ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 5609

Received 25th January 2025,
Accepted 6th March 2025

DOI: 10.1039/d5cc00422e

rsc.li/chemcomm

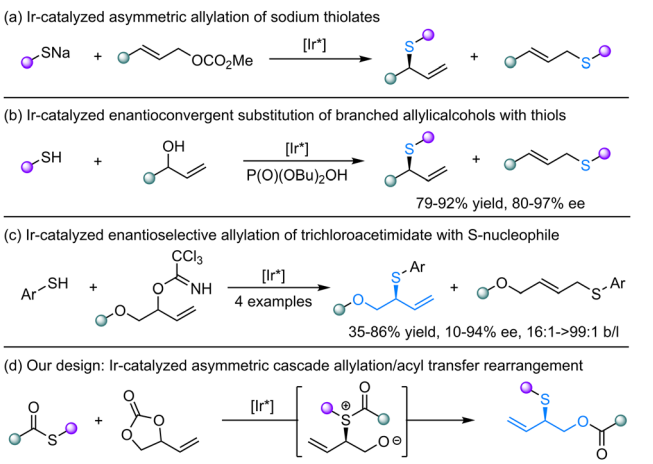
Synthesis of chiral β-hydroxy allylic sulfides *via* iridium-catalyzed asymmetric cascade allylation/acyl transfer rearrangement†

Jun Wei,[a] Zhi-Yuan Yi,[a] Zhuan Jin,[a] Yi Liu,[a] Zuo-Fei Wang,[a] Xiu-Qin Dong *[a] and Chun-Jiang Wang *[ab]

Iridium-catalyzed asymmetric allylation/acyl transfer rearrangement of thioesters and vinyl ethylene carbonate (VEC) has been developed. A wide range of structurally important chiral β-hydroxy allylic sulfide derivatives could be prepared in good yields with excellent enantioselectivity.

Sulfur-containing compounds are important building blocks, serving as key synthons and ligands in organic synthesis, and are widely found as the privileged subsets in bioactive molecules and pharmaceuticals.[1] As a unique member of the organosulfur compound family, chiral β-hydroxy allylic sulfide derivatives containing multiple functional groups play an important role in the field of pharmaceutical science, possess vital and diverse biological activities, and work as valuable molecular tools in the design of pharmaceutical molecules.[2–4] For example, anti-HIV 4′-thionucleoside[3] and potent inhaled leukotriene antagonist Sulukast (LY170680)[4] were identified with these privileged motifs. Given the prevalence and importance, developing efficient and concise synthetic approaches to access chiral β-hydroxy allylic sulfide derivatives from readily accessible starting materials is still in high demand.

The transition metal-catalyzed asymmetric allylic substitutions have been considered as a powerful tool for preparing enantioenriched carbon–carbon (C–C) or carbon–heteroatom (C–X) motifs in organic synthesis.[5] Heteroatoms, especially sulfur atoms, inherently own strong affinities toward transition-metal complexes, which resulted in poisoning transition metal catalysts and inhibiting catalytic turnover.[6] Owing to this challenge, the transition metal-catalyzed allylation of some sulfur nucleophiles to generate achiral allyl sulfides and sulfones has been underdeveloped; meanwhile, the related enantioselective allylation of sulfur nucleophiles remains to be less reported. Gais's group developed Pd-catalyzed asymmetric allylation of sulfur nucleophiles in around 2000, which was mainly restricted to sulfinates and more acidic aromatic thiols such as 2-pyrimidinethiol, 4-chlorothiophenol, and 2-pyridinethiol.[7] In 2010, Zhao's group reported Ir-catalyzed asymmetric allylation of sodium thiophenoxides and aliphatic thiolates with allyl carbonates in good yields and excellent enantioselectivities (Scheme 1a).[8] In 2012, Carreira and coworkers developed Ir-catalyzed asymmetric allylation of racemic branched allylic alcohols with thiols in good to excellent enantioselectivity using dibutyl phosphate as the promoter (Scheme 1b).[9] In 2018, Samec, Orthaber, and coworkers described Pd-catalyzed intermolecular enantiospecific substitution of chiral allylic alcohols with a wide range of N-, S-, C-, and O-centered nucleophiles, a variety of aryl and alkyl thiols performed smoothly with good to excellent yields and enantio-specificities.[10] Recently, Nguyen and coworkers realized Ir/diene-catalyzed asymmetric allylation of racemic, branched allylic trichloroacetimidates with



Scheme 1 (a–c) Previous research works and (d) our new synthetic strategy design.

