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PAPER

Chiral-Sc catalyzed asymmetric Michael addition/protonation of thiols with enones in water†

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Asymmetric Michael reactions and enantioselective protonations between enones and thiols were catalyzed by a $Sc(OTf)_3$–chiral 2,2′-bipyridine complex in water. The remarkable governing of the enantioselectivity for simple introduction of protons despite their abnormally high mobility in water may provide us with new synthetic opportunities as well as significant chemical advances.

Introduction

Exploring organic reactions in water is one of the hottest topics in modern organic chemistry.[1] Not only is water nontoxic, inexpensive and environmentally benign, but it also sometimes leads to unexpected and unpredicted results.[2] Organic chemistry in water provides us with the potential to develop innovative artificial catalytic systems, which might perform selective chemical reactions in cells. Intensive efforts have therefore been dedicated to advances in catalytic systems in aqueous media in our laboratory.[3] However, the construction of asymmetric environments in water poses considerable difficulties, such as weakness of noncovalent interactions between substrates, chiral ligands and metal ions under competitive polar conditions. We have focused on the use of multidentate ligands as possible solutions to these issues. Especially given its potential for chelating with many transition metal ions, a chiral catalyst comprising a 2,2′-bipyridine backbone is one of the most attractive candidates for "privileged" ligands, which catalyze many chemical reactions in water selectively. To date, chiral 2,2′-bipyridine complexes chelating with Sc(III), Fe(II), Cu(II), Zn(II) and Bi(III) ions have proved to be robust and excellent catalysts for the promotion of several catalytic asymmetric reactions in water/aqueous media.[4]

Asymmetric Michael addition of thiols to α,β-unsaturated ketones is often observed in biosynthesis as well as in the synthesis of biologically active organosulfur compounds such as diltiazem (a calcium antagonist).[5] Despite impressive contributions made in recent years, reported examples with excellent enantioselectivity have been limited mostly to cyclic enones. Therefore, we initially focused on establishing a more efficient catalytic system, especially for acyclic enones.[6] In principle, Michael addition of thiols is an ideal reaction that proceeds with perfect atom economy under proton-transfer conditions to afford enantiomerically enriched building blocks without employing any auxiliary groups. This concept invoked a novel strategy for the construction of an asymmetric carbogenic center *via* enantioselective proton transfer in proton-rich environments. Proton transfer in water is the most fundamental phenomenon in redox processes and therefore it plays an essential role in biological processes such as muscle contraction and the electron transport chain in the mitochondrial matrix. Here we describe chiral Sc-catalyzed asymmetric Michael addition and enantioselective protonation using thiols and enones in water.

Results and discussion

Asymmetric Michael addition of thiols with enones

The asymmetric Michael reaction of benzalacetone **2a** with benzylmercaptan **3a** was initially conducted under various conditions. We first tested the combination of Sc^{3+} and chiral 2,2′-bipyridine **1**[7] because we have already revealed that this combination creates excellent asymmetric environments in several reactions, such as the enantioselective hydroxymethylation of silyl enol ethers,[4a,b,g,l,m] ring-opening reactions of *meso*-epoxides,[4c–m] Nazarov cyclizations,[4j] and allylations[4k] in water and organic solvents (Table 1). For scandium species, $Sc(DS)_3$ (DS = $OSO_3C_{12}H_{25}$) (a Lewis acid–surfactant combined catalyst)[8] gave better results than $Sc(OTf)_3$ (entries 1, 2). To avoid the formation of undesired side products under acidic conditions and to enhance the nucleophilicity of thiols, the addition of bases was examined. It was found that in the presence of 10 mol % of $Sc(OTf)_3$, **1**, and 20 mol% of pyridine, the reaction was significantly accelerated and the desired Michael adduct was obtained in 85% yield with 91% ee (entry 3).[9] In the presence of pyridine, $Sc(DS)_3$ also accelerated the reaction slightly, but the

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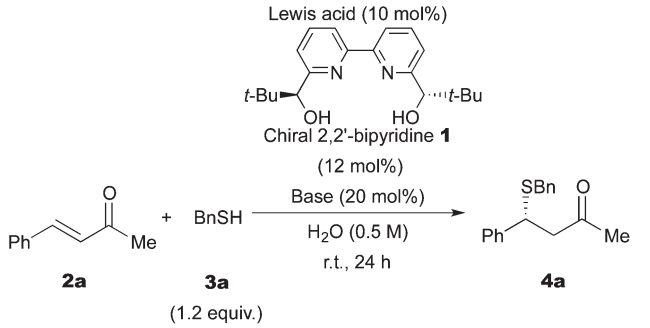
†Electronic supplementary information (ESI) available. CCDC 874881 (compound **6a**) and 874880 (compound **8a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26264a

Table 1 Effect of scandium sources and bases

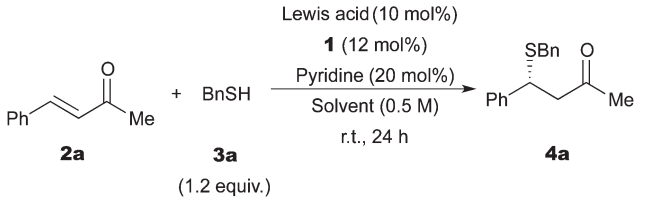


Entry	Lewis acid	Base (mol%)	Yield[a] (%)	ee (%)
1	$Sc(OTf)_3$	—	34	57
2	$Sc(OSO_3C_{12}H_{25})_3$	—	81	72
3	$Sc(OTf)_3$	Pyridine (20)	85	91
4	$Sc(OSO_3C_{12}H_{25})_3$	Pyridine (20)	94	72
5	$Sc(OTf)_3$	Pyrrolidine (20)	99	26
6	$Sc(OTf)_3$	Et_3N (20)	75	73
7	$Sc(OTf)_3$	NMM (20)	90	70
8	$Sc(OTf)_3$	DABCO (20)	77	77
9	$Sc(OTf)_3$	DMAP (20)	88	78
10	$Sc(OTf)_3$	2,6-Lutidine (20)	91	89
11	$Sc(OTf)_3$	DTBP (20)	25	70
12	$Sc(OTf)_3$	Methylimidazole (20)	81	78
13	$Sc(OTf)_3$	Phenanthroline (20)	85	79
14	$Sc(OTf)_3$	DBU (20)	86	80
15	$Sc(OTf)_3$	LiOH (20)	93	88
16	$Sc(OTf)_3$	NaOH (20)	91	90
17	$Sc(OTf)_3$	KOH (20)	93	90
18	$Sc(OTf)_3$	CsOH (20)	Quant	90
19	$Sc(OTf)_3$	Pyridine (40)	89	91
20	$Sc(OTf)_3$	Pyridine (30)	91	91
21	$Sc(OTf)_3$	Pyridine (15)	85	91
22	$Sc(OTf)_3$	Pyridine (10)	83	92
23	$Sc(OTf)_3$	Pyridine (5)	84	91
24	$Sc(OTf)_3$	LiOH (40)	98	5
25	$Sc(OTf)_3$	NaOH (40)	89	4
26	$Sc(OTf)_3$	KOH (40)	96	4
27	$Sc(OTf)_3$	CsOH (40)	93	7
28	$Sc(OTf)_3$	NaOH (10)	83	87
29	$Sc(OTf)_3$	NaOH (5)	73	87

[a] Isolated yield. NMM: *N*-methylmorpholone; DMAP: 4-dimethylaminopyridine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

enantioselectivity remained unchanged (entry 4). A number of other bases were also examined (entries 5–18). It was interesting to find that in almost all cases, higher enantioselectivities were observed when using inorganic bases or organic bases as additives compared with when no additives were used. Use of pyrrolidine as an additive afforded almost quantitative formation of the Michael adduct, with poor selectivity (entry 5). This may be ascribed to its strong basicity or high nucleophilicity. Tertiary amines used as additives led to adducts with approximately 70–77% ee (entries 6–8). Even in the presence of a highly nucleophilic amine such as 1,4-diazabicyclo[2,2,2]-octane (DABCO), an undesired competitive Michael adduct of the amine was not obtained. By contrast, unsaturated heterocycles such as pyridine allowed the formation of the adducts in high yields and with higher selectivities, except for 2,6-di-*tert*-butylpyridine (DTBP), which is almost insoluble in water (entries 9–14). Alkali metal hydroxides as additives afforded almost the

Table 2 Effect of solvents and metal cations



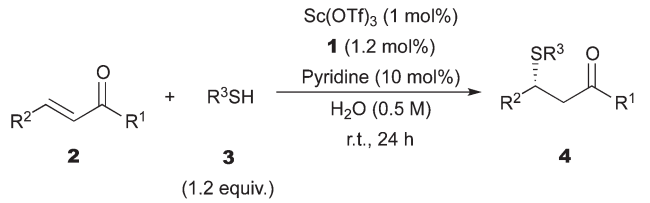
Entry	Lewis acid	Solvent	Yield (%)	ee (%)
1	$Sc(OTf)_3$	H_2O	84	91
2	$Sc(OTf)_3$	H_2O–THF = 1 : 9	54	64
3	$Sc(OTf)_3$	H_2O–EtOH = 1 : 9	90	59
4	$Sc(OTf)_3$	CH_2Cl_2	93	28
5	$Sc(OTf)_3$	THF	91	31
6	$Sc(OTf)_3$	EtOH	88	63
7	$Sc(OTf)_3$	Toluene	82	75
8	$Zn(OTf)_2$	H_2O	45	0
9	$Cu(OTf)_2$	H_2O	19	4
10	$Fe(OTf)_2$	H_2O	46	7
11	$Bi(OTf)_3$	H_2O	2	1
12	$Lu(OTf)_3$	H_2O	73	66
13[a]	$Sc(OTf)_3$	H_2O	83	92
14	5 mol% $Sc(OTf)_3$	H_2O	87	90
15	3 mol% $Sc(OTf)_3$	H_2O	94	90
16	1 mol% $Sc(OTf)_3$	H_2O	91	91
17[b]	0.5 mol% $Sc(OTf)_3$	H_2O	92	91

[a] 20 mol% ligand **1** was used. [b] Reaction time 48 h.

same results as pyridine did (entries 15–18).[10] The catalytic system is not much affected by the amount of pyridine added (entries 19–23). However, it was found that when the amount of NaOH was decreased, the enantioselectivity decreased slightly. In the presence of 40 mol% of alkali metal hydroxides, the yields were high but the enantioselectivities decreased significantly.

By using an exquisite set of the catalyst and the additive, we next investigated the effect of representative solvents and metal cations in this reaction (Table 2). Among the representative solvents, water emerged as being the most suitable (entries 1–7). Notably, the reactions in organic solvents led to the desired adduct in moderate selectivities (entries 4–7) even if the reactions were conducted in aqueous–organic mixed solvents (entries 2, 3). For metal cations, we tested Fe(II), Cu(II), Zn(II) and Bi(III), which were reported to be efficient Lewis acids in asymmetric reactions in aqueous media.[4,11] However, they were not very effective here (entries 8–11). When homologous Lu(III) was employed as a Lewis acid instead of Sc(III), a comparatively sufficient level of enantioselectivity was obtained (entry 12). For the $Bi(OTf)_3$–chiral 2,2′-bipyridine **1** catalyzed asymmetric hydroxymethylation in aqueous media, it has already been reported that an excess amount of **1** enhances both reactivity and enantioselectivity.[4l] Careful examination of the ligand/Sc ratio showed that slightly higher enantioselectivity was obtained when 10 mol% of $Sc(OTf)_3$ and 20 mol% of **1** were used (entry 13). Because reducing the amount of the chiral source is favorable, a 1 : 1.2 ratio of $Sc(OTf)_3$ to ligand **1** was chosen; this was examined, as was reducing the catalyst loading (entries 14–17). The Michael adduct was obtained in 91% yield with 91% ee using 1 mol% of $Sc(OTf)_3$ and 1.2 mol% of **1** in the presence of

Table 3 Substrate generality of asymmetric Michael addition



	Substrate **2**					
Entry	R^1	R^2		Thiol **3**	Yield (%)	ee (%)
1	Ph	Me	**2a**	BnSH **3a**	**4a** 92	93
2	Ph	Ph	**2b**	BnSH **3a**	**4b** 83	94
3	C_5H_{11}	Me	**2c**	BnSH **3a**	**4c** 65	85
4	Me	Et	**2d**	BnSH **3a**	**4d** 84	84
5	Me	Ph	**2e**	BnSH **3a**	**4e** 88	90
6	*p*-ClC_6H_4	Me	**2f**	BnSH **3a**	**4f** 82	92
7	2-Thienyl	Me	**2g**	BnSH **3a**	**4g** 76	85
8[a]	Ph	Ph	**2b**	EtSH **3b**	**4h** 80	97
9[a,b]	Ph	Ph	**2b**	*i*-PrSH **3c**	**4i** 81	86
10[a,b]	Ph	Ph	**2b**	*c*-C_5H_9SH **3d**	**4j** 91	93
11	Ph	Ph	**2b**	*p*-*t*-$BuC_6H_4CH_2SH$ **3e**	**4k** 87	90
12	Ph	Ph	**2b**	*p*-$ClC_6H_4CH_2SH$ **3f**	**4l** 89	90
13	Ph	Ph	**2b**	2-furylCH$_2$SH **3g**	**4m** 88	94
14	Ph	Ph	**2b**	PhSH **3h**	**4n** 92	44
15	–$(CH_2)_3$–		**2h**	BnSH **3a**	**4o** 75	8

[a] 5 mol% of $Sc(OTf)_3$, 6 mol% of **1**, and 10 mol% of pyridine used. [b] Reaction time 48 h.

