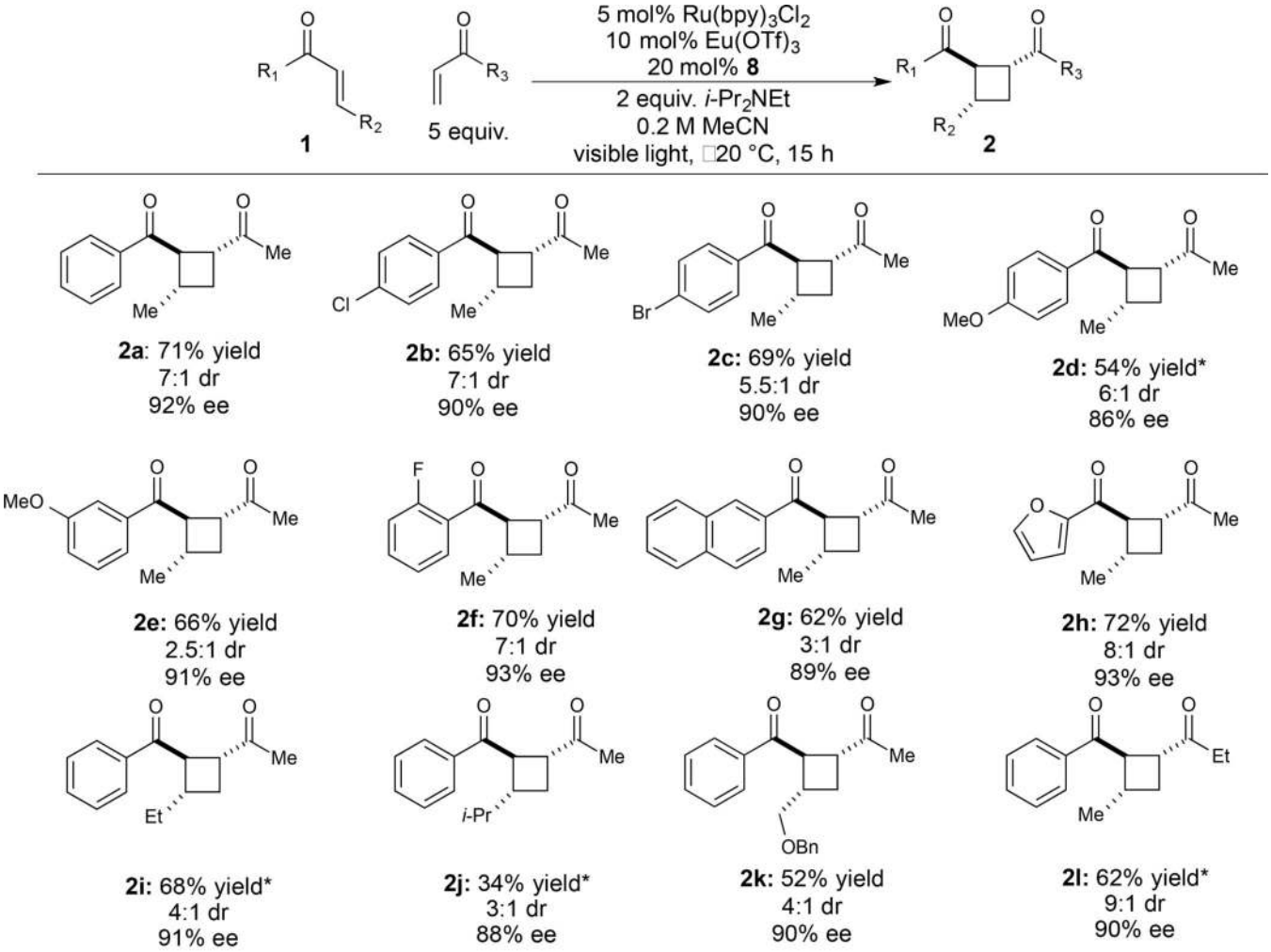


Fig. 3. Substrate scope of the enantioselective [2+2] cycloaddition reaction

Diastereomer ratios measured by ^{1}H NMR analysis of the unpurified reaction mixtures. Reported yields represent total isolated yields of the 1,2-*cis* and 1,2-*trans* isomers. For each entry, yields represent the average of two reproducible experiments. *Reaction conducted for 24 h.