[a] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei, 430072, P. R. China. E-mail: cjwang@whu.edu.cn, xiuqindong@whu.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai, 230021, China

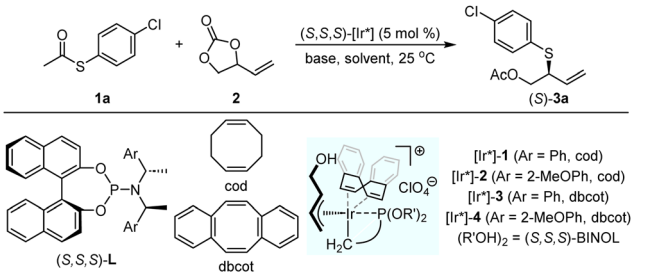
† Electronic supplementary information (ESI) available: Experimental procedures, and NMR spectra of the compounds. CCDC 2411685. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5cc00422e

various heteroatom nucleophiles, including carboxylic acids, aromatic amines and aromatic thiols.[11] This broadened the synthetic strategy to access chiral allylic C–O, C–N, and C–S units in moderate to high yields with good to excellent regio-/enantioselectivity, and there are only four examples involving the construction of chiral β-hydroxy allylic sulfides (Scheme 1c). Although some progress has been made, it could not completely resolve the susceptibility of S-centered nucleophiles to coordinate and thus deactivate transition metal catalysts. Therefore, it is highly desirable to develop an alternative and efficient method to construct chiral β-hydroxy allylic sulfides from easily accessible starting materials with high reactivity and enantioselective control. Recently, Liu and co-workers developed chemo/stereo-selective Rh-catalyzed [1,4]-acyl rearrangement of α-diazo carbonyl compounds and thioesters, and thioesters were employed as efficient partners and could well depress the mentioned poisoning effect.[12] Inspired by this progress and our continuous interest in exploring new asymmetric allylation-triggered cascade synthetic strategies,[13] we made efforts to explore reliable protocols for the construction of structurally important chiral β-hydroxy allylic sulfides. As shown in Scheme 1d, we envisioned that thioesters could be utilized as masked thiols for Ir-catalyzed asymmetric allylation of vinyl ethylene carbonate (VEC), and the resulting zwitterionic intermediates would undergo acyl transfer rearrangement to give the final chiral β-hydroxy allylic sulfide products. To our knowledge, thioesters have not been used as nucleophiles in transition-metal catalyzed asymmetric allylation reactions. We herein fulfilled this design with a new strategy to realize the asymmetric allylation of S-centered nucleophiles in high yields with excellent regio-/enantioselectivities.

To test our hypothesis, we attempted to investigate Ir-catalyzed asymmetric cascade allylation/acyl transfer rearrangement between model substrates *S*-(4-chlorophenyl)ethanethioate **1a** and racemic VEC **2**. Gratifyingly, we observed the desired chiral β-hydroxy allylic sulfide **3a** with moderate results promoted by (*S*,*S*,*S*)-**[Ir*]-1** catalyst with Feringa's type of chiral phosphoramidite ligand **L1**[14] with Cs_2CO_3 as the base in DCM at 25 °C (60% yield, 69% ee, Table 1, entry 1). A series of inorganic and organic bases were investigated to further improve thereaction results (entries 2–7). DABCO could provide the best result with high yield and good enantioselectivity (entry 7). A variety of common solvents were further screened, and the desired allyl sulfide **3a** could be obtained in these solvents (entries 8–12). Taking into account the yield and enantioselectivity, dichloroethane was selected as the optimal solvent for further screening of the reaction parameters (87% yield, 81% ee, entry 8). Other iridium catalysts (*S*,*S*,*S*)-**[Ir*]-2-4** did not give better results (entries 13–15). Considering the possibility of a kinetic resolution (KR) process of racemic VEC **2**,[13] more amount of VEC **2** with 3 equivalents was used, and comparable yield and high enantioselectivity was obtained, which displayed that it should involve a KR process (82% yield, 88% ee, entry 16). Better enantioselectivity was achieved when the reaction was conducted at 50 °C with 12 h (94% ee, entry 17).

