Synthetic Methods

DOI: 10.1002/anie.201408781

Thiyl Radicals: From Simple Radical Additions to Asymmetric Catalysis**

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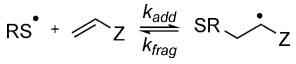
asymmetric catalysis · enantioselectivity · radicals · synthetic methods · thiols

Radicals derived from thiols, often termed as thiyl radicals, are important intermediates in biological processes as well as in synthetic organic chemistry.[1] The ubiquitous nature of such intermediates is mainly due to their ease of formation and inherent reactivity: the S–H homolytic bond dissociation energy (BDE) is about 87 kcal mol^{-1} for alkanethiols, 79 kcal mol^{-1} for thiophenols, and the S–S BDE is about 50–65 kcal mol^{-1} for disulfides.[1] Thiyl radicals are capable of abstracting a hydrogen atom from ethers as well as allylic and benzylic systems reversibly. These properties make them unique for the design of new organocatalysts.

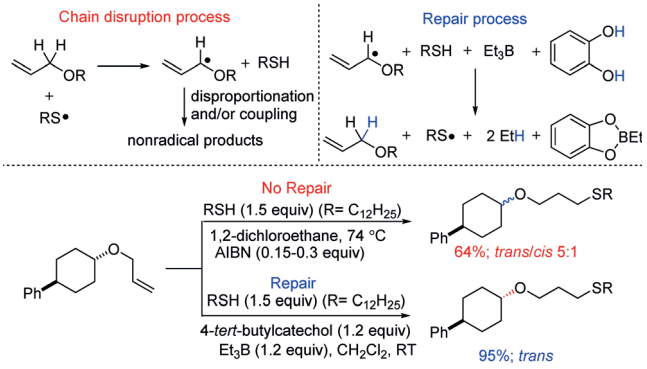
The ability of thiyl radicals to add to carbon–carbon and carbon–heteroatom multiple bonds makes them one of the powerful intermediates in chemical synthesis. The addition of these radicals to olefins is generally facile and reversible (Table 1).[1] The rate of addition and fragmentation become important parameters while designing a synthesis based on thiyl radicals. Also, these radicals have been utilized as organocatalysts in a variety of transformations. In this article we highlight the recent noteworthy contributions towards the use of thiyl radicals in organic reactions: simple radical additions as well as asymmetric catalysis.

Table 1: Rate constants for the reversible addition of thiyl radicals to olefins.



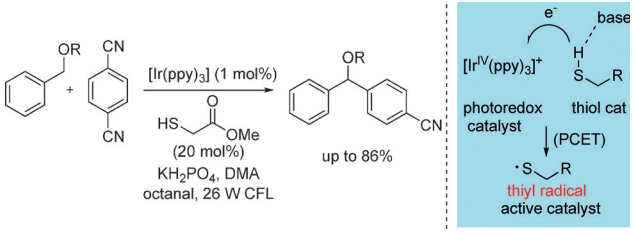
Entry	Z	Thiol	k_{add} [M^{-1} s^{-1}]	k_{frag} [s^{-1}]
1	Ph	*p*-ClC$_6$H$_4$SH	2.7×10^7	–
2	OBu	*p*-ClC$_6$H$_4$SH	1.8×10^5	2.3×10^6
3	CN	*p*-ClC$_6$H$_4$SH	4.6×10^5	2.0×10^6
4	Bu	*p*-ClC$_6$H$_4$SH	1.5×10^4	1.5×10^7
5	Bu	*n*BuSH	7.0×10^6	–

Recently, Renaud and co-workers reported a significant solution to thiol-ene coupling reactions (TEC) involving weak allylic and benzylic C–H bonds (Scheme 1).[2] Hydrogen-atom abstraction at these positions often plagues these chain reactions. A potential solution proposed in this work was to conduct the reaction in the presence of triethylborane and catechol. Under these reaction conditions, a unique repair mechanism is operative where an allylic (or benzylic) system and thiyl radicals are regenerated and results in an improved radical-chain process and leads to higher chemical efficiency.



Scheme 1. Repair of thiol-ene reactions.