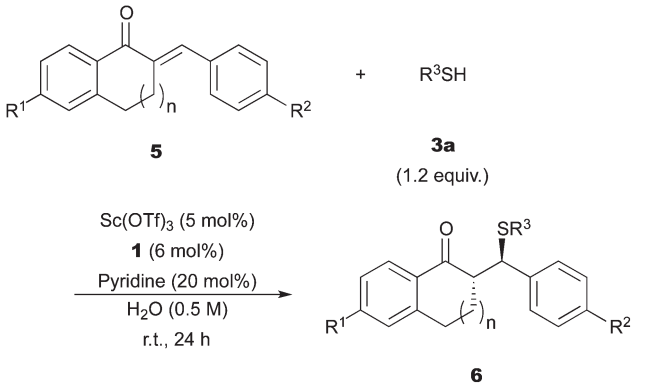
10 mol% of pyridine (entry 16). It is noteworthy that the same level of enantioselectivity was achieved using 0.5 mol% of $Sc(OTf)_3$ by extending the reaction time to 48 h (entry 17). Throughout these investigations, it was found that using a combination of $Sc(OTf)_3$, as a Lewis acid, and water, as a solvent, is the key to obtaining high yield and high enantioselectivity in the asymmetric Michael addition of enone **2a** to thiol **3a**.

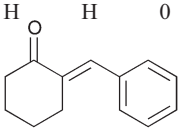
Under optimal conditions, the substrate scope of several enones and thiols was surveyed in the presence of an exquisite set of $Sc(OTf)_3$, chiral 2,2′-bipyridine **1** and pyridine (Table 3). Enantiomerically enriched adducts were obtained with both aliphatic and aromatic enones (entries 1–11). Since several aliphatic thiols are less reactive than benzylmercaptan **3a**, the amount of the catalyst and the reaction time were optimized in each case. The conditions were further applied to a heteroaromatic enone or thiol. The desired adducts were obtained with high enantioselectivities (entries 12, 13). Highly reactive thiophenol **3h** exhibited lower enantioselectivity, probably because of competitive progress of a noncatalytic pathway (entry 14). The significant decrease in enantioselectivity in cyclic enone **2h** provided us with an important suggestion regarding the stereochemistry (entry 15) (*vide infra*).

Enantioselective protonation with thiols and enones

In the chiral Sc-catalyzed Michael addition of thiols to α,β-unsaturated enones, substituents at the α-position of enones might provide us with a new strategy for the construction of two successive stereogenic centers. As a model, the Michael addition of benzylmercaptan **3a** to tetralone-derived enone **5a** was carried

Table 4 Substrate generality of asymmetric Michael addition/protonation (**1**)



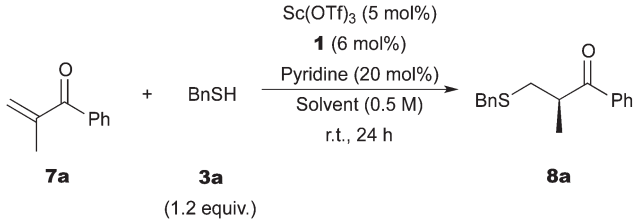
	Substrate **5**						
Entry	R^1	R^2	*n*		Yield (%)	dr (*syn*/*anti*)	ee (%)
1	H	H	1	**5a**	**6a** 90	90/10	96[a]
2	H	OMe	1	**5b**	**6b** 75	95/5	97[a]
3	H	Cl	1	**5c**	**6c** 56	94/6	97[a]
4	OMe	H	1	**5d**	**6d** 83	97/3	98[a]
5	H	H	0	**5e**	**6e** 85	68/32	97[a]
6				**5f**	**6f** 76	62/38	96[a]

[a] ee of the major isomer.

out in water, using our ternary catalytic system (Table 4). Very interestingly, the corresponding product was obtained in high yield with high diastereo- and enantioselectivities (entry 1). Both electron-withdrawing and electron-donating substituents afforded high selectivities, although they affected electrophilicity at the β-position of enones (entries 2, 3). On the other hand, when indanone-derived enone **5e** or cyclohexanone-derived enone **5f** was employed as a substrate, the diastereoselectivity decreased despite the high enantioselectivity (entries 5, 6).

These unexpected results indicated a potential application to chiral Sc-catalyzed enantioselective protonation in water. A pioneering challenge for catalytic enantioselective protonation without isolation of enolate equivalents was used in the chiral samarium-catalyzed Michael addition of 4-*tert*-butylbenzylmercaptan in dichloromethane (DCM).[12] Other catalytic enantioselective protonations such as tandem 1,4-addition,[13] Rh-catalyzed hydroarylation,[14] decarboxylative reaction,[15] coupling of ketenes with aldehydes,[16] Nazarov cyclization[17] and umpolung[18] have also been reported. Recently, a few chiral catalysts were reported for catalytic Michael-type enantioselective protonation using thiols.[19] However, most of them require strictly anhydrous and basic conditions, and extremely high or low temperatures, to obtain high selectivity, and the substrate scope is relatively narrow. Furthermore, the high mobility of protons in water has made enantioselective protonation in water impossible. To the best of our knowledge, catalytic enantioselective protonation that proceeds in aqueous media at room temperature under an ambient atmosphere is currently limited to one example, namely

Table 5 Optimization of reaction conditions in the asymmetric Michael addition/protonation



Entry	Lewis acid	Solvent	Yield (%)	ee (%)
1	$Sc(OTf)_3$	H_2O	76	67
2[a]	$Sc(OTf)_3$	H_2O	36	0
3	$Sc(OTf)_3$	CH_2Cl_2	54	−5
4	$Sc(OTf)_3$	THF	43	−15
5	$Sc(OTf)_3$	EtOH	54	−19
6	$Sc(OTf)_3$	Toluene	39	−17
7	$Sc(OTf)_3$	H_2O–THF = 1 : 9	45	−16
8	$Sc(OTf)_3$	H_2O–EtOH = 1 : 9	51	−21
9	$Sc(OSO_3C_{12}H_{25})_3$	H_2O	34	−21
10	$ScCl_3{\cdot}6H_2O$	H_2O	79	−3
11	$Sc(OAc)_3$	H_2O	81	−10
12	$Zn(OTf)_2$	H_2O	58	4
13	$Fe(OTf)_2$	H_2O	45	13
14	$Lu(OTf)_3$	H_2O	72	8

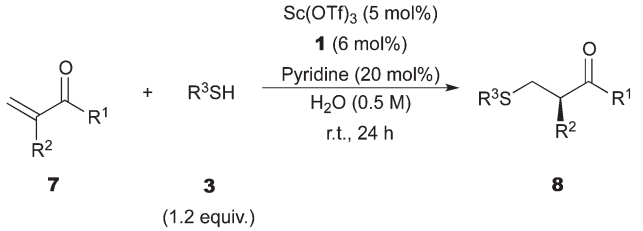
[a] Without pyridine.

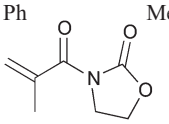
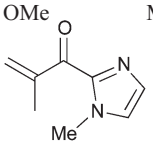
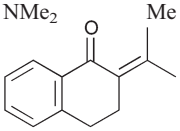
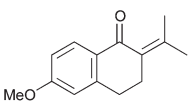
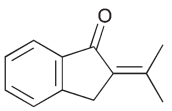
Nazarov cyclization in water, albeit with moderate selectivity (75% yield, 32% ee).[4j]

Initially, 2-methyl-1-phenyl-2-propen-1-one **7a** was treated with benzylmercaptan **3a** using our ternary catalytic system in water (Table 5). The reaction proceeded smoothly, to afford the desired protonated adduct **8a** in 78% yield with 67% ee, although a fast racemic reaction proceeded competitively in the presence of pyridine (entry 1).[20] Recrystallization of **8a** enabled us to obtain the enantiopure compound with >99% ee. By contrast, no enantioselectivity of the product was observed in the absence of pyridine (entry 2). When the protonation was carried out in organic solvents such as DCM, the enantioselectivity was very low (entries 3–6). In mixed aqueous solvents, H_2O–THF and H_2O–EtOH, the enantioselectivity was slightly improved. The configuration of the product was opposite to that obtained in water (entries 7, 8). When other scandium species were employed instead of $Sc(OTf)_3$, the same tendency was observed (entries 9–11). Poor enantioselectivity was obtained in the presence of other metal cations such as Zn(II) and Fe(II) (entries 12, 13). In the case of $Lu(OTf)_3$, the enantioselectivity was also low (entry 14). This is in contrast to the asymmetric Michael reaction, when good enantioselectivity was obtained (Table 2, entry 12). This disparity implies the outstanding potential of Sc(III) for enantioselective protonation in water.

Substrate generality was examined under optimal conditions (Table 6). Various types of ketones, including those with terminal olefins in the structure, led to the corresponding products in good to high yields with moderate to good enantioselectivities, although a fast racemic reaction proceeded competitively in the presence of pyridine (entries 1–12). When oxazolidinone **7i** was employed instead of a ketone, the reaction also proceeded to afford the corresponding adduct with good enantioselectivity

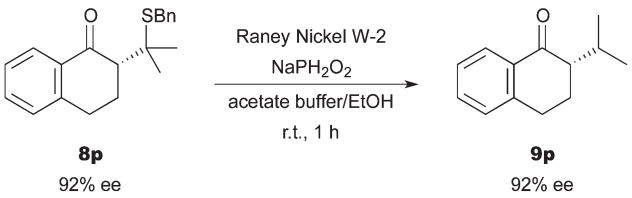
Table 6 Substrate generality of asymmetric Michael addition/protonation (**2**)



Entry	Substrate **7** R^1	R^2		Thiol **3**	Yield (%)	ee (%)
1	Ph	Me	**7a**	BnSH **3a**	**8a** 78	67
2	Ph	Bu	**7b**	BnSH **3a**	**8b** 60	69
3	Ph	Ph	**7c**	BnSH **3a**	**8c** 75	74
4	*p*-OMe–C_6H_4	Me	**7d**	BnSH **3a**	**8d** 85	54
5	*p*-Br–C_6H_4	Me	**7e**	BnSH **3a**	**8e** 74	70
6	Ph	Bn	**7f**	BnSH **3a**	**8f** 70	60
7	*m*-CF_3–C_6H_4	Bn	**7g**	BnSH **3a**	**8g** 51	63
8	*p*-OMe–C_6H_4	Bn	**7h**	BnSH **3a**	**8h** 74	60
9	Ph	Me	**7a**	*p*-Cl–$C_6H_4CH_2$-SH **3b**	**8i** 78	53
10	Ph	Me	**7a**	*p*-OMe–$C_6H_4CH_2$-SH **3c**	**8j** 82	60
11	Ph	Me	**7a**	*p*-*t*-Bu–$C_6H_4CH_2$-SH **3d**	**8k**74	58
12	Ph	Me	**7a**	2-FurylCH_2SH **3e**	**8l** 92	60
13			**7i**	BnSH **3a**	**8m** 29	68
14	OMe	Me	**7j**	BnSH **3a**	**8n** 7	21
15			**7k**	BnSH **3a**	**8o** 83	3
16	NMe_2	Me	**7l**	BnSH **3a**	NR	
17[a]			**7m**	BnSH **3a**	**8p** 37	92
18[a]			**7n**	BnSH **3a**	**8q** 26	94
19[a]			**7o**	BnSH **3a**	**8r** 56	45

[a] Reaction time 96 h. NR: no reaction.