With the optimized reaction conditions in hand, we then focused on the substrate scope evaluation. As summarized in Table 2, a variety of thioesters were tolerated well to give the

Table 1 Optimization of the reaction conditions[a]

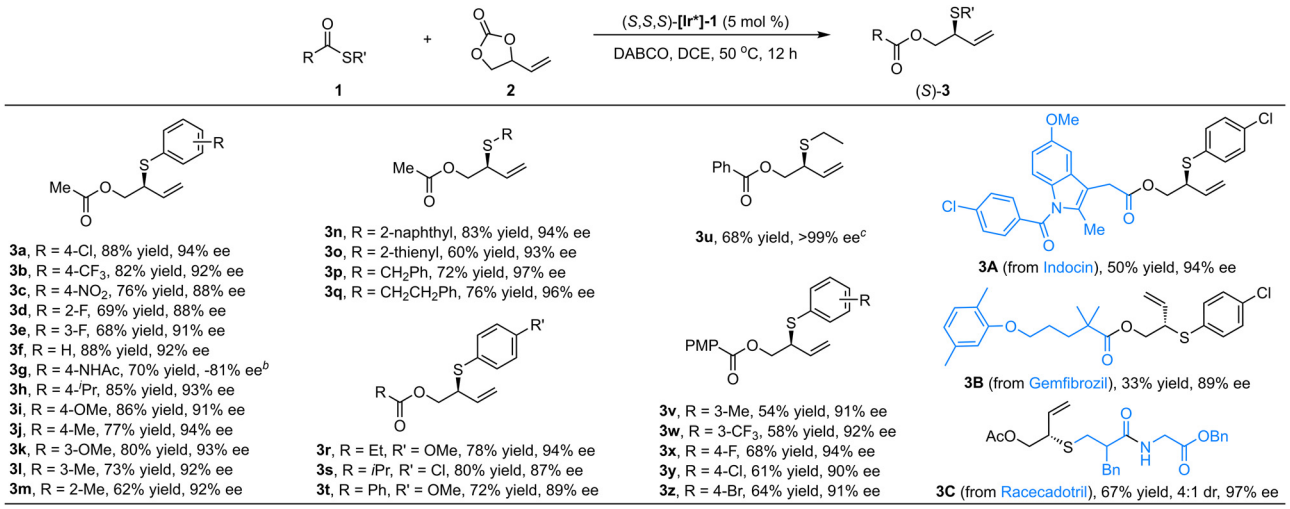


Entry	[Ir*]	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	**[Ir*]-1**	DCM	Cs_2CO_3	60	69
2	**[Ir*]-1**	DCM	K_3PO_4	25	64
3	**[Ir*]-1**	DCM	K_2CO_3	32	56
4	**[Ir*]-1**	DCM	DBU	62	75
5	**[Ir*]-1**	DCM	NEt_3	68	60
6	**[Ir*]-1**	DCM	DIPEA	56	60
7	**[Ir*]-1**	DCM	DABCO	85	77
8	**[Ir*]-1**	DCE	DABCO	87	81
9	**[Ir*]-1**	$CHCl_3$	DABCO	51	88
10	**[Ir*]-1**	THF	DABCO	45	90
11	**[Ir*]-1**	Toluene	DABCO	47	81
12	**[Ir*]-1**	CH_3CN	DABCO	30	77
13	**[Ir*]-2**	DCE	DABCO	54	92
14	**[Ir*]-3**	DCE	DABCO	73	74
15	**[Ir*]-4**	DCE	DABCO	53	88
16[d]	**[Ir*]-1**	DCE	DABCO	82	88
17[e]	**[Ir*]-1**	DCE	DABCO	88	94

[a] Unless otherwise mentioned, all reactions were carried out with **1a** (0.2 mmol), **2** (0.4 mmol), and base (0.2 mmol) in 2 mL solvent in the presence of 5 mol% (*S*,*S*,*S*)-**[Ir*]** catalyst at 25 °C for 12 h. [b] Yield is isolated yield. [c] ee value was determined by HPLC on a chiral phase. [d] **1a** (0.2 mmol), **2** (0.6 mmol), 25 °C, 12 h. [e] **1a** (0.2 mmol), **2** (0.6 mmol), 50 °C, 12 h.

