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An organic thiyl radical catalyst for enantioselective cyclization

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A diverse array of chiral organocatalysts have been developed that rely on acid–base interactions to promote enantioselective ionic reactions via the movement of electron pairs. The stereocontrol of radical reactions using organocatalysts is an alternative approach, and several studies have shown that synthetically useful reactivity can result by controlling the movement of single electrons. However, in these studies, it is still an acid-based organocatalyst which forms a closed-shell intermediate with substrate prior to the radical reaction and imparts chiral information, and use of a chiral organic radical directly as catalyst has only rarely been explored. Here, we report the design of an organic thiyl radical catalyst with a carefully designed chiral pocket constructed around a chiral thiol precatalyst. The resulting catalyst was used to effect highly diastereo- and enantioselective C–C bond-forming radical cyclizations.

Asymmetric organocatalysis has recently risen to prominence as a third class of asymmetric catalysis, following metal catalysis and biocatalysis[1]. Whereas organocatalysis has clear advantages in terms of operational simplicity, low toxicity and minimization of environmental impact, one critical limitation is the uniformity of the reaction mechanism compared with other catalyses. Chiral organocatalysts are normally equipped with acidic and/or basic functionalities to facilitate ionic reactions based on the movement of two electrons, with catalyst–substrate interactions—such as hydrogen bonding, ion pairing and enamine–iminium formation—playing a key role[2–7].

A radical reaction based on the movement of single electrons is an alternative way to form bonds without the help of transition-metal catalysts[8] and is widely used in biocatalysis[9]. Several groundbreaking approaches using chiral organocatalysts and Lewis acids have already emerged in efforts to open up a new horizon in the field of asymmetric catalysis[10–17]. These methods rely on the use of the acid–base sites of a catalyst, which interact with a substrate to form a closed-shell intermediate. This intermediate subsequently undergoes radical reactions relying on an external source. Accordingly, they are classified as asymmetric acid–base catalysis mediating enantioselective radical reactions.

The thiyl radical is a unique functionality that has the ability to directly generate a radical in a substrate and promote radical bond-forming reactions[8,18,19]. Its utility in asymmetric catalysis is seemingly a promising way to enable a fully radical-mediated organocatalytic transformation. Despite the fact that such a possibility was documented in the 1990s as a way to promote asymmetric C–H bond formation[20,21], this field has not been explored further, so whether this strategy can be applied to radical C–C bond formation remains undetermined. Given the proficiency of biocatalysis (for example, by benzylsuccinate synthase[22]) to carry out this challenging task, it should also be achievable by organic chemists. Here, we succeed in designing a chiral organic thiyl radical catalyst that promotes highly diastereo- and enantioselective radical cyclization of electron-deficient vinylcyclopropanes and vinyl ethers with the rigorous stereocontrol of radical C–C bond formation[23,24].

Results and discussion

Catalyst design. As a starting point to this study we examined the catalytic activity of a variety of binaphthyl-modified catalysts