(entry 13). This adduct can be readily transformed to various functional groups. The reaction of α,β-unsaturated ester **7j**, which is known to be less reactive than ketones, afforded the poor result (entry 14). In the case of imidazole-derived ketone **7k**, an almost racemic product was obtained (entry 15). An α,β-unsaturated amide did not react under the conditions (entry 16). When a dimethyl-substituted terminal olefin was introduced to tetralone in order to suppress the undesired



Scheme 1 Desulfurization with RANEY® Nickel W-2.

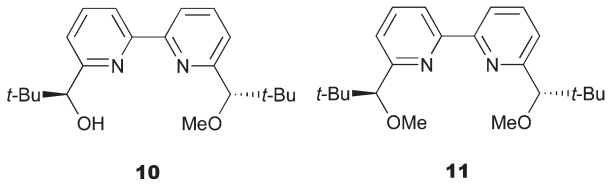


Fig. 2 Structure of chiral 2,2′-bipyridine derivatives.

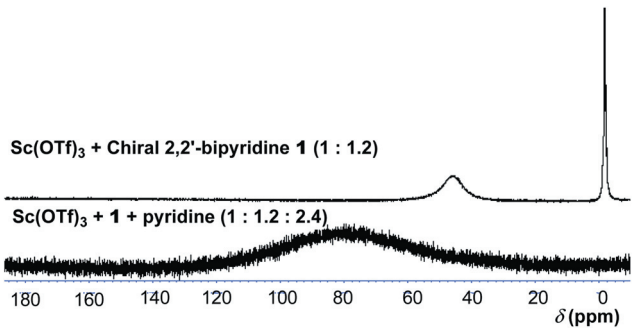


Fig. 1 ^{45}Sc NMR spectrum of a Sc–**1** complex in D_2O.

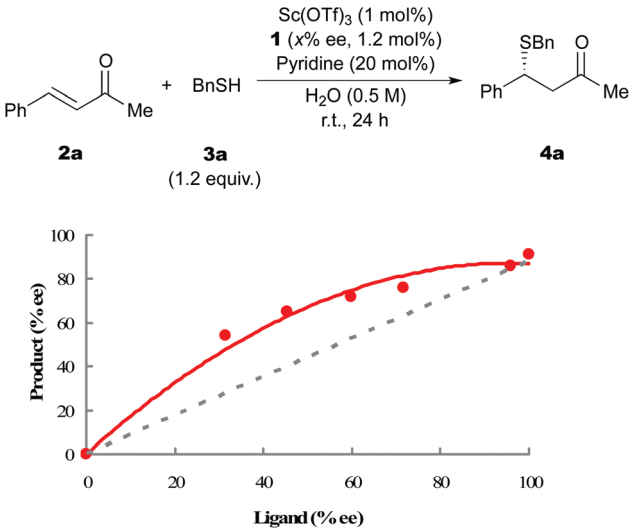


Fig. 3 Observation of the non-linear effect in chiral Sc-catalyzed reaction of **2a** with **3a**.

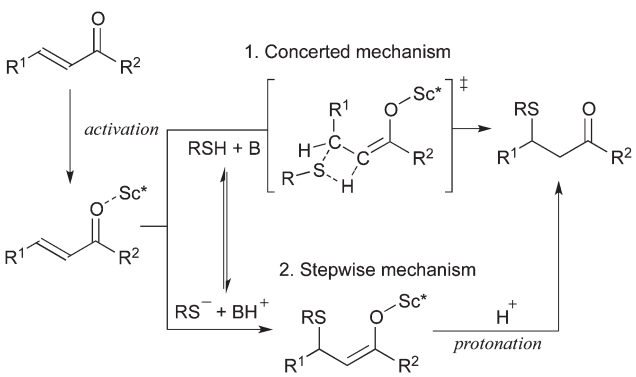
base-catalyzed racemic pathway, the product was obtained with moderate to high enantioselectivity (entries 17, 18). By contrast, an indanone derivative led to poor enantioselectivity (entry 19).

Finally, the product **8p** was converted to **9p** through desulfurization with RANEY® Nickel W-2. No racemization was observed in this transformation. The absolute configuration of **8p** was determined by comparison of the major enantiomer of **9p** (HPLC) (Scheme 1).[21,22]

Reaction mechanism

In this reaction, the $Sc(OTf)_3$–chiral 2,2′-bipyridine **1** complex and pyridine (used as an additive) play crucial roles in both the reactivity and the enantioselectivity. ^{45}Sc NMR spectroscopy (Fig. 1) revealed that the catalytic system prepared by simply mixing $Sc(OTf)_3$ and 1.2 equiv. of **1** in water turned out to be in dynamic equilibrium between two environmentally distinct scandium species. One spectrum (δ = 0.0 ppm) is assigned to the Sc(III) ion,[23] and the other (δ = 47.3 ppm) is considered to be a 1 : 1 Sc–ligand complex.

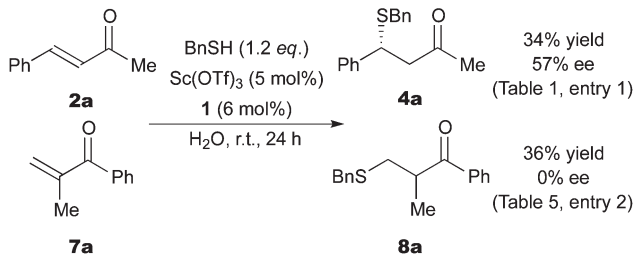
Crystallographic analysis of the chiral scandium complex formed with **1** has been characterized as having pentagonal bipyramidal geometry.[4a] The reaction proceeded sluggishly when chiral 2,2′-bipyridine derivative **10** or **11** was employed, where one or both hydroxyl groups are protected by a methyl group.[24] Therefore, it appears that **1** coordinates to a scandium ion in a tetradentate fashion in water. On the other hand, ^{45}Sc NMR spectroscopy indicated that the Sc(III) ion (δ = 0.0 ppm) disappeared in the ternary catalytic system consisting of Sc $(OTf)_3$, ligand **1** and pyridine. The significantly downfield chemical shift (δ = 79.7 ppm) suggests interaction between the scandium ion and pyridine. Judging from a ^{19}F NMR spectrum, the interaction between scandium and the triflate anion has complete ionic character.[25] The observation of a positive nonlinear



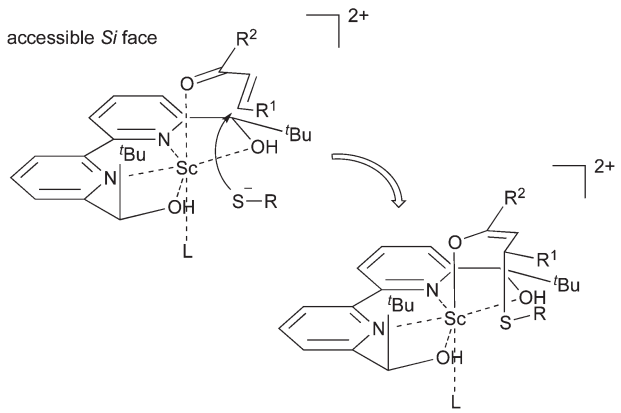
Scheme 2 Possible reaction mechanism for a catalytic pathway.

effect in the asymmetric Michael addition of thiols with simple enones may be ascribed to the low solubility of the heterodimeric chiral 2,2′-bipyridine ligand in water (Fig. 2 and 3).

The ternary catalytic system comprising the Lewis acid and the base exhibits two distinct reaction pathways. One is a desired cooperative pathway depicted by precise orchestration of the Lewis acid–base. The other is a base-catalyzed undesired pathway with no chiral induction. In this base-catalyzed pathway, the rate-determining step is an attack of thiolates on enones to generate enolates.[26] On the other hand, the desired catalytic pathway may have multiple steps (Scheme 2). The initial trigger of the reaction is catalytic generation of an activated enone, which has been confirmed by significant changes in



Scheme 3 Reaction in the absence of pyridine.



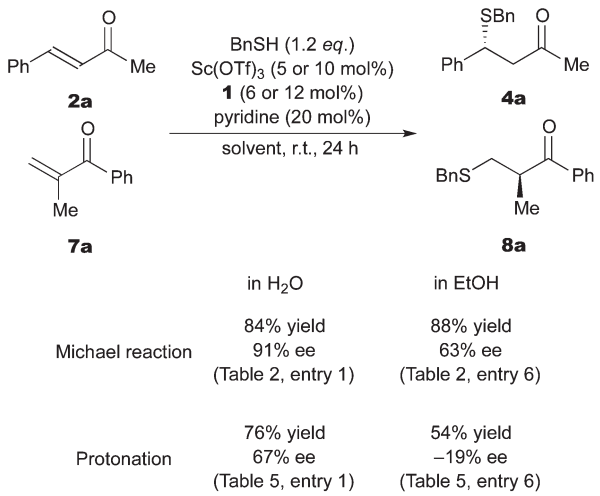
Scheme 4 Plausible reaction mechanism *via* a stepwise process.

^{13}C chemical shifts.[27] The activated enone is then amenable to nucleophilic addition of either *thiol* or *thiolate*, which is under acid–base equilibrium.[28] Cronin and co-workers have suggested that the nucleophilic addition of *thiols* in aqueous media proceeds *via* a concerted mechanism.[29] By contrast, the addition of *thiolates* involves a stepwise mechanism, *via* the formation of enolate intermediates.

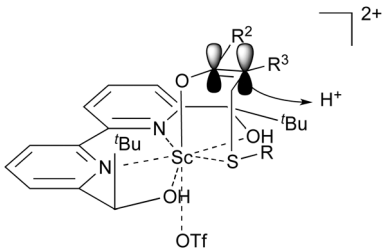
The observation of significant acceleration by addition of pyridine strongly suggests that the major nucleophilic species are not *thiols*, but *thiolate* anions. The nucleophilic attack of *thiolate* anions leads to products *via* a stepwise process. On the other hand, in the absence of pyridine, the nucleophilic attack of *thiols* is possible. The experimental data using the β-substituted enone and the α-substituted enone showed that the β-substituted enone led to an optically active adduct, whereas the α-substituted enone led to a racemic product (Scheme 3). Since the concerted process should influence stereochemistry on the carbon atom, at both the α-position and the β-position, these results indicate that the major reaction pathway is a stepwise process, even for the attack of *thiols*.

The stepwise process involves two enantiofacial differentiations: nucleophilic attack and a protonation step. In the light of the X-ray structure of the Sc–chiral-2,2′-bipyridine complex previously reported, a nucleophile prefers to attack the Si face in order to rationalize the observed sense of chiral induction (Scheme 4). This tendency of the nucleophilic attack seems to be the same even in organic solvents, although there the selectivity is lower (Table 2, entries 2–7).

On the other hand, water and other organic solvents differ in enantiofacial differentiation at the protonation step (Table 5, entries 1 *vs.* 3–6). For example, the results obtained in H_2O and in EtOH are compared in Scheme 5.



Scheme 5 Comparison of reaction medium.



Scheme 6 Enantiofacial differentiation of protons.

Given significant competition of the racemic pathway against the desired catalytic pathway, minimization of structural fluctuation through the interaction between scandium and sulfur may play an important role in governing the enantioselectivity. According to the stereochemistry observed in the enantioselective protonation, a proton should be introduced preferentially, as shown in Scheme 6.

In ethanol or other organic solvents, only a pyridinium cation generated *via* equilibrium with thiols can behave as a proton source, and enantiofacial differentiation must be based upon steric hindrance. However, this explanation may also apply in the case of aqueous media. It is considered that the key factor for chiral induction is the abnormally high mobility of protons in water, the value of which is $>10^3$ times greater than in organic solvents.[30]

To examine the deuterium kinetic isotope effect, the reaction of **7a** with **3a** was carried out in D_2O. Theoretically, deuteration should be slower than protonation. This was verified by simple comparison of reaction rates (Fig. 4B).

As expected, there was a prominent isotope effect in the reaction of **7a** with **3a** (**B**), compared with Michael addition (**A**), which seems to originate from the activation energies in the protonation/deuteration step. A proton is introduced predominantly in an initial stage of the reaction, with excellent reproducibility, despite significant competition of an undesired pathway catalyzed by pyridine (Table 7, entry 1).