desired chiral β-hydroxy allylic sulfides. These substrates bearing electron-withdrawing (**1a–e**), electron-neutral (**1f**), and electron-donating (**1g–m**) substituents on the phenyl ring of thiol motifs went through this transformation smoothly, delivering products **3a–3m** in 62–88% yields with 81–94% ee. Notably, the high tolerance of substituents was well maintained regardless of the *para*-, *ortho*- or *meta*-positions on the phenyl ring. The substrate **1n** bearing a bulky naphthyl group worked well to afford product **3n** in 83% yield with 94% ee. To our delight, the heteroaromatic thiophenyl substituted and aliphatic thioesters were suitable substrates to generate the desired products **3o–3q** and **3u** in excellent results. On the other hand, a series of thioester substrates derived from different carboxylic acids were investigated to further assess the generality. The methyl group in the acyl motif was replaced by other alkyl chains including ethyl (**1r**), isopropyl (**1s**), and other aryl (**1t**, **1v–1z**) groups, which served as good reaction partners to deliver products **3r–3s**, **3t** and **3v–3z** in 54–80% yields with 87–94% ee. Notably, the units of some important drugs and bioactive molecules could be readily embedded in thioester substrates. The thioesters **1A** and **1B** derived from anti-inflammatory drug indocin[15] and anti-hyperlipidemia drug gemfibrozil[16] were applied, and easily converted into products **3A–3B** in moderate yields with high enantioselectivity. Remarkably, neutral endopeptidase inhibitor racemic racecadotril[17] was used directly as

Table 2 Substrate scope study[a]



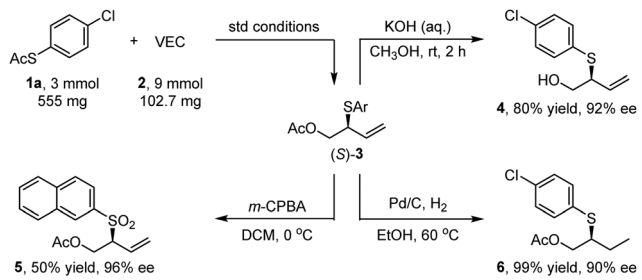
[a] All reactions were carried out with **1** (0.2 mmol), **2** (0.6 mmol), and DABCO in 2 mL DCE in the presence of 5.0 mol % (*S*,*S*,*S*)-[Ir*]-**1** as the catalyst at 50 °C for 12 h. [b] Using 5.0 mol% (*R*,*R*,*R*)-[Ir*]-**1** as the catalyst. [c] Using 10.0 mol% (*S*,*S*,*S*)-[Ir*]-**1** catalyst.

the thioester substrate, giving product **3C** in 67% yield with 4 : 1 dr and 97% ee.

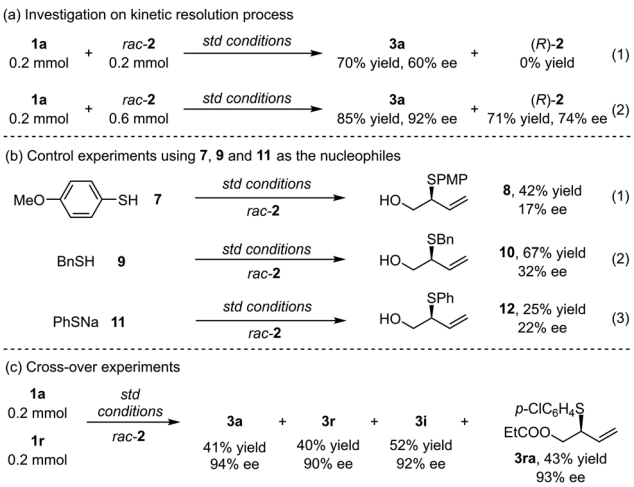
The synthetic application was demonstrated through scale-up synthesis, and product **3a** was obtained in 75% yield without loss of enantioselectivity (92% ee, Scheme 2). Additionally, the highly functionalized β-hydroxy allylic sulfides could be converted into other important sulfur-containing molecules. The ester group of compound **3a** was easily hydrolyzed under basic conditions, affording compound **4** in 80% yield with 92% ee. The thioether group of compound **3n** was oxidized into a sulfonyl group by *m*-chloroperoxybenzoic acid (*m*-CPBA) to deliver product **5** in 50% yield with 96% ee. In addition, compound **6** was obtained through hydrogenation catalyzed by Pd/C in nearly quantitative yield without erosion of the ee value.