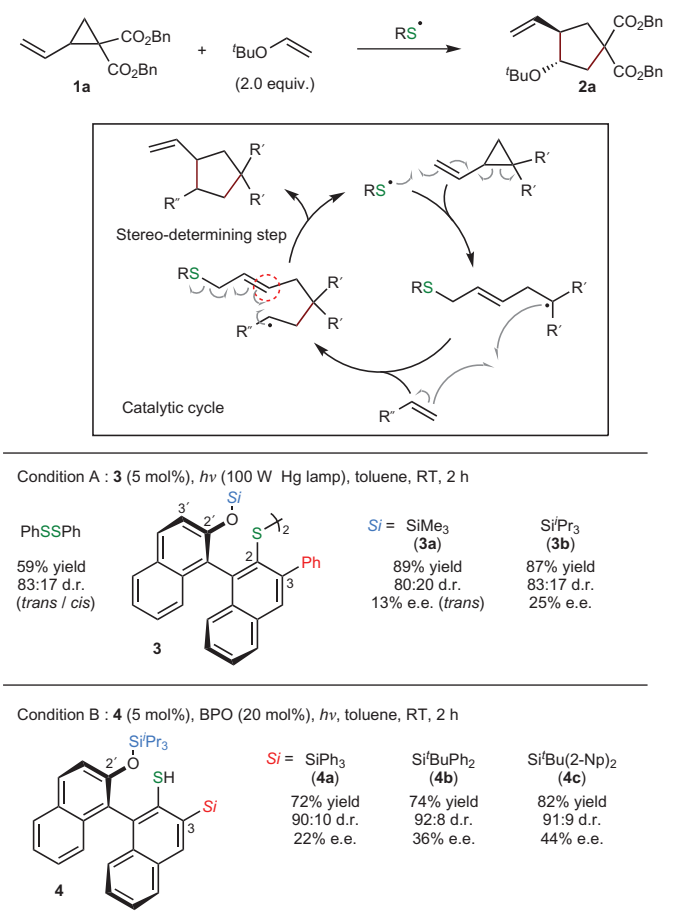

Figure 1 | Initial foray into the development of the chiral organic radical catalyst. The reaction proceeds via (1) addition of the thiyl radical to vinylcyclopropane and ring-opening of the cyclopropane, (2) reaction of the radical species with vinyl ether and (3) stereo-determining radical cyclization and regeneration of the thiyl radical. Catalyst design using a binaphthyl scaffold provided a proof of concept, but underlined the need for the complete redesign of the catalyst to achieve high enantioselectivity.

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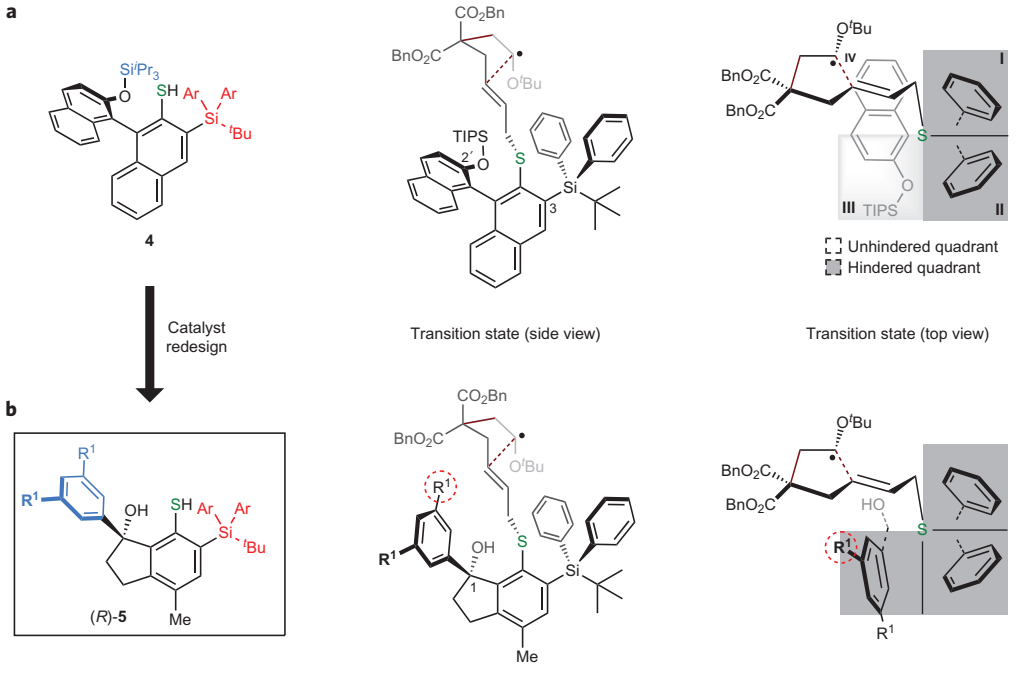


Figure 2 | Design of a new scaffold for enantioselective radical cyclization. a, Analysis of binaphthyl catalyst **4** suggested that the bulky silyl groups at the C3 position should effectively block the first and second quadrants around the sulfur atom and confine the movement of the alkyl radical intermediate. Consequently, we concluded that the silyloxy group at C2′ did not block the third quadrant sufficiently, resulting in poor stereoselectivity. **b**, A redesigned catalyst **5** was based on an indanol core. In this case the diarylsilyl moiety and the aryl group at C1 were expected to occupy each of the three quadrants to deliver a more selective catalyst. TS, transition state; TIPS, Si^{i}Pr$_3$.