The definitive H/D ratio of the product was finally 10/90, although a total H/D ratio in this system is <1/>99, including an

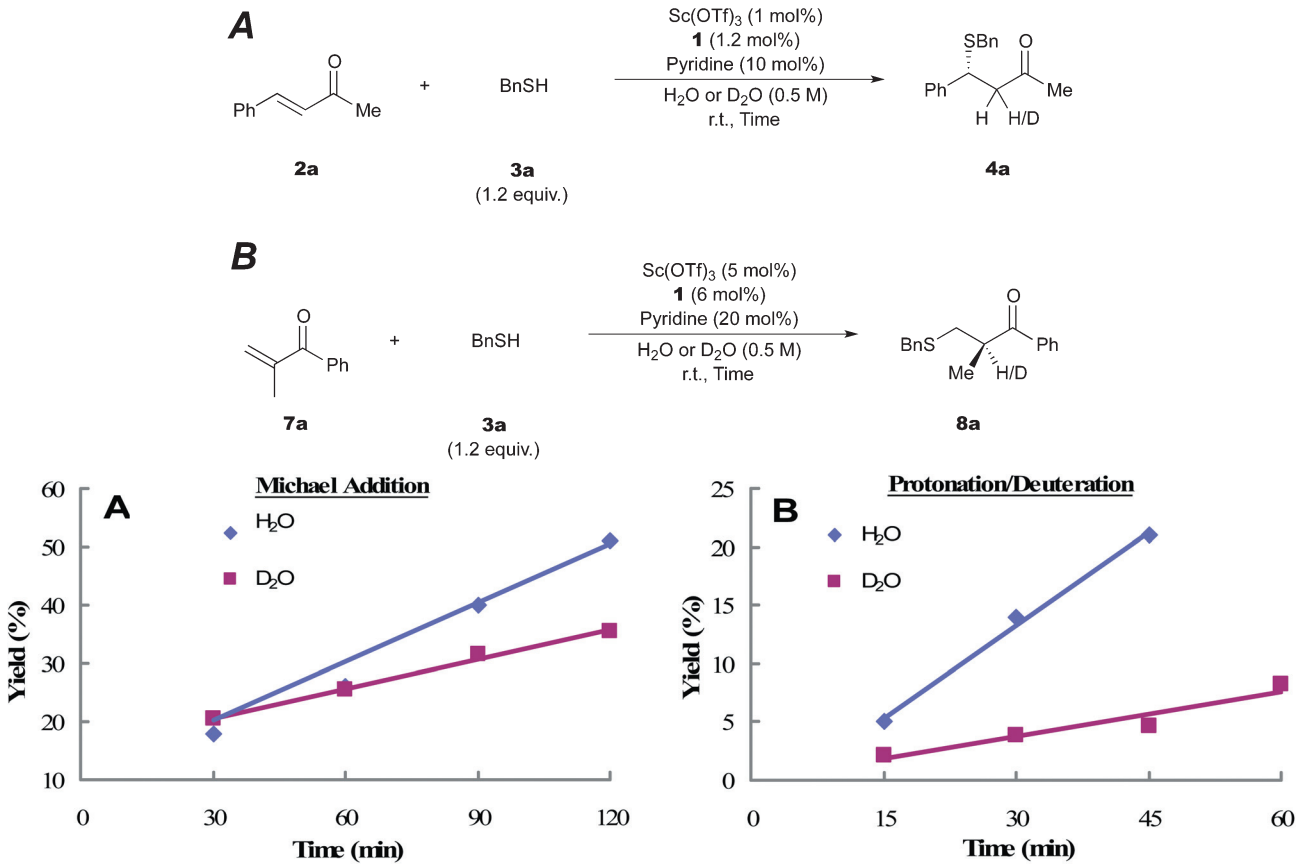
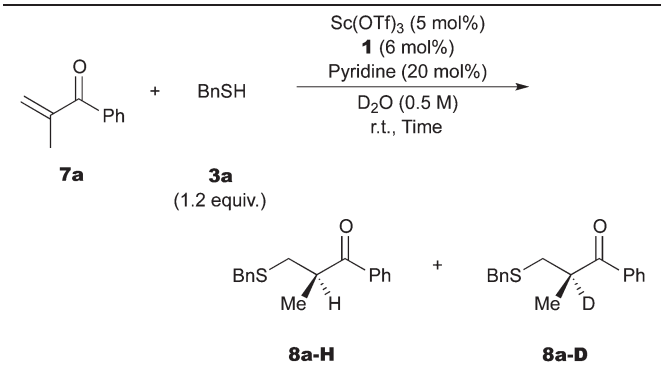


Fig. 4 Deuterium kinetic isotope effect in the reaction rate of Michael addition and protonation/deuteration.

Table 7 Protonation/deuteration in D_2O



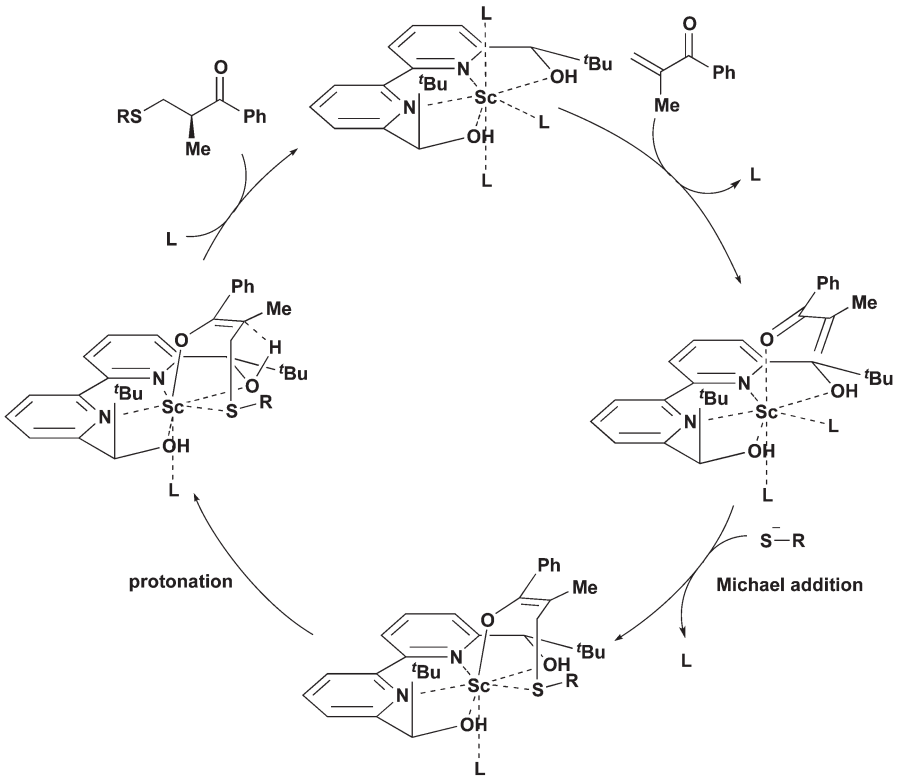
Entry	Time (h)	Conditions	Total yield (%)	H/D ratio
1	1 h	—	14 (6)[b]	43/57
2[a]	24 h	—	71 (7)[b]	10/90
3	24 h	BnSH (3 equiv.)	72 (7)[b]	10/90

[a] The same level of enantioselectivity (67% ee) was observed as that observed in H_2O. [b] Yield of the protonated product **8a-H** was described in parentheses.

exchangeable proton in thiol (entry 2).[31] It is also noteworthy that the proton was barely introduced after an initial stage; the protonated product **8a-H** was obtained in 6% yield within 1 h and 7% yield within 24 h. Employing twice the amount of thiol did not affect the definitive H/D ratio, which excludes the involvement of a free proton in the total reaction system. In that sense, the hydroxyl groups in chiral 2,2′-bipyridine **1** seem to function as proton sources in this catalytic system.[32] Interestingly, this significantly high H/D ratio corresponds to the amount of the hydroxyl groups in the chiral scandium catalyst formed with $Sc(OTf)_3$ and **1**. In addition, the enantiofacial differentiation shown in Scheme 6 implies the proactive involvement in enantioselective protonation of such hydroxyl groups. As shown in Scheme 6, this hydrogen can be affected by the reactive π-orbital of enolate. Unfortunately, this simplest of explanation imposes limitations on the demonstration of immediate evidence because of the proton-rich environment. Based upon such insight into the sense of chiral induction, a possible reaction mechanism is postulated in Scheme 7. Because of the ionic character that exists between the scandium cation and the triflate anion, ligand exchange with the solvent molecule seems to be very fast on the scandium atom. As the proton-transfer rate is in the order of picoseconds, the rate-determining step must be the Michael addition step of thiolate anions with enones.

Conclusions

We have developed a new catalytic system for the asymmetric Michael addition of thiols to enones and enantioselective



Scheme 7 Possible catalytic cycle for enantioselective protonation. Due to labile ligand exchange, the catalyst structure should be $[(\text{Ligand})\text{Sc}^{\text{III}}\text{-}(\text{H}_2\text{O})_m(\text{py})_n(\text{OTf})_{3-m-n}]^{(m+n)+}$(m + *n*) OTf^-, py = pyridine.

protonation in water. In both processes, water plays key roles in reactivity and selectivity. For the asymmetric Michael reactions, the reactions proceeded in both water and organic solvents, but higher selectivity was obtained in water. In the protonation, lower yields and low enantioselectivities were obtained in organic solvents. It is noted that highly enantioselective protonation occurred in water. The remarkable governing of the enantioselectivity for the simple introduction of protons despite their abnormally high mobility in water may provide us with not only new synthetic opportunities but also significant chemical advances. Further investigations to develop new catalytic systems or reactions in water that allow for enantioselective proton transfer are currently underway.

Experimental

General

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECX-600 or ECX-500 spectrometer, operating at 600 MHz or 500 MHz for ^{1}H and 150 MHz or 125 MHz for ^{13}C NMR in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as the internal standard (δ = 0) for ^{1}H NMR and $CDCl_3$ was used as the internal standard (δ = 77.0) for ^{13}C NMR. The aqueous solution of $ScCl_3$ [$Sc(H_2O)_6^{3+}$] served as the external standard (δ = 0) for ^{45}Sc NMR analysis. Infrared (IR) spectra were obtained using a JASCO FT/IR-4200 spectrometer. Data are represented as frequency of absorption (cm^{-1}). All melting points were determined on a YAZAWA micro-melting point BY-1 apparatus and are uncorrected. High-performance liquid chromatography was carried out using the following apparatus: SHIMADZU LC-10ATvp (liquid chromatograph), SHIMADZU SPD-10A (UV detector) and SHIMADZU C-R8A (Chromatopac) using Daicel chiralpak® or chiralcel® columns. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F from Wako Pure Chemical Industries, Ltd. High resolution mass spectra (HRMS) were recorded using a JEOL JMS-T100TD (DART) spectrometer. Optical rotations were measured on a JASCO P1010 polarimeter using a 2 mL cell with 1 dm path length. Data are reported as follows: $[\alpha]_D^T$ (*c* in g per 100 mL, solvent). Deionized water from a MILLIPORE MilliQ machine (Gradient A 10) was used as a solvent without further treatment. Deuterium oxide purchased from ACROS (99.8 atom% D incorporated) was used without further treatment. All organic solvents used were commercially available dry solvents, which were distilled appropriately under an argon atmosphere or were stored over molecular sieves prior to use. Thiols **3** were commercially available and were used without any purification prior to use. $Sc(OTf)_3$,[33] $Sc(OSO_3C_{12}H_{25})_3$ [8] and $Bi(OTf)_3$ [34] were prepared by known methods. Other metal salts were commercially available.

Chiral 2,2′-bipyridine **1**[7,35] and **10**[4k] and **11**[7] were synthesized using protocols described in the literature. α,β-Unsaturated ketones **2** are commercially available and were distilled or recrystallized prior to use. α-Branched ketones **7j** and **7l** are commercially available and were distilled prior to use. Other ketones **5a**,[36] **5b**,[36] **5c**,[37] **5d**,[36] **5e**,[37] **5f**,[38] **7a**,[39] **7b**,[40] **7c**,[39] **7d**,[41] **7e**,[41] **7f**,[39] **7i**,[42,43] **7k**,[44] **7m**,[45] and **7n**[45] were prepared by the following procedures.[40] Similarly, **7g**, **7h**, and **7o** were prepared.

7g: 2-benzyl-1-(3-(trifluoromethyl)phenyl)prop-2-en-1-one. Colorless oil; ^{1}H NMR (600 MHz): δ = 3.80 (s, 2H), 5.68 (s, 1H), 5.82 (s, 1H), 7.17–7.44 (m, 5H), 7.55 (t, 1H, J = 7.6 Hz), 7.76 (d, 1H, J = 7.6 Hz), 7.87 (d, 1H, J = 7.6 Hz), 7.95 (s, 1H). ^{13}C NMR (150 MHz): δ = 38.1, 126.1, 126.5, 127.8, 128.4, 128.6, 128.8, 129.1, 132.5, 138.2, 138.3, 147.3, 196.1.