To investigate the possible reaction mechanism, a series of control experiments were conducted. Owing to the racemic VEC **2** involved in this protocol, we turned our attention to the investigation of a possible KR process as the amount of *rac*-VEC **2** was increased from 0.2 mmol to 0.6 mmol, and product **3a** could be obtained with improved yield and enantioselectivity; meanwhile, the left (*R*)-**2** was recovered in good enantioselectivity (Scheme 3a). These results displayed that the KR process should be involved. In addition, *p*-methoxythiophenol **7**, benzylmercaptan **9** and sodium phenylthiolate **11** were employed as the nucleophiles, and poor reaction results were obtained (Scheme 3b). These results showed different behaviors among thiols, thiolate, and thioesters as nucleophilic reagents and revealed the superiority of thioesters over thiols and thiolate in this protocol. Furthermore, the cross-over experiments of thioesters **1a**, **1r**, and *rac*-VEC **2** were carried out, and products **3a**/**3r** and cross-reaction products **3i**/**3ra** were observed with nearly the same ratio (Scheme 3c). These reaction results disclosed that this transformation undergoes intermolecular cross-acyl transfer rearrangement; however, we cannot fully rule out intramolecular 1,4-acyl transfer rearrangement.

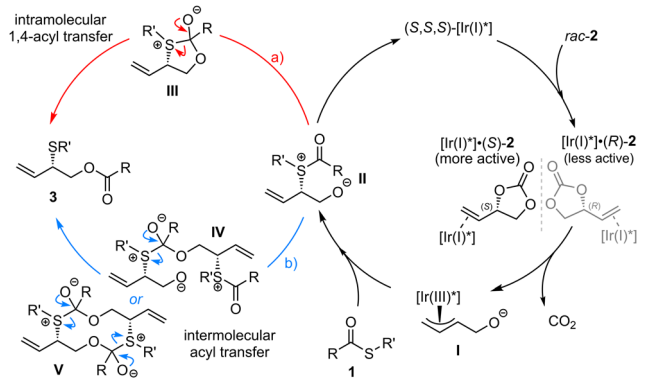
As shown in Scheme 4, a proposed reaction mechanism was provided to elucidate the possible reaction pathway based on these above results and previous studies.[13b] The (*S*,*S*,*S*)-[Ir(I)*] catalytic species coordinated with racemic VEC **2** to give [Ir(I)*]·(*S*)-**2** and [Ir(I)*]·(*R*)-**2** complexes with different activities. The



Scheme 2 Scale-up experiment and synthetic transformations.



Scheme 3 (a) Investigation on kinetic resolution process, (b) control experiments, (c) cross-over experiments.



Scheme 4 Proposed reaction mechanism.

following decarboxylative oxidation addition with more reactive [Ir(I)*]·(*S*)-**2** *via* the KR process gave zwitterionic Ir-π-allyl species **I** along with the release of CO_2. The subsequent nucleophilic attack of thioester **1** delivered intermediate **II**, which may go through two reaction pathways. As described in pathway a, it underwent intramolecular nucleophilic addition of the oxygen anion to the carbonyl group to generate intermediate **III**, and the following 1,4-acyl transfer rearrangement gave the final product **3**. Meanwhile, as shown in pathway b, nucleophilic addition of the oxygen anion of intermediate **II** to the carbonyl group in another intermediate **II** initiates a chain-type intermolecular acyl transfer rearrangement (**IV**) or undergoes a bimolecular ten-membered intermediate (**V**)[13c] to form product **3**. Based on the cross-over experimental results, this cascade protocol probably undergoes intermolecular acyl transfer rearrangement and cannot exclude intramolecular 1,4-acyl transfer rearrangement.

In summary, an unprecedented Ir-catalyzed allylation/acyl transfer rearrangement of readily available thioesters and VEC was successfully developed. A variety of structurally important chiral β-hydroxy allylic sulfide derivatives could be obtained in moderate to high yields with excellent enantioselective control. It owned the superiorities of readily available starting materials, wide substrate scope generality, good post-functionalization of drugs and bioactive molecules, and excellent regio-/enantioselectivity. The synthetic application proceeded well through a scale-up experiment and functional group transformations.