MacMillan and co-workers have developed organocatalytic functionalization of sp^3 C–H bonds (Scheme 2). Thiols when subjected to proton-coupled electron-transfer (PCET) oxidation in presence of the excited photoredox catalyst [Ir^{IV}(ppy)$_3$]$^+$ generate electrophilic thiyl radicals. These radicals can abstract benzylic hydrogen atoms to generate



Scheme 2. Arylation of benzylic ethers using thiyl radicals. DMA = dimethylacetamide, ppy = 2-phenylpyridine.

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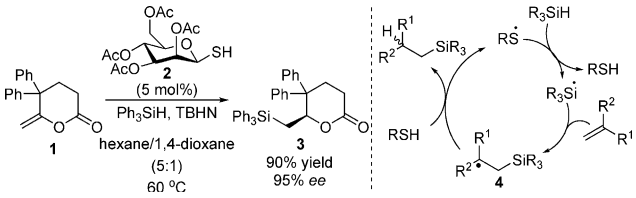
[**] According to IUPAC nomenclature, sulfur-centered radicals are called as sulfanyl radicals. In this manuscript we refer to them with their more common name, thiyl radicals.

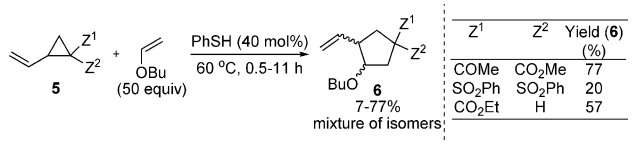
carbon-centered radicals (typical rate constants of ca. $10^4\,M^{-1}s^{-1}$). The benzylic radical then couples with a radical anion generated by a single-electron transfer (SET) from the excited $[Ir^{III}(ppy)_3]$ to *p*-dicyanobenzene and yields coupled product.[3]

Until recently most of the thiyl-radical-mediated organic processes have not led to the formation of C–C bonds enantioselectively and the use of organic chiral radicals as a catalyst has been rarely explored. Chemists have used chiral tin hydride as catalysts in enantioselective organic transformations albeit with poor to moderate control of selectivity.[4] A pioneering example in the area of asymmetric organocatalysis was the use of carbohydrate-derived thiols as polarity reversal catalysts to promote C–H bond formation enantioselectively.[5] By using catalytic amounts of thiol as protic polarity reversal catalysts, Roberts and co-workers have developed asymmetric hydrosilylation of prochiral alkenes (Scheme 3). The prochiral radical **4** abstracts a hydrogen atom from the homochiral thiol **2**, thus affording **3** in high yield and excellent selectivity (95% *ee*).



Scheme 3. Carbohydrate-derived thiols as protic polarity reversal catalysts. TBHN = Di-*tert*-butylhyponitrite.

Oshima and co-workers reported radical cyclization using benzenesulfanyl radicals as the organocatalyst (Scheme 4). Although the reactions were moderately efficient, a mixture

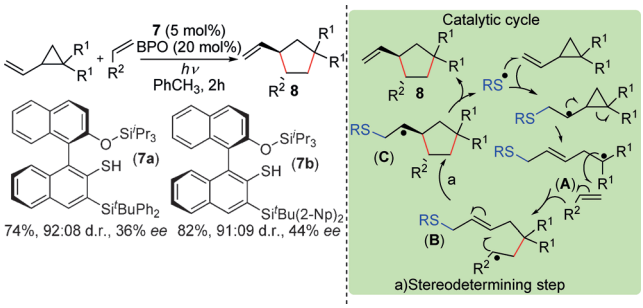


Z^1	Z^2	Yield (**6**) (%)
COMe	CO_2Me	77
SO_2Ph	SO_2Ph	20
CO_2Et	H	57

Scheme 4. Benzenesulfanyl-mediated radical cyclizations.

of diastereomers were obtained (**6**).[6] It is interesting to note that no radical initiator is used in this reaction.