7h: 2-benzyl-1-(4-methoxyphenyl)prop-2-en-1-one. Colorless oil; ^{1}H NMR (600 MHz): δ = 3.80 (s, 2H), 3.90 (s, 3H), 5.52 (s, 1H), 5.58 (s, 1H), 6.81–6.85 (m, 2H), 7.10–7.26 (m, 5H), 7.72–7.74 (m, 2H). ^{13}C NMR (150 MHz): δ = 38.7, 55.4, 113.4, 124.7, 126.3, 128.4, 129.1, 131.9, 138.6, 147.7, 163.1, 196.4.

7o: 2-benzylidene-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. Colorless oil; ^{1}H NMR (600 MHz): δ = 1.87 (s, 3H), 2.14 (s, 3H), 2.72 (t, 2H, J = 6.2 Hz), 2.84 (t, 2H, J = 6.5 Hz), 3.78 (s, 3H), 6.66 (d, 1H, J = 2.1 Hz), 6.81–6.83 (m, 1H), 8.05 (d, 1H, J = 8.9 Hz). ^{13}C NMR (150 MHz): δ = 23.0, 23.3, 28.6, 30.3, 53.3, 112.0, 112.8, 128.3, 130.1, 130.3, 144.7, 145.7, 162.8, 189.9.

Typical experimental procedure for Michael reaction and protonation in water

A 0.005 M aqueous Sc(OTf)$_3$ solution (800 μL, 0.004 mmol) was added to chiral 2,2′-bipyridine **1** (1.6 mg, 0.0048 mmol) and the mixture was stirred for 1 h at room temperature. After the successive addition of pyridine (3.2 μL, 0.04 mmol), benzalacetone **2a** (58.5 mg, 0.4 mmol) and benzylthiol **3a** (56.3 μL, 0.48 mmol), the reaction mixture was vigorously stirred for 24 h at room temperature. The resulting mixture was diluted with water. The aqueous layer was extracted with DCM (three times), and then the combined organic layers were washed with $CuSO_4$ aq., and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (elution: chloroform–ethyl acetate = 200 : 1) to afford the corresponding Michael adduct **4a** (99.8 mg, 92% yield). The enantiomeric excess was determined by chiral HPLC analysis.

Analytical data for Michael reactions of thiols 4a–m

Michael reactions of thiols **4a**,[46] **4b**,[46] **4c**,[46] **4d**,[46] **4e**,[47] **4f**,[46] **4g**,[46] **4h**,[48] **4i**,[48] **4j**,[48] **4k**,[48] **4l**,[48] and **4m**[48] are literature-known; obtained analytical data for these compounds are in full agreement with reported data. The absolute configurations of the optically active compounds were determined by comparison of the measured HPLC data with the values reported in the literature.[46–48]

4a: (*R*)-4-(benzylthio)-4-phenylbutan-2-one.[46] Colorless oil; IR (neat): ν = 3060, 3027, 2917, 1716, 1600, 1492, 1452, 1416, 1358, 1329, 1240, 1154, 1074, 1024, 761, 699 cm^{-1}. ^{1}H NMR (500 MHz): δ = 1.99 (s, 3H), 2.91 (m, 2H), 3.47 (dd, 2H, J = 13.3, 19.1 Hz), 4.19 (t, 1H, J = 7.4 Hz), 7.18–7.34 (m, 10H). ^{13}C NMR (125 MHz): δ = 30.4, 35.6, 43.8, 49.9, 126.9, 127.3, 127.9, 128.4, 128.5, 128.8, 137.7, 141.4, 205.2. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 8.3 min (*R*), t_R = 9.7 min (*S*).

4b: (*R*)-3-(benzylthio)-1,3-diphenylpropan-1-one.[46] Colorless solid; mp 60–62 °C; IR (KBr): ν = 3058, 3023, 2894, 1679, 1595, 1448, 1341, 1224, 981, 921, 727, 693 cm^{-1}. ^{1}H NMR (600 MHz): δ = 3.37–3.50 (m, 4H), 4.38 (d, 1H, J = 5.1 Hz), 7.12–7.25 (m, 8H), 7.30–7.34 (m, 4H), 7.45 (t, 1H, J = 7.2 Hz), 7.77 (d, 2H, J = 6.9 Hz). ^{13}C NMR (150 MHz): δ = 35.8, 44.1, 45.2, 127.0, 127.3, 128.0, 128.5, 128.5, 128.9, 133.1, 136.6, 137.8, 141.7, 196.7. HPLC (Daicel Chiralcel OJ-H, *n*hexane–*i*–PrOH = 4 : 1, flow rate = 1.0 mL min^{-1}); t_R = 22.6 min (*S*), t_R = 33.1 min (*R*).

4c: (*S*)-4-(benzylthio)nonan-2-one.[46] Colorless oil; IR (neat): ν = 2954, 2927, 2856, 1715, 1455, 1419, 1359, 1157, 701 cm^{-1}. ^{1}H NMR (600 MHz): δ = 0.86 (t, 3H, J = 7.2 Hz), 1.16–1.37 (m, 6H), 1.46–1.50 (m, 2H), 2.08 (s, 3H), 2.63 (ddd, 2H, J = 6.7, 16.7, 20.2 Hz), 3.03 (t, 1H, J = 6.9 Hz), 3.73 (dd, 2H, J = 13.1, 8.3 Hz), 7.21–7.33 (m, 5H). ^{13}C NMR (150 MHz): δ = 14.0, 22.5, 26.2, 30.5, 31.5, 35.0, 40.3, 49.6, 126.9, 128.4, 128.9, 138.5, 207.0. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 8.0 min (*S*), t_R = 8.7 min (*R*).

4d: (*S*)-5-(benzylthio)hexan-3-one.[46] Colorless oil; IR (neat): ν = 3061, 3028, 2973, 2934, 1712, 1494, 1454, 1410, 1361, 1239, 1199, 1115, 1070, 1027, 986, 769, 701 cm^{-1}. ^{1}H NMR (600 MHz): δ = 1.02 (t, 3H, J = 7.2 Hz), 1.26 (d, 3H, J = 6.9 Hz), 2.34–2.37 (m, 2H), 2.50 (dd, 1H, J = 8.2, 16.7 Hz), 2.66 (dd, 1H, J = 7.6, 16.7 Hz), 3.15–3.21 (m, 1H), 3.75 (dd, 2H, J = 13.1, 7.9 Hz), 7.21–7.32 (m, 5H). ^{13}C NMR (150 MHz): δ = 7.6, 21.5, 35.0, 35.5, 36.5, 49.5, 127.0, 128.5, 128.8, 138.3, 209.2. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 0.8 mL min^{-1}); t_R = 13.2 min (*R*), t_R = 14.1 min (*S*).

4e: (*S*)-3-(benzylthio)-1-phenylbutan-1-one.[47] Colorless oil; IR (neat): ν = 3584, 3060, 3027, 2964, 2921, 1683, 1597, 1580, 1493, 1449, 1353, 1221, 1180, 1071, 986, 753, 690, 641 cm^{-1}. ^{1}H NMR (500 MHz): δ = 1.33 (d, 3H, J = 6.8 Hz), 3.05 (dd, 1H, J = 9.1, 17.0 Hz), 3.29 (dd, 1H, J = 5.1, 17.0 Hz), 3.34–3.41 (m, 1H), 1.53–1.58 (m, 1H), 3.80 (dd, 2H, J = 13.6, 17.6 Hz), 7.21–7.26 (m, 1H), 7.28–7.36 (m, 4H, J = 9.5), 7.40–7.48 (m, 2H), 7.53–7.56 (m, 1H), 7.83–7.92 (m, 2H). ^{13}C NMR (125 MHz): δ = 21.4, 35.3, 35.6, 46.0, 126.9, 128.0, 128.5, 128.6, 128.8, 133.1, 136.8, 138.3, 198.0. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 7.1 min (*S*), t_R = 7.8 min (*R*).

4f: (*R*)-4-(benzylthio)-4-(4-chlorophenyl)butan-2-one.[46] Colorless oil; IR (neat): ν = 3437, 2922, 1716, 1596, 1453, 1417, 1367, 1201, 1099, 953, 699 cm^{-1}. ^{1}H NMR (600 MHz): δ = 2.02 (s, 3H), 2.89 (d, 2H, J = 7.6 Hz), 3.42 (d, 1H, J = 13.7 Hz), 3.52 (d, 1H, J = 13.7), 4.16 (t, 3H, J = 7.5 Hz), 7.18–7.29 (m, 9H). ^{13}C NMR (150 MHz): δ = 30.5, 35.7, 43.0, 49.8, 127.1, 128.5, 128.7, 128.9, 129.3, 132.9, 137.5, 140.1, 204.9. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 19.8 min (*R*), t_R = 20.9 min (*S*).

4g: (*R*)-4-(benzylthio)-4-(thiophen-2-yl)butan-2-one.[46] Colorless oil; IR (neat): ν = 3583, 3063, 3028, 2918, 1713, 1493, 1450, 1417, 1360, 1242, 1154, 1043, 701, 661 cm^{-1}. ^{1}H NMR (600 MHz): δ = 2.05 (s, 3H), 2.97 (ddd, 2H, J = 7.2, 16.8,

21.3 Hz), 3.61 (dd, 2H, J = 13.7, 18.5 Hz), 4.51 (t, 1H, J = 7.2 Hz), 6.91 (m, 2H), 7.22–7.26 (m, 4H), 7.28–7.31 (m, 2H). ^{13}C NMR (150 MHz): δ = 30.5, 35.9, 39.1, 50.8, 124.8, 125.8, 126.4, 127.1, 128.5, 128.9, 137.6, 146.3, 204.9. HPLC (Daicel Chiralpak AD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 13.1 min (*S*), t_R = 15.0 min (*R*).

4h: (*R*)-3-(ethylthio)-1,3-diphenylpropan-1-one.[48] Colorless solid; mp 57–60 °C; IR (KBr): ν = 2968, 2923, 1683, 1594, 1448, 1409, 1365, 1338, 1222, 979, 752, 713, 695 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.17 (t, 3H, J = 7.2 Hz), 2.36 (q, 2H, J = 7.6 Hz), 3.54 (dd, 2H, J = 3.7, 7.2 Hz), 4.59 (t, 1H), 7.26–7.55 (m, 8H), 7.92 (d, 2H, J = 8.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): d = 14.3, 25.4, 43.9, 45.3, 127.2, 127.8, 128.1, 128.5, 128.6, 133.2, 136.7, 142.2, 197.0. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 12.4 min (*R*), t_R = 15.7 min (*S*).

4i: (*R*)-3-(isopropylthio)-1,3-diphenylpropan-1-one.[48] Colorless solid; mp 77–80 °C; IR (KBr): ν = 3061, 2965, 2924, 2866, 1638, 1589, 1449, 1364, 1334, 1222, 979, 750, 710, 694 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.06 (d, 3H, J = 6.9 Hz), 1.20 (d, 3H, J = 6.9 Hz), 2.56 (sep, 1H, J = 6.7 Hz), 3.45 (m, 2H), 4.56 (t, 1H, J = 1.7 Hz), 7.12–7.15 (m, 1H), 7.21–7.24 (m, 2H), 7.35–7.38 (m, 4H), 7.46–7.49 (m, 1H), 7.84 (d, 2H, J = 7.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 22.9, 23.4, 34.6, 43.3, 45.7, 127.1, 127.8, 128.1, 128.5, 128.6, 133.2, 136.8, 142.6, 197.0. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 10.8 min (*R*), t_R = 12.2 min (*S*).

4j: (*R*)-3-(cyclopentylthio)-1,3-diphenylpropan-1-one.[48] Colorless solid; mp 67–69 °C; IR (KBr): ν = 2953, 2861, 1714, 1682, 1595, 1493, 1449, 1410, 1361, 1337, 1229, 1075, 1050, 980, 749, 725, 700, 687 cm^{-1}. ^{1}H NMR (500 MHz): δ = 1.31–1.38 (m, 1H), 1.41–1.54 (m, 2H), 1.57–1.81 (m, 4H), 1.93–2.00 (m, 1H), 2.80 (ddd, 1H, J = 7.4, 7.2, 14.3 Hz), 3.53 (q, 2H, J = 7.1 Hz), 4.59 (t, 1H, J = 7.1 Hz), 7.19–7.22 (m, 1H), 7.26–7.31 (m, 2H), 7.41–7.45 (m, 4H), 7.52–7.55 (m, 1H), 7.90–7.91 (m, 2H). ^{13}C NMR (125 MHz): δ = 24.7, 24.9, 33.1, 34.0, 43.1, 44.4, 45.5, 127.1, 127.7, 128.1, 128.1, 128.4, 128.6, 133.1, 136.8, 197.0. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 12.4 min (*R*), t_R = 13.6 min (*S*).