This work was supported by the National Key R&D Program of China (2023YFA1506700), NSFC (22271226, 22371216, 22071186, and 22071187), National Youth Talent Support Program. The authors thank Ms Hai-Yan Tao from the College of Chemistry and Molecular Sciences of Wuhan University for her kind help in HPLC analysis.

Data availability

All experimental procedures, characterisation data, mechanistic investigations, NMR spectra and HPLC spectra can be found in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) M. C. Bagley, *et al.*, *Chem. Rev.*, 2005, **105**, 685; (*b*) J. J. Petkowski, *et al.*, *J. Nat. Prod.*, 2018, **81**, 423; (*c*) K. L. Dunbar, *et al.*, *Chem. Rev.*, 2017, **117**, 5521; (*d*) N.-Z. Wang, *et al.*, *Nat. Prod. Rep.*, 2020, **37**, 246.
2 (*a*) N. Morita and N. Krause, *Angew. Chem., Int. Ed.*, 2006, **45**, 1897; (*b*) D. A. Kuntz, *et al.*, *Tetrahedron: Asymmetry*, 2005, **16**, 25; (*c*) J. Bránalt, *et al.*, *J. Org. Chem.*, 1994, **59**, 1783.
3 R. J. Young, *et al.*, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2599.
4 (*a*) J. R. Boot, *et al.*, *Br. J. Pharmacol.*, 1989, **98**, 259; (*b*) C. D. W. Brooks and J. B. Summers, *J. Med. Chem.*, 1996, **39**, 2629.
5 (*a*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*b*) J. F. Hartwig and L. M. Stanley, *Acc. Chem. Res.*, 2010, **43**, 1461; (*c*) N. A. Butta and W.-B. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 7929; (*d*) J. Qu and G. Helmchen, *Acc. Chem. Res.*, 2017, **50**, 2539; (*e*) Q. Cheng, *et al.*, *Chem. Rev.*, 2019, **119**, 1855.
6 (*a*) L. L. Hegedus and R. W. McCabe, *Catalyst Poisoning*, Marcel Dekker, New York, 1984; (*b*) A. T. Hutton, *Comprehensive Coordination Chemistry*, ed. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, UK, 1984, vol. 5, p. 1151.
7 (*a*) M. Frank and H.-J. Gais, *Tetrahedron: Asymmetry*, 1998, **9**, 3353; (*b*) H.-J. Gais, *et al.*, *Tetrahedron Lett.*, 2000, **41**, 3809; (*c*) H.-J. Gais, *et al.*, *Chem. – Eur. J.*, 2003, **9**, 4202.
8 (*a*) S.-C. Zheng, *et al.*, *Org. Lett.*, 2010, **12**, 4454; (*b*) N. Gao, *et al.*, *Org. Lett.*, 2011, **13**, 1514; (*c*) J. Cai, *et al.*, *RSC Adv.*, 2017, **7**, 256; (*d*) N. Gao and X. Zhao, *Eur. J. Org. Chem.*, 2013, 2708.
9 M. Roggen and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 8652.
10 S. Akkarasamiyo, *et al.*, *Chem. – Eur. J.*, 2018, **24**, 3488.
11 M. K. Arachchia and H. M. Nguyen, *Adv. Synth. Catal.*, 2021, **363**, 4239.
12 X.-S. Liu, *et al.*, *Nat. Commun.*, 2021, **12**, 7298.
13 (*a*) Z.-Y. Yi, *et al.*, *J. Am. Chem. Soc.*, 2022, **144**, 20025; (*b*) L. Xiao, *et al.*, *Angew. Chem., Int. Ed.*, 2021, **60**, 24930; (*c*) Q. Xiong, *et al.*, *Org. Lett.*, 2022, **24**, 2579; (*d*) W.-Y. Wang, *et al.*, *Chem. Commun.*, 2024, **60**, 5086; (*e*) K. Tian, *et al.*, *Fundam. Res.*, 2024, **4**, 77.
14 B. L. Feringa, *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620.
15 D. A. Godoy, *et al.*, *Bull. Emerg. Trauma.*, 2017, **5**, 143.
16 A. Ghosh, *et al.*, *J. Neurochem.*, 2017, **141**, 423.
17 M. Eberlin, *et al.*, *Front. Pharmacol.*, 2012, **3**, 93.