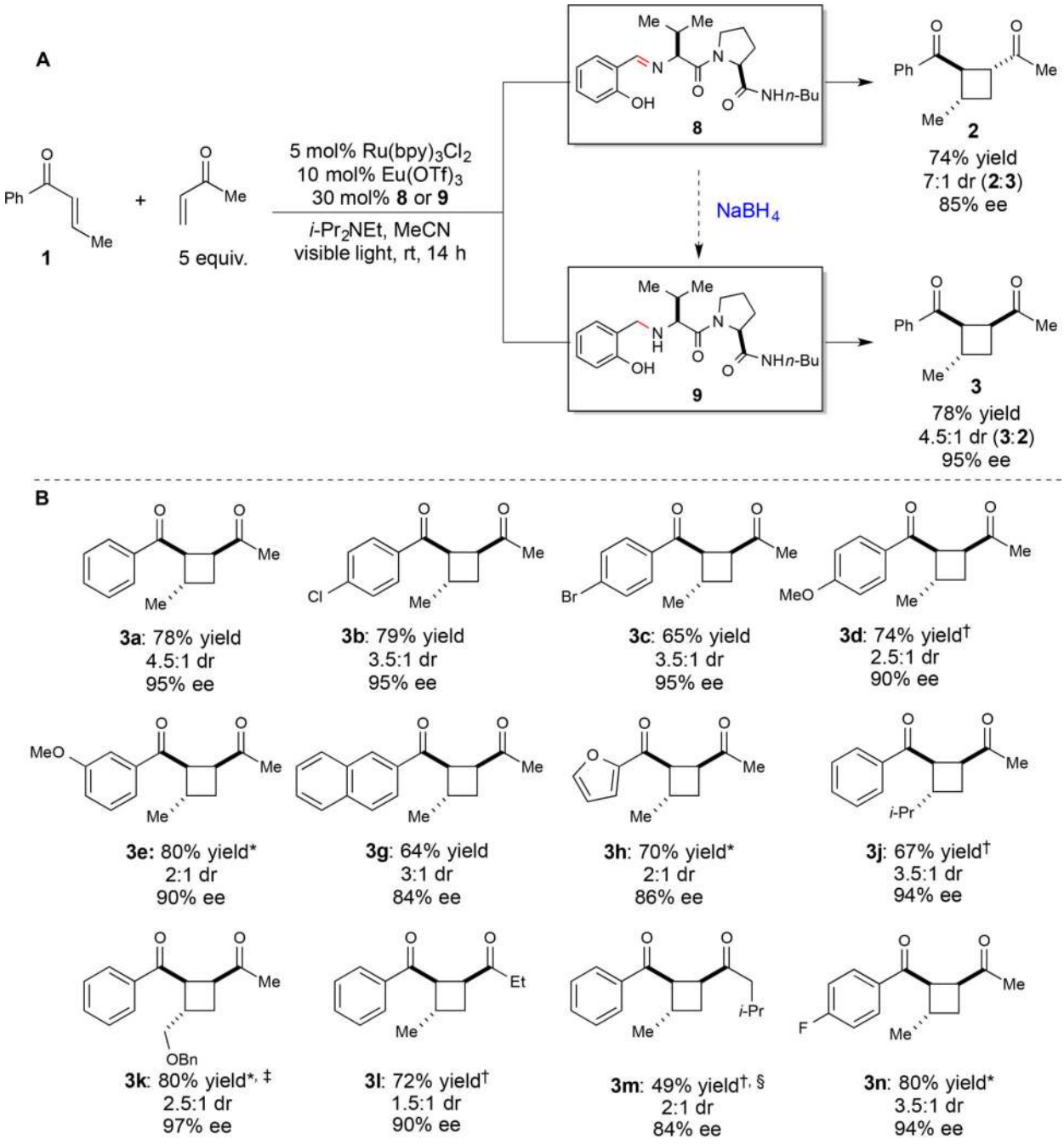


Fig. 4. Diastereocontrol through independent modification of chiral Lewis acid structure

(**A**) Stereoselective access to 1,2-*cis* cycloadducts **3** through reduction of chiral Schiff base ligand **8** to amine **9**. (**B**) Substrate scope of 1,2-*cis* cyclobutanes via enantioselective [2+2] photocycloaddition. Diastereomer ratios measured by ^{1}H NMR analysis of the unpurified reaction mixtures. Reported yields represent total isolated yields of the 1,2-*cis* and 1,2-*trans* isomers. For each entry, yields represent the average of two reproducible

experiments. *Reaction conducted for 14 h. †Reaction conducted for 36 h. ‡Reaction conducted at 37 °C. §Isolated yield of only *cis* isomer. rt, room temperature.