4k: (*R*)-3-((4-(*tert*-butyl)benzyl)thio)-1,3-diphenylpropan-1-one.[48] Colorless solid; mp 82–84 °C; IR (KBr): ν = 3429, 2960, 1682, 1450, 1363, 1342, 1230, 754, 705, 696 cm^{-1}. ^{1}H NMR (500 MHz): δ = 1.29 (s, 9H), 3.43–3.56 (m, 4H), 4.48 (dd, 1H, J = 6.2, 7.9 Hz), 7.14 (d, 2H, J = 7.9 Hz), 7.19–7.22 (m, 1H), 7.27–7.31 (m, 4H), 7.35–7.39 (m, 4H), 7.40–7.51 (m, 1H), 7.83 (d, 2H, J = 7.9 Hz). ^{13}C NMR (125 MHz): δ = 31.3, 34.4, 35.3, 44.1, 45.2, 125.3, 127.2, 128.0, 128.4, 128.5, 128.5, 133.1, 134.7, 136.6, 141.7, 149.7, 196.7. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 7 : 3, flow rate = 0.5 mL min^{-1}); t_R = 23.7 min (*R*), t_R = 30.3 min (*S*).

4l: (*R*)-3-((4-chlorobenzyl)thio)-1,3-diphenylpropan-1-one.[48] Colorless solid; mp 79–80 °C; IR (KBr): ν = 3060, 3028, 1686, 1596, 1489, 1449, 1334, 1226, 1092, 749, 694 cm^{-1}. ^{1}H NMR (600 MHz): δ = 3.36–3.45 (m, 4H), 4.34 (t, 1H, J = 6.9 Hz), 7.03–7.05 (m, 2H), 7.13–7.18 (m, 3H), 7.22–7.24 (m, 2H), 7.27–7.29 (m, 2H), 7.32–7.35 (m, 2H), 7.45–7.47 (m, 1H), 7.76–7.78 (m, 1H). ^{13}C NMR (150 MHz): δ = 35.2, 44.1, 45.2, 127.4, 128.0, 128.5, 128.6, 130.2, 132.7, 136.4, 136.6, 141.6, 196.6. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 7 : 3, flow rate = 0.5 mL min^{-1}); t_R = 25.2 min (*S*), t_R = 38.5 min (*R*). HRMS calcd for $C_{22}H_{20}OSCl^+$ ([M + H]$^+$): 367.09234, found 367.09084.

4m: (*R*)-3-((furan-2-ylmethyl)thio)-1,3-diphenylpropan-1-one.[48] Colorless oil; IR (KBr): ν = 3061, 3029, 1686, 1597, 1449, 1227, 1150, 1011, 748 cm^{-1}. ^{1}H NMR (600 MHz): δ = 3.46–3.50 (m, 2H), 3.55–3.60 (m, 2H), 4.57 (dd, 1H, J = 6.2, 8.2 Hz), 6.11 (d, 1H, J = 3.5 Hz), 6.28 (d, J = 1.3 Hz), 7.20–7.23 (m, 1H), 7.25–7.33 (m, 3H), 7.40–7.42 (m, 4H), 7.51–7.55 (m, 1H), 7.86 (d, 2H, J = 7.6 Hz). ^{13}C NMR (150 MHz): δ = 27.8, 44.0, 45.0, 107.6, 110.3, 127.3, 128.0, 128.0, 128.2, 128.5, 133.1, 136.6, 141.3, 142.0, 151.3, 196.5. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 7 : 3, flow rate = 0.5 mL min^{-1}); t_R = 23.3 min (*S*), t_R = 31.1 min (*R*).

Analytical data for Michael additions and protonations 6a–f

Absolute configuration of **6d** was determined by X-ray diffraction. Configurations of **6a**, **6b**, **6c**, **6e**, **6f** were determined by analogy.

6a: (*R*)-2-((*R*)-(benzylthio)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one. Colorless oil; IR (neat) ν = 3060, 3027, 2934, 1680, 1600, 1453, 1298, 1227, 1025 cm^{-1}. ^{1}H NMR (600 MHz, *syn*/*anti* = 90/10): δ = 1.62–1.69 (m, 1H), 2.26–2.31 (m, 1H), 2.83–2.90 (m, 3H), 3.44 (dd, 2H, J = 13.1, 51.5 Hz), 4.66 (m, 0.1 H), 4. 71 (d, 0.9 H, J = 4.8 Hz), 7.06–7.22 (m, 10H), 7.33 (dd, 1H, J = 6.2, 7.6 Hz), 7.39 (d, 2H, J = 7.6 Hz), 7.89 (d, 1H, J = 6.9 Hz). ^{13}C NMR (150 MHz): δ = 25.2, 28.8, 35.9, 47.2, 53.2, 126.5, 126.9, 127.1, 127.6, 128.0, 128.3, 128.5, 128.6, 128.8, 128.8, 129.7, 132.3, 133.2, 137.8, 138.8, 143.5, 196.5. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 13.2 min (*syn*, major), t_R = 15.5 min (*anti*, major), t_R = 16.8 min (*anti*, minor), t_R = 19.4 min (*syn*, minor). HRMS calcd for $C_{24}H_{23}OS^+$ ([M + H]$^+$): 359.14696, found 359.14674.

6b: (*R*)-2-((*R*)-(benzylthio)(4-methoxyphenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one. White solid (mixture); IR (KBr): ν = 2933, 2834, 1681, 1602, 1509, 1249, 1032 cm^{-1}. ^{1}H NMR (600 MHz, *syn*/*anti* = 95/5): δ = 1.64–1.71 (m, 1H), 2.27–2.30 (m, 1H), 2.83–2.86 (m, 3H), 3.43 (dd, 2H, J = 13.1, 53.6 Hz), 3.70 (s, 3H), 4.58 (m, 0.05 H), 4.69 (m, 0.95 H), 6.73–6.75 (m, 2H), 7.06–7.21 (m, 7H), 7.30–7.34 (m, 3H), 7.89 (d, 1H, J = 7.6 Hz). ^{13}C NMR (150 MHz): δ = 25.1, 28.6, 35.8, 46.5, 53.3, 55.1, 113.3, 126.5, 126.9, 127.6, 128.3, 128.5, 128.8, 130.8, 133.2, 137.9, 143.5, 158.6, 196.6. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 4 : 1, flow rate = 1.0 mL min^{-1}); t_R = 12.6 min (*anti*, major), t_R = 17.5 min (*anti*, minor), t_R = 19.3 min (*syn*, major), t_R = 26.0 min (*syn*, minor). HRMS calcd for $C_{25}H_{25}O_2S^+$ ([M + H]$^+$): 389.15752, found 389.15789.

6c: (*R*)-2-((*R*)-(benzylthio)(4-chlorophenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one. Yellow solid (mixture); IR (KBr): ν = 2932, 1682, 1599, 1489, 1228, 1092 cm^{-1}. ^{1}H NMR

(600 MHz, *syn*/*anti* = 94/6): δ = 1.60–1.66 (m, 1H), 2.26–2.30 (m, 1H), 2.82–2.89 (m, 3H), 3.45 (dd, 2H, J = 13.1, 66.3 Hz), 4.58 (m, 0.06 H), 4.73 (d, 0.94H, J = 4.1 Hz), 7.08–7.24 (m, 9H), 7.28–7.37 (m, 3H), 7.86–7.88 (m, 1H). ^{13}C NMR (150 MHz): δ = 25.0, 28.8, 35.9, 46.5, 53.2, 126.6, 127.0, 127.6, 128.1, 128.4, 128.5, 128.8, 131.2, 132.2, 132.9, 133.4, 137.3, 137.5, 143.5, 196.1. HPLC (Daicel Chiralpak AD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 26.0 min (*syn*, major), t_R = 33.3 min (*syn*, minor), t_R = 40.5 min (*anti*, major), t_R = 49.1 min (*anti*, minor). HRMS calcd for $C_{24}H_{22}ClOS^+$ ([M + H]$^+$): 393.10799, found 393.10827.

6d: (*R*)-2-((*R*)-(benzylthio)(phenyl)methyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. White solid; mp 99–101 °C; IR (KBr): ν = 2949, 1668, 1602, 1258, 1058 cm^{-1}. ^{1}H NMR (600 MHz, *syn*/*anti* = 97/3): δ = 1.65–1.71 (m, 1H), 2.29–2.33 (m, 1H), 2.83–2.90 (m, 3H), 3.49 (dd, J = 13.1, 48.1 Hz), 3.79 (s, 3H), 4.71 (m, 0.03 H), 4.79 (d, 0.97 H, J = 4.8 Hz), 6.56 (s, 1H), 6.73–6.75 (m, 1H), 7.13–7.26 (m, 9H), 7.43 (d, J = 8.2 Hz), 7.91 (d, 1H, J = 8.2 Hz). ^{13}C NMR (150 MHz): δ = 25.2, 29.0, 36.0, 47.3, 52.9, 55.3, 112.2, 113.1, 126.0, 126.9, 127.1, 128.0, 128.3, 128.9, 129.7, 130.1, 137.9, 138.9, 146.0, 163.4, 195.2. HPLC (Daicel Chiralpak AD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 11.1 min (*syn*, minor), t_R = 12.3 min (*syn*, major), t_R = 14.2 min (*anti*, minor), t_R = 16.0 min (*anti*, major). HRMS calcd for $C_{25}H_{25}O_2S^+$ ([M + H]$^+$): 389.15752, found 389.15437.

6e: (*R*)-2-((*R*)-(benzylthio)(phenyl)methyl)-2,3-dihydro-1*H*-inden-1-one. Colorless oil; IR (neat): ν = 3060, 3028, 2918, 1710, 1606, 1493, 1451, 1294, 1207, 1029 cm^{-1}. ^{1}H NMR (600 MHz, *syn*/*anti* = 68/32): δ = 3.0–3.2 (m, 3H), 3.43–3.60 (m, 3H), 4.55 (d, 0.68H, J = 2.3 Hz), 4.64 (d, 0.32H, J = 3.4 Hz), 7.11–7.46 (m, 13H), 7.56–7.59 (m, 1H), 7.77–7.78 (m, 1H). ^{13}C NMR (150 MHz): δ = 28.74, 29.5, 35.8, 36.0, 48.6, 49.8, 52.4, 53.5, 123.8, 124.0, 126.2, 126.4, 126.9, 127.0, 127.1, 127.2, 127.3, 127.4, 128.0, 128.2, 128.3, 128.4, 128.6, 128.8, 128.9, 129.3, 134.6, 134.9, 136.4, 136.7, 137.2, 137.4, 137.6, 141.4, 153.6, 204.9. HPLC (Daicel Chiralpak AD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 7.8 min (*syn*, minor), t_R = 8.3 min (*syn*, major), t_R = 9.6 min (*anti*, major), t_R = 10.6 min (*anti*, minor). HRMS calcd for $C_{23}H_{21}OS^+$ ([M + H]$^+$): 345.13131, found 345.13089.

6f: (*R*)-2-((*R*)-(benzylthio)(phenyl)methyl)cyclohexanone. Colorless oil; IR (neat): ν = 3027, 2936, 2861, 1712, 1493, 1450, 1126, 1070 cm^{-1}. ^{1}H NMR (600 MHz, *syn*/*anti* = 62/38): δ = 1.25–1.28 (m, 1H), 1.50–1.58 (m, 1H), 1.65–1.74 (m, 2H), 1.81–1.85 (m, 1H), 1.91–1.96 (m, 0.5H), 2.16–2.19 (m, 0.5H), 2.26–2.33 (m, 2H), 2.72–2.77 (m, 1H), 3.42 (dd, 1H, J = 6.2, 13.1 Hz), 3.51 (dd, 1H, J = 13.7, 22.7 Hz), 4.12 (d, 0.5H, J = 8.9 Hz), 4.25 (d, 0.5H, J = 7.6 Hz), 7.19–7.35 (m, 9H). ^{13}C NMR (150 MHz): δ = 23.5, 24.4, 27.7, 28.0, 30.8, 31.7, 35.5, 35.7, 41.3, 42.0, 47.2, 48.4, 56.2, 56.4, 126.8, 126.9, 127.2, 128.2, 128.3, 128.5, 128.9, 129.0, 129.1, 137.9, 139.8, 141.8, 209.9, 210.7. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 15.0 min (*anti*, major), t_R = 16.1 min (*anti*, minor), t_R = 19.1 min (*syn*, minor), t_R = 25.1 min (*syn*, major). HRMS calcd for $C_{20}H_{23}S^+$ ([M + H]$^+$): 311.14696, found 311.14676.