Maruoka and co-workers have shown that such radical cyclizations could be realized with high stereocontrol (both diastereo- and enantiocontrol). In this regard, the latest report on the use of chiral thiyl radicals to achieve C–C bond formation in a selective manner is highly novel and very noteworthy (Scheme 5).[7] The proposed mechanism involves an initial addition of a chiral thiyl radical to the less substituted end of a vinylcyclopropane (ca. rate constant of $10^6\,M^{-1}s^{-1}$). The cyclopropane undergoes a rapid ring-opening (typical rates of 10^8–$10^9\,s^{-1}$) and results in the formation of a stable electrophilic radical (**A**, R^1 = electron-withdrawing group). The electrophilic radical then adds to an electron-rich alkene intermolecularly to form a radical intermediate (**B**).

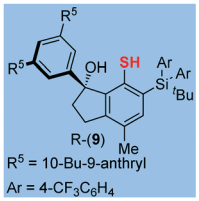


Scheme 5. Chiral thiyl radical catalyzed addition and cyclization. BPO = benzoylperoxide.

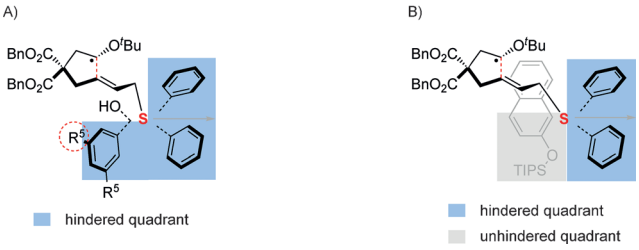
This step is followed by a stepwise cyclization resulting in the formation of the radical (**C**), and then β-fragmentation to yield the vinylcyclopentanes **8**. The cyclization step is the stereocontrolling step (step a) and the catalytic turnover is achieved by a β-fragmentation process. It is important to note that kinetics of each step is favorable for the catalysis to work effectively. Initial chiral radical generation was attempted through photocleavage of chiral disulfides (not shown in Scheme 5). Although good diastereoselectivity (*cis/trans* ≈ 80:20) and *ee* values of up to 25% were achieved, the authors eventually used chiral thiols to develop the concept of a chiral thiyl radical catalyst. This choice is mainly due to failed attempts in developing sterically congested disulfides. After screening several binaphthyl-based thiols under radical conditions (Scheme 5: thiol, benzoyl peroxide, *hν*, $PhCH_3$) the best result was obtained using catalyst **7b** (82%, d.r. = 91:09, *ee* = 44%).

They postulated that the silyloxy group at the C2′ position of the catalyst **7** (Scheme 6 B) provides a poor steric bias. After systematic studies (not included here) the authors designed the chiral catalyst (*R*)-**9** (Scheme 6) which could provide the necessary shielding of one face of the prochiral

Entry	R^1	R^2	R^3	R^4	Yield [%]	d.r. (C3/C4)	*ee* [%]
1	CO_2Me	CO_2Me	^tBuO	H	93	93:07	88/–
2	CO_2Bn	CO_2Bn	$^iPr_3SiO$	H	93	>95:05	90/–
3	Ac	Ac	^tBuO	H	99	>95:05	88/–
4	CO_2H	COPh	^tBuO	H	95	>95:05	84/75
5	CO_2Me	COMe	^tBuO	H	98	>95:05	90/89



Transition states of radical cyclization reactions



Scheme 6. Substrate scope and transition states. Reaction transition state with catalyst (*R*)-**9** (A) and catalyst **7** (B) in the chiral thiyl mediated asymmetric radical cyclization.

alkene (Scheme 6 A) and hence achieve high enantioselectivity. With the new chiral catalyst (*R*)-**9** and optimized reaction conditions, the authors studied the scope of the reaction. High diastereoselectivity (95:05) and *ee* values of up to 90% could be achieved by this method. Free carboxylic acid groups are also tolerated under the reaction conditions (entry 4, Scheme 6). Another noteworthy aspect of the work is that only 3 mol% of the catalyst is required to carry out the reaction. This is important especially in light of the high molecular weight of the catalyst.

These elegant contributions from different scientists highlight the significance of thiyl radicals in organic synthesis. In particular, the chemistry reported by the groups of Roberts and Maruoka on the use of chiral thiols in radical reactions is a significant advancement in the field of asymmetric catalysis.

Received: September 10, 2014
Published online: October 22, 2014

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