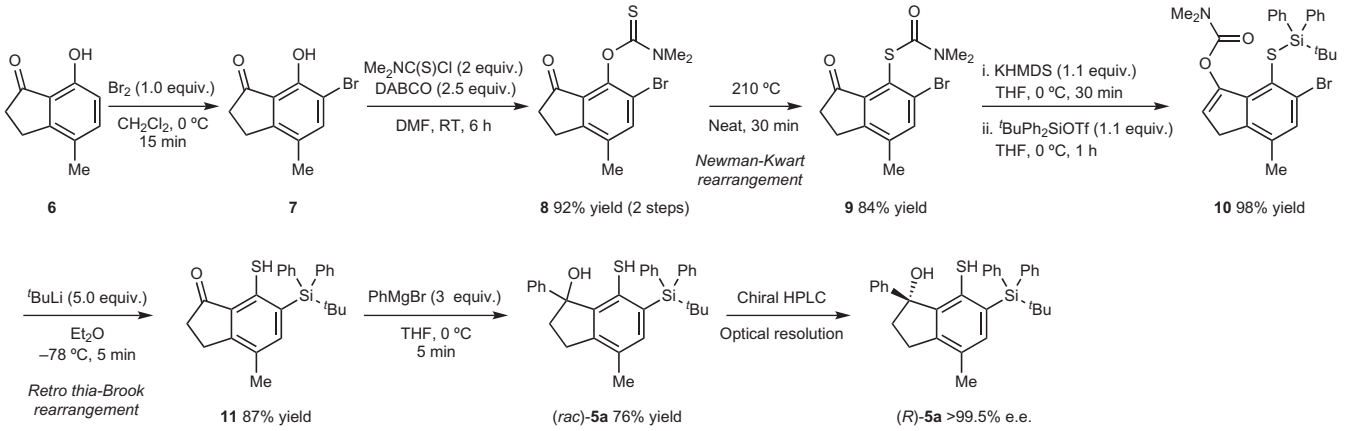
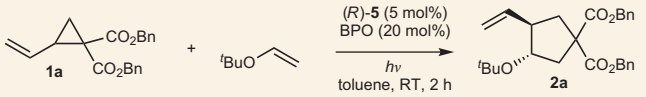


Figure 3 | Synthesis of a new chiral thiol. The key steps in the synthesis are the carbamoyl transfer from the thiol to the enol oxygen (**9** to **10**), and successive retro thia-Brook rearrangement to install the bulky silyl group *ortho* to the thiol (**10** to **11**). The carbamoyl moiety is removed during the work-up of the retro thia-Brook rearrangement. The synthesis is completed by addition of an aryl Grignard reagent to the unmasked ketone and resolution by high-performance liquid chromatography (HPLC) provides the chiral catalyst.

in the reaction of dibenzyl vinylcyclopropanedicarboxylate **1a** and *tert*-butyl vinyl ether (Fig. 1). A thiyl radical was photolytically generated from the corresponding chiral disulfides. For comparison, the benchmark reaction using diphenyl disulfide gave cyclopentane **2a** in 59% yield with modest diastereoselectivity. This radical cyclization is known not to follow the Beckwith–Houk model and preferably gives the *trans* isomer[24,25], and we confirmed that the diastereoselectivity was not affected by a thiyl radical-mediated hydrogen abstraction after the radical cyclization. In addition, it is complementary to the related Lewis-acid- and transition-metal-catalysed reactions in terms of the regioselectivity and reactivity profile[26,27]. After extensive screening of chiral catalysts we identified lead catalysts **3** with which meaningful enantioselectivities could be obtained. The steric bulk surrounding the sulfur atom was apparently critical, and our attempt to synthesize more congested disulfides failed. To circumvent this problem we opted to generate the thiyl radical from a chiral thiol and benzoyl peroxide (BPO) under photo-irradiation (condition B). A follow-up experiment indicated that BPO was more likely to function as an oxidant rather than a radical initiator. Catalysts **4b** and **4c** bearing a diaryl(*tert*-butyl)silyl group at C3 were particularly effective, and enantioselectivities of ~40% enantiomeric excess (e.e.) were achieved. Notably, a catalyst-controlled increase in diastereoselectivity was also observed. However, further attempts at improving the selectivities of this reaction using binaphthyl-based catalysts were in vain, highlighting the difficulty of rigorously controlling this radical cyclization.