Analytical data for protonations 8a–r

Absolute configuration of **8a** was determined by X-ray crystallography analysis. Configurations of **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **8h**, **8i**, **8j**, **8k**, **8l**, **8n**, and **8o** were determined by analogy. Configuration of **8m** was assigned by comparison of literature data.[49] The absolute configuration of **8p** was assumed from the stereochemistry of desulfonated compound **9p**. The configurations of **8q** and **8r** were determined by analogy.

8a: (*R*)-3-(benzylthio)-2-methyl-1-phenylpropan-1-one. White solid; mp 54–56 °C; IR (KBr): ν = 2964, 2929, 1675, 1450, 1226, 969, 677 cm^{-1}. ^{1}H NMR (600 MHz): δ = 1.16 (d, 3H, J = 6.9 Hz), 2.47 (dd, 1H, J = 6.9, 13.1 Hz), 2.87 (q, 1H, J = 6.2 Hz), 3.48 (dd, 1H, J = 6.9, 14.4 Hz), 3.65 (s, 2H), 7.16–7.24 (m, 5H), 7.36–7.39 (m, 2H), 7.50–7.52 (m, 1H), 7.76–7.79 (m, 1H). ^{13}C NMR (150 MHz): δ = 17.7, 34.7, 37.3, 41.1, 127.0, 128.3, 128.5, 128.6, 128.8, 133.1, 136.2, 202.8. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}); t_R = 12.8 min (*R*), t_R = 16.5 min (*S*). HRMS calcd for $C_{17}H_{19}OS^+$ ([M + H]$^+$): 271.11566, found 271.11381. $[\alpha]_D^{20}$ = +30.54 (c = 1.0, $CHCl_3$).

8b: (*R*)-2-((benzylthio)methyl)-1-phenylhexan-1-one. Colorless oil; IR (neat): ν = 2956, 2928, 2858, 1678, 1596, 1450, 1229, 700 cm^{-1}. ^{1}H NMR (600 MHz): δ = 0.72–0.75 (m, 3H), 1.07–1.18 (m, 4H), 1.44–1.51 (m, 1H), 1.60–1.67 (m, 1H), 2.50–2.53 (m, 1H), 2.81 (dd, 1H, J = 8.25, 13.1 Hz), 3.43–3.47 (m, 1H), 3.61 (s, 2H), 7.15–7.23 (m, 5H), 7.36–7.39 (m, 2H), 7.47–7.50 (m, 1H), 7.77–7.79 (m, 2H). ^{13}C NMR (150 MHz): δ = 13.8, 22.7, 29.3, 32.3, 33.4, 37.4, 46.3, 127.0, 128.3, 128.5, 128.6, 128.9, 133.0, 137.3, 138.4, 203.0. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 10.7 min (*S*), t_R = 11.6 min (*R*). HRMS calcd for $C_{20}H_{25}OS^+$ ([M + H]$^+$): 313.16261, found 313.16312. $[\alpha]_D^{20}$ = +14.10 (c = 1.0, $CHCl_3$).

8c: (*R*)-3-(benzylthio)-1,2-diphenylpropan-1-one. Yellow oil; IR (neat): ν = 3060, 3027, 2918, 1679, 1450, 1230, 698 cm^{-1}. ^{1}H NMR (600 MHz): δ = 2.73 (dd, 1H, J = 6.2, 13.1 Hz), 3.27 (dd, 1H, J = 8.3, 13.1 Hz), 3.57 (d, 2H, J = 4.1 Hz), 4.48 (dd, 1H, J = 6.2, 8.2 Hz), 7.11–7.27 (m, 12H), 7.36–7.38 (m, 1H), 7.73–7.76 (m, 2H). ^{13}C NMR (150 MHz): δ = 35.3, 37.5, 54.2, 127.0, 127.5, 128.1, 128.4, 128.5, 128.7, 128.9, 129.0, 133.0, 136.4, 138.2, 138.7, 198.5. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 7.8 min (*S*), t_R = 8.8 min (*R*). HRMS calcd for $C_{22}H_{21}OS^+$ ([M + H]$^+$): 333.13131, found 333.12972. $[\alpha]_D^{20}$ = −105.61 (c = 1.0, $CHCl_3$).

8d: (*R*)-3-(benzylthio)-1-(4-methoxyphenyl)-2-methylpropan-1-one. White solid; mp 91–94 °C; IR (KBr): ν = 2972, 2927, 2839, 1667, 1602, 1454, 1235, 1174, 1024, 845, 700 cm^{-1}. ^{1}H NMR (600 MHz): δ = 1.13 (d, 3H, J = 6.9 Hz), 2.43–2.46 (m, 1H), 2.84–2.87 (m, 1H), 3.42 (q, 1H, J = 6.9 Hz), 3.79 (s, 2H), 6.84 (m, 2H), 7.16–7.22 (m, 5H), 7.77–7.77 (m, 1H). ^{13}C NMR (150 MHz): δ = 17.8, 34.9, 37.3, 40.6, 55.4, 113.8, 127.0, 128.5, 128.8, 129.1, 130.6, 138.5, 163.5, 201.3. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 15.7 min (*S*), t_R = 17.5 min (*R*). HRMS calcd for $C_{18}H_{21}O_2S^+$ ([M + H]$^+$): 301.12622, found 301.12631. $[\alpha]_D^{20}$ = +8.68 (c = 1.0, $CHCl_3$).

8e: (*R*)-3-(benzylthio)-1-(4-bromophenyl)-2-methylpropan-1-one. White solid; mp 70–73 °C; IR (neat): ν = 2966, 2920, 1679, 1581, 1225, 833, 701 cm^{-1}. ^1H NMR (600 MHz): δ = 1.19 (d, 3H, J = 6.9 Hz), 2.52 (dd, 1H, J = 6.9, 13.1 Hz), 2.90 (dd, 1H, J = 6.9, 13.1 Hz), 3.43 (q, 1H, J = 6.9 Hz), 3.71 (s, 2H), 7.23–7.32 (m, 4H), 7.56–7.60 (m, 3H), 7.63–7.69 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.6, 34.7, 37.3, 41.2, 127.1, 128.3, 128.6, 128.8, 129.5, 129.8, 131.8, 131.9, 134.9, 201.8. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 4.8 min (*S*), t_R = 7.6 min (*R*). HRMS calcd for $C_{17}H_{18}OSBr^+$ ([M + H]$^+$): 349.02617, found 349.02532. $[\alpha]_D^{20}$ = +10.53 (c = 1.0, $CHCl_3$).

8f: (*R*)-2-benzyl-3-(benzylthio)-1-phenylpropan-1-one. Colorless oil; IR (neat): ν = 3060, 3026, 2919, 1678, 1597, 1493, 1449, 1230, 698 cm^{-1}. ^1H NMR (600 MHz): δ = 2.50 (dd, 1H, J = 5.5, 13.1 Hz), 2.74 (q, 1H, J = 6.9 Hz), 2.83 (dd, 1H, J = 8.2, 13.1 Hz), 2.94 (q, 1H, J = 6.9 Hz), 3.54 (dd, 2H, J = 13.7, 17.2 Hz), 3.71–3.73 (m, 1H), 6.99–7.01 (m, 2H), 7.07–7.09 (m, 3H), 7.12–7.18 (m, 5H), 7.30–7.33 (m, 2H), 7.42–7.45 (m, 1H), 7.65–7.68 (m, 2H). ^{13}C NMR (150 MHz): δ = 32.9, 37.2, 38.3, 48.5, 126.40, 127.0, 128.3, 128.4, 128.5, 128.5, 128.5, 128.8, 129.0, 133.0, 137.0, 138.4, 138.8, 202.3. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 11.9 min (*R*), t_R = 12.8 min (*S*). HRMS calcd for $C_{23}H_{23}OS^+$ ([M + H]$^+$): 347.14696, found 347.14757. $[\alpha]_D^{20}$ = −3.53 (c = 1.0, $CHCl_3$).

8g: (*R*)-2-benzyl-3-(benzylthio)-1-(3-(trifluoromethyl)phenyl) propan-1-one. Colorless oil; IR (neat): ν = 3063, 3029, 1688, 1609, 1495, 1453, 1331, 1170, 1127, 1072, 804, 751 cm^{-1}. ^1H NMR (600 MHz): δ = 2.54 (dd, 1H, J = 5.5, 13.1 Hz), 2.76 (q, 1H, J = 6.9 Hz), 2.83–2.86 (m, 1H), 3.53–3.59 (m, 3H), 6.91–6.94 (m, 2H), 7.02–7.20 (m, 8H), 7.40–7.42 (m, 1H), 7.63–7.66 (m, 1H), 7.72–7.79 (m, 2H). ^{13}C NMR (150 MHz): δ = 33.2, 37.4, 38.7, 49.1, 122.7, 124.5, 125.0, 15.1, 126.6, 127.1, 128.5, 128.6, 128.8, 128.9, 129.1, 129.3, 130.9, 131.1, 131.3, 137.7, 138.2, 138.4, 201.5. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 19 : 1, flow rate = 0.5 mL min^{-1}); t_R = 20.6 min (*S*), t_R = 22.3 min (*R*). HRMS calcd for $C_{24}H_{22}F_3OS^+$ ([M + H]$^+$): 415.13434, found 415.13134.

8h: (*R*)-2-benzyl-3-(benzylthio)-1-(4-methoxyphenyl)propan-1-one. White solid; mp 97–100 °C; IR (KBr): ν = 3014, 2928, 1670, 1596, 1455, 1367, 1235, 1166, 1024, 931, 854, 763, 701, 605 cm^{-1}. ^1H NMR (600 MHz): δ = 2.50 (dd, 1H, J = 5.5, 13.1 Hz), 2.80 (q, 1H, J = 6.9 Hz), 2.88 (dd, 1H, J = 8.2, 13.1 Hz), 2.98–3.01 (m, 1H), 3.54 (d, 2H, J = 3.4 Hz), 3.70–3.75 (m, 1H), 3.85 (s, 3H), 6.78 (d, 2H, J = 8.9 Hz), 7.00 (d, 2H, J = 8.2 Hz), 7.06–7.19 (m, 8H), 7.67 (d, 2H, J = 8.3 Hz). ^{13}C NMR (150 MHz): δ = 33.1, 37.2, 38.4, 48.0, 56.4, 113.6, 126.3, 126.9, 128.4, 128.5, 128.8, 129.0, 130.6, 163.4, 200.6. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 12.1 min (*S*), t_R = 14.5 min (*R*). HRMS calcd for $C_{24}H_{25}OS^+$ ([M + H]$^+$): 377.15752, found 377.15695. $[\alpha]_D^{20}$ = −8.47 (c = 1.0, $CHCl_3$).

8i: (*R*)-3-((4-chlorobenzyl)thio)-2-methyl-1-phenylpropan-1-one. Colorless oil; IR (neat): ν = 2971, 2927, 1680, 1489, 1451, 1230, 1092, 972, 700 cm^{-1}. ^1H NMR (600 MHz): δ = 1.15 (d, 2H, J = 6.9 Hz), 2.45 (dd, 1H, J = 6.9, 13.1 Hz), 2.84 (dd, 1H, J = 6.9, 13.1 Hz), 3.43–3.49 (m, 1H, J = 6.9), 3.59 (dd, 2H, J = 14.1, 17.5 Hz), 7.14–7.18 (m, 5H), 7.36–7.39 (m, 2H), 7.48–7.50 (m, 1H), 7.77 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.7, 34.7, 36.6, 41.1, 128.2, 128.6, 128.7, 130.1, 132.8, 133.2, 136.1, 137.0, 202.6. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 15.7 min (*S*), t_R = 17.1 min (*R*). HRMS calcd for $C_{18}H_{18}OSCl^+$ ([M + H]$^+$): 305.07669, found 305.07709. $[\alpha]_D^{20}$ = +10.12 (c = 1.0, $CHCl_3$).

8j: (*R*)-3-((4-methoxybenzyl)thio)-2-methyl-1-phenylpropan-1-one. Colorless oil; IR (neat): ν = 2966, 2930, 1680, 1608, 1510, 1451, 1247, 1177, 1033, 971, 701 cm^{-1}. ^1H NMR (600 MHz): δ = 1.5 (d, 3H, J = 6.9 Hz), 2.45 (dd, 1H, J = 7.8, 13.1 Hz), 2.84 (dd, 1H, J = 6.2, 13.1 Hz), 3.46 (q, 1H, J = 6.8), 3.60 (d, 2H, J = 2.8 Hz), 3.71 (s, 3H), 6.74 (d, 2H, J = 9 Hz), 7.12–7.14 (m, 2H), 7.35–7.38 (m, 2H), 7.46–7.49 (m, 1H), 7.76–7.78 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.6, 34.6, 36.6, 41.1, 55.2, 113.9, 128.1, 128.3, 129.9, 130.3, 133.0, 136.2, 158.6, 202.8. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 8.2 min (*S*), t_R = 9.3 min (*R*). HRMS calcd for $C_{18}H_{21}O_2S^+$ ([M + H]$^+$): 301.12622, found 301.12691. $[\alpha]_D^{20}$ = +16.39 (c = 1.0, $CHCl_3$).