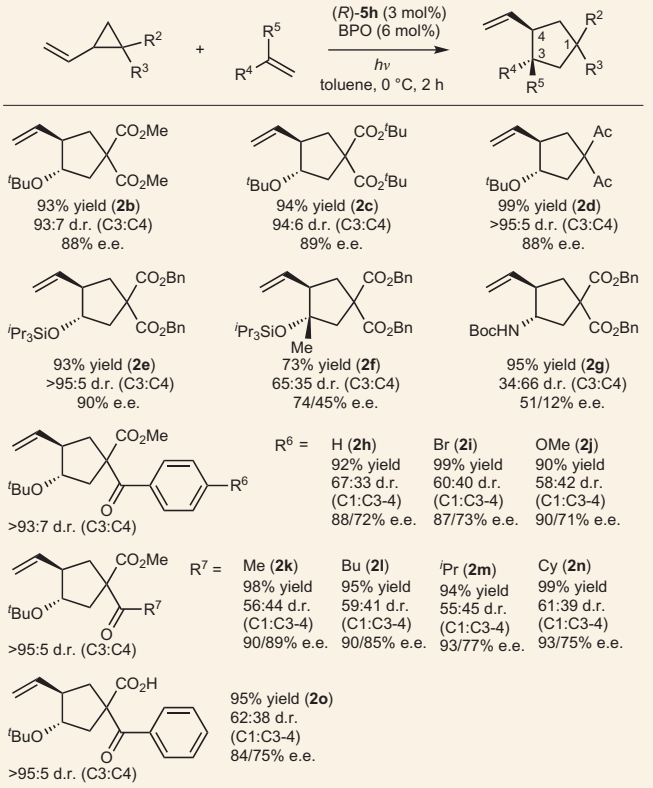
Table 1 | Optimization of the catalyst structure.



Entry	Ar	R^1	Yield (%)*	d.r. (*trans:cis*)†	e.e. (%)‡
1	Ph	H (**5a**)	75	75:25	24
2	Ph	Ph (**5b**)	79	79:21	22
3	Ph	^{t}Bu (**5c**)	82	82:18	36
4	Ph	$SiPh_3$ (**5d**)	80	92:8	63
5§	Ph	$SiPh_3$ (**5d**)	95	95:5	67
6§	Ph	2,6-Me_2-4-^{t}Bu-C_6H_2 (**5e**)	64	92:8	67
7§	Ph	10-Bu-9-anthryl (**5f**)	89	94:6	77
8§	2-naphthyl	10-Bu-9-anthryl (**5g**)	62	>95:5	81
9§	4-$CF_3C_6H_4$	10-Bu-9-anthryl (**5h**)	69	95:5	87
10‖	4-$CF_3C_6H_4$	10-Bu-9-anthryl (**5h**)	81	95:5	86
11¶	4-$CF_3C_6H_4$	10-Bu-9-anthryl (**5h**)	90	95:5	86
12‖,#	4-$CF_3C_6H_4$	10-Bu-9-anthryl (**5h**)	95	95:5	86

Performed with **1a** (0.07 mmol), vinyl ether (0.14 mmol) and **5** (5 mol%) in toluene (0.7 ml). *Isolated yield of the major diastereomer. †Diastereomeric ratio, determined by ^{1}H NMR analysis of the crude material. ‡e.e. of the major diastereomer, determined by chiral HPLC. §Performed at 0 °C. ‖**5** (3 mol%) and BPO (6 mol%) at 0 °C on 0.1 mmol scale. ¶Performed with **1a** (1.0 mmol), vinyl ether (1.5 mmol), **5h** (1 mol%) and BPO (3 mol%) in toluene (3 ml) at 0 °C. #Under sunlight.

Table 2 | Substrate scope.



To overcome this hurdle we decided to design an unprecedented chiral scaffold using the lessons learned in the above experiments (Fig. 2). We postulated that the bulky silyl group of **4** at C3 is essential for blocking the first and second quadrants around the sulfur atom and for confining the movement of the alkyl radical intermediate (Fig. 2a). Its failure as chiral catalyst is assumed to arise from the poor steric influence provided by the silyloxy group at C2′, which fills the third quadrant. To be successful as a catalyst, this third quadrant must be filled with a bulky substituent that effectively shields one prochiral face of the alkene moiety. To fulfil this criterion we designed a chiral thiol **5** based on an indanol unit (Fig. 2b). The diarylsilyl moiety and the aryl group at C1 were expected to occupy each of the three quadrants to deliver a deep and concise chiral pocket. From molecular modelling, we postulated the extension of 3,5-substituents of the C1 aryl group would have a significant influence on the enantioselectivity.

As shown in Fig. 3, the simplest catalyst, **5a**, which has a phenyl group at C1, was synthesized by a high-yielding six-step sequence and with optical resolution, starting from hydroxyindanone **6**. This procedure was designed to minimize the number of steps and to allow access to a variety of catalysts by using **9** and **11** as branching points.

We initially examined several catalysts with different aryl groups at the C1 position (Table 1, entries 1–4). This study demonstrated that the introduction of sterically bulky groups at 3,5-positions of the aryl group was effective in achieving higher enantioselectivities, as underlined by the result using 3,5-di(triphenylsilyl)phenyl-substituted thiol **5d** (entry 4). At this stage the reaction temperature was optimized to 0 °C, which improved the stereoselectivities to 95:5 diastereomeric ratio (d.r.) and 67% e.e. (entry 5). Further elaboration of the catalyst led to the identification of **5f**, bearing a 10-butyl-9-anthryl group (entries 6 and 7). We then turned our focus to the *ortho* silyl moiety of the catalyst. Of the several diaryl (*tert*-butyl)silyl-substituted catalysts screened (for example, entry 8), catalyst **5h**, bearing 4-(trifluoromethyl)phenyl groups, was found to be optimal (entry 9). Although this reaction proceeded in a variety of solvents, including ethers, alcohols and haloalkanes, toluene was found to be the best in terms of stereoselectivities. Under the optimized reaction conditions, the catalyst loading was lowered to 3 mol% without deteriorating the yield and selectivities (entry 10). We also confirmed that the catalyst loading could be further lowered to 1 mol% in a scaled-up (1 mmol scale) experiment (entry 11), thereby offsetting the high molecular weight of the catalyst[28]. Although, for convenience, a ultraviolet lamp was routinely used, the reaction also proceeded smoothly using sunlight as a benign source of photo-irradiation (entry 12). On the other hand, the reaction did not proceed at all in the dark. The absolute configuration of **2a** was unambiguously determined by X-ray crystallographic analysis after derivatization (see Supplementary Fig. 4), and matched our prediction (Fig. 2b).

Diastereo- and enantioselective radical cyclization. With the optimal reaction conditions in hand we turned our attention to the examination of the substrate scope (Table 2). The use of other alkyl esters gave the corresponding products **2b** and **2c** with slightly higher enantioselectivities. In addition to diesters, a diketone could also be utilized, affording diacetyl cyclopentane **2d** in good yield and high stereoselectivity. Among other electron-rich alkenes, triisopropylsilyl vinyl ether was utilized to give *trans*-cyclopentane **2e** exclusively with 90% e.e. A tertiary alcohol moiety was incorporated in the product (**2f**) by the use of a 2-propenyl silyl ether, albeit with lower stereoselectivities. Use of ene-carbamate gave chiral cyclopentyl amine **2g** with modest stereoselectivity. Use of simple alkenes such as styrene and 1-hexene resulted in poor conversion and selectivities (data not shown). Further modification of the catalyst structure and reaction conditions could possibly resolve these issues in the future.

We then turned our attention to the use of vinylcyclopropanes with a keto ester unit. Even though the remote stereocentre at C1 stemming from the keto ester moiety could not be effectively controlled by the catalyst, the diastereoselectivity across the C3–4 stereocentres remained high (over 93:7 in every case). Both aryloyl and alkanoyl esters, which were used as a mixture of diastereomers, underwent radical cyclization to give **2h**–**2n** with high enantioselectivities. Finally, to highlight the distinctive reactivity of radicals,

which are expected to be inert to polar functionalities, we conducted the reaction using an unprotected vinylcyclopropanecarboxylic acid. The desired product **2o** was obtained without any difficulty in good yield and enantioselectivity. This orthogonal reactivity of this radical catalysis compared with conventional acid–base catalysis could be harnessed to enable streamlined stereoselective synthesis free from protecting groups.

Conclusion

We have designed a novel chiral organic thiyl radical catalyst for achieving highly diastereo- and enantioselective radical cyclization. Given the inability of conventional chiral scaffolds to provide an efficient chiral environment for this reaction, it was imperative to build a new chiral motif from scratch. By doing so, we have proved for the first time that thiyl radical catalysis can be applied to asymmetric radical C–C bond formation. This study should encourage further development of new chiral organic thiyl radical catalysts and reactions.

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Author contributions

T.H. conceived the study and wrote the manuscript. T.H. and Y.K. designed experiments and Y.K. performed experiments. K.M. organized the research.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.M.

Competing financial interests

The authors declare no competing financial interests.