8k: (*R*)-3-((4-(*tert*-butyl)benzyl)thio)-2-methyl-1-phenylpropan-1-one. Colorless oil; IR (neat): ν = 2963, 2869, 1681, 1596, 1451, 1364, 1230, 971, 701 cm^{-1}. ^1H NMR (600 MHz): δ = 1.15 (d, 3H, J = 6.9 Hz), 1.23 (s, 9H), 2.47 (dd, 1H, J = 6.9, 13.1 Hz), 2.88 (dd, 1H, J = 6.2, 13.1 Hz), 3.46 (q, 1H, J = 6.9 Hz), 3.62 (s, 2H), 7.14–7.17 (m, 2H), 7.23–7.24 (m, 2H), 7.35–7.37 (m, 2H), 7.46–7.48 (m, 1H), 7.77–7.78 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.7, 31.3, 34.5, 34.8, 36.9, 41.1, 125.4, 128.3, 128.5, 128.6, 133.1, 135.4, 136.2, 149.9, 202.8. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 9.4 min (*S*), t_R = 11.7 min (*R*). HRMS calcd for $C_{21}H_{28}OS^+$ ([M + H]$^+$): 327.17826, found 327.17792. $[\alpha]_D^{20}$ = +19.23 (c = 1.0, $CHCl_3$).

8l: (*R*)-3-((furan-2-ylmethyl)thio)-2-methyl-1-phenylpropan-1-one. Colorless oil; IR (neat): ν = 2971, 2928, 1680, 1594, 1451, 1230, 972, 790, 701 cm^{-1}. ^1H NMR (600 MHz): δ = 1.17 (d, 3H, J = 6.9 Hz), 2.51–2.54 (m, 1H), 2.94 (dd, 1H, J = 6.9, 13.1 Hz), 3.52 (q, 1H, J = 6.9 Hz), 3.64 (dd, 2H, J = 9.6, 14.4 Hz), 6.09 (d, 1H, J = 3.4Hz), 6.22–6.22 (m, 1H), 7.26 (m, 1H), 7.37–7.40 (m, 2H), 7.47–7.50 (m, 1H), 7.83–7.84 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.7, 29.1, 34.9, 41.1, 107.5, 110.4, 128.3, 128.3, 128.6, 128.6, 133.1, 136.1, 142.1, 151.6, 202.7. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 15.3 min (*R*), t_R = 16.5 min (*S*). HRMS calcd for $C_{15}H_{17}O_2S^+$ ([M + H]$^+$): 261.09492, found 261.09377. $[\alpha]_D^{20}$ = +15.76 (c = 1.0, $CHCl_3$).

8m: (*R*)-3-(3-(benzylthio)-2-methylpropanoyl)oxazolidin-2-one.[49] Colorless oil; IR (neat): ν = 2977, 2921, 1777, 1696, 1387, 1266, 1225, 1044, 757, 704 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.20 (d, 3H, J = 6.9 Hz), 2.42–2.45 (m, 1H), 2.80–2.83 (m, 1H), 3.74 (d, 2H, J = 3.4 Hz), 3.99–4.13 (m, 3H), 4.41–4.44 (m, 2H), 7.22–7.33 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.4, 34.6, 36.4, 37.6, 42.7, 61.9, 126.9, 128.5, 128.9, 138.1, 153.2, 175.8. HPLC (Daicel Chiralcel OD-H,

n-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 32.8 min (*S*), t_R = 44.6 min (*R*). HRMS calcd for $C_{14}H_{18}NO_3S^+$ ($[M + H]^+$): 280.10074, found 280.09974. $[\alpha]_D^{20}$ = +58.8 (*c* = 1.09, $CHCl_3$).

8n: (*R*)-methyl 3-(benzylthio)-2-methylpropanoate. Colorless oil; IR (neat): ν = 2924, 1735, 1455, 1212, 1160, 1096, 701 cm^{-1}. ^1H NMR (600 MHz): δ = 1.13 (d, 3H, *J* = 6.9 Hz), 2.40 (dd, 1H, *J* = 6.9, 13.1 Hz), 2.57 (q, 1H, *J* = 6.9 Hz), 2.68 (dd, 1H, *J* = 6.9, 13.1 Hz), 3.61 (s, 3H), 3.64 (s, 2H), 7.16–7.25 (m, 5H). ^{13}C NMR (150 MHz): δ = 16.8, 34.5, 36.6, 39.8, 51.8, 127.0, 128.5, 128.8, 175.5. HPLC: Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}: t_R = 12.8 min (*S*), t_R = 13.4 min (*R*). HRMS calcd for $C_{12}H_{17}O_2S^+$ ($[M + H]^+$): 225.09492, found 225.09485.

8o: 3-(benzylthio)-2-methyl-1-(1-methyl-1*H*-imidazol-2-yl)-propan-1-one. Colorless oil; IR (neat): ν = 2968, 2927, 1672, 1407, 1290, 1155, 972, 773, 702 cm^{-1}. ^1H NMR (600 MHz): δ = 1.26 (d, 3H, *J* = 6.9 Hz), 2.51 (dd, 1H, *J* = 6.2, 13.1 Hz), 2.84–2.88 (m, 1H), 3.74 (d, 2H, *J* = 2.1 Hz), 4.00 (s, 3H), 4.20 (dd, 1H, *J* = 6.9, 14.4 Hz), 7.04 (s, 1H), 7.16 (s, 1H), 7.20–7.31 (m, 5H). ^{13}C NMR (150 MHz): δ = 17.3, 34.1, 36.2, 40.9, 126.8, 127.2, 128.3, 128.4, 128.9, 129.1, 138.2, 138.2, 142.5, 195.1. HPLC (Daicel Chiralpak AS-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 0.5 mL min^{-1}, racemic); t_R = 19.6 min (*S*), t_R = 20.5 min (*R*). HRMS calcd for $C_{15}H_{19}N_2OS^+$ ($[M + H]^+$): 275.12181, found 275.12209.

8p: (*R*)-2-(2-(benzylthio)propan-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one. Colorless oil; IR (neat): ν = 2965, 2929, 1684, 1453, 1216, 913, 748, 711 cm^{-1}. ^1H NMR (600 MHz): δ = 1.36 (s, 3H), 1.73 (s, 3H), 1.91–1.99 (m, 1H), 2.49 (dd, 1H, *J* = 4.1, 13.1 Hz), 2.62–2.70 (m, 2H), 2.87–2.92 (m, 1H), 3.69 (s, 2H), 7.10–7.15 (m, 2H), 7.20–7.26 (m, 5H), 7.34–7.36 (m, 1H), 7.86 (d, 1H, *J* = 7.6 Hz). ^{13}C NMR (150 MHz): δ = 24.2, 26.5, 29.2, 29.6, 33.3, 49.2, 55.5, 126.4, 126.9, 127.7, 128.4, 128.5, 129.0, 132.9, 134.3, 138.3, 143.5, 198.7. HPLC (Daicel Chiralcel OJ-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 12.9 min (*S*), t_R = 14.4 min (*R*). HRMS calcd for $C_{20}H_{23}OS^+$ ($[M + H]^+$): 311.14696, found 311.14716. $[\alpha]_D^{20}$ = −5.39 (*c* = 1.0, $CHCl_3$).

8q: (*R*)-2-(2-(benzylthio)propan-2-yl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. Colorless oil; IR (neat): ν = 2964, 1674, 1600, 1249, 1106, 1028, 1094, 711 cm^{-1}. ^1H NMR (600 MHz): δ = 1.42 (s, 3H), 1.81 (s, 3H), 1.98–2.04 (m, 1H), 2.48–2.51 (m, 1H), 2.64–2.73 (m, 2H), 2.91–2.95 (m, 1H), 3.76 (s, 2H), 3.84 (s, 3H), 6.62 (d, 1H, *J* = 2.1 Hz), 6.78–6.80 (m, 1H), 7.20–7.33 (m, 5H), 7.92 (d, 1H, *J* = 8.9 Hz). ^{13}C NMR (150 MHz): δ = 24.4, 26.5, 29.5, 29.9, 33.3, 49.4, 55.2, 55.3, 112.1, 113.0, 126.8, 127.8, 128.5, 129.0, 129.6, 138.4, 146.0, 163.2, 197.4. HPLC (Daicel Chiralpak AD-H, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 29.9 min (*S*), t_R = 35.0 min (*R*). HRMS calcd for $C_{21}H_{25}O_2S^+$ ($[M + H]^+$): 341.13977, found 341.14070.

8r: (*R*)-2-(2-(benzylthio)propan-2-yl)-2,3-dihydro-1*H*-inden-1-one. Colorless oil; IR (neat): ν = 2965, 2926, 1704, 1606, 1460, 1275, 1096, 752 cm^{-1}. ^1H NMR (600 MHz): δ = 1.22 (s, 3H), 1.67 (s, 3H), 2.71 (q, 1H, *J* = 4.1 Hz), 3.08–3.12 (m, 1H), 3.29 (dd, 1H, *J* = 4.1, 17.9 Hz), 3.69 (q, 2H, *J* = 11.7 Hz), 7.11–7.14 (m, 1H), 7.18–7.21 (m, 4H), 7.25–7.28 (m, 1H), 7.36–7.38 (m, 1H), 7.48–7.51 (m, 1H), 7.62 (d, 1H, *J* = 7.6 Hz). ^{13}C NMR (150 MHz): δ = 24.1, 28.8, 31.2, 33.2, 48.9, 55.6, 123.6, 126.2, 126.9, 127.2, 128.4, 128.9, 134.7, 13.6, 137.9, 153.4, 206.0. HPLC (Daicel Chiralcel OD-H, *n*-hexane–*i*-PrOH = 9 : 1, flow rate = 1.0 mL min^{-1}); t_R = 7.2 min (*S*), t_R = 7.7 min (*R*). HRMS calcd for $C_{19}H_{21}OS^+$ ($[M + H]^+$): 297.13131, found 297.13191.

Desulfurization of protonated products and determination of absolute configurations

RANEY® Ni W-2 (suspension in EtOH, 2 mL) was added to a solution of protonated product **8p** (0.1 mmol) in acetate buffer (pH 5.2, 1 mL) and a 1 : 1 mixture of EtOH (2 mL), followed by the addition of $NaPH_2O_2{\cdot}H_2O$ (1.0 mmol) immediately. The resultant suspension was stirred for 1 h at room temperature, and the reaction mixture was filtered. Water was added to the filtrate, and the aqueous layer was then extracted with ether. The combined organic layers were successively washed with satd $NaHCO_3$ aq. and brine, and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (elution: *n*-hexane–AcOEt = 10 : 1) to afford the desulfurized product **9p** as a colorless oil.

9p: (*S*)-2-isopropyl-3,4-dihydronaphthalen-1(2*H*)-one.[22] Colorless oil; ^1H NMR (600 MHz): δ = 0.84 (d, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 7.6 Hz), 1.85–1.91 (m, 1H), 2.05–2.10 (m, 1H), 2.23–2.27 (m, 1H), 2.43–2.47 (m, 1H), 2.84–2.97 (m, 2H), 7.14–7.23 (m, 2H), 7.36–7.38 (m, 1H), 7.95 (d, 1H, *J* = 8.2 Hz). ^{13}C NMR (150 MHz): δ = 18.4, 20.6, 23.4, 26.1, 28.5, 53.7, 126.5, 127.4, 128.5, 132.9, 133.0, 143.9, 199.8. HPLC (Daicel Chiralpak AS, *n*-hexane–*i*-PrOH = 100 : 1, flow rate = 1.0 mL min^{-1}); t_R = 8.8 min (*R*), t_R = 9.7 min (*S*).

Deuterium kinetic isotope effect experiments

The reaction of **7a** with **3a** in D_2O was carried out as described in the typical procedure for Michael reactions. The resulting mixture was diluted with water. The aqueous layer was extracted with dichloromethane (three times), and the combined organic layers were washed with $CuSO_4$ aq., and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (elution: chloroform–ethyl acetate = 200 : 1) to afford the protonated adduct **8a-H** and deuterated adduct **8a-D** as a mixture. The H/D ratio of the product mixture was determined by ^1H NMR analysis. The enantiomeric excess was determined by chiral HPLC analysis.

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Notes and references

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