

Cite this: *RSC Adv.*, 2019, 9, 1214

Phosphine-promoted [4 + 3] annulation of allenolate with aziridines for synthesis of tetrahydroazepines: phosphine-dependent [3 + 3] and [4 + 3] pathways†

Honglei Liu,^{‡a} Yan Lin,^{‡a} Yan Zhao,^a Miaoren Xiao,^b Leijie Zhou,^a Qijun Wang,^a Cheng Zhang,^{ib} Dongqi Wang,^b Ohyun Kwon^{id}*^{bc} and Hongchao Guo^{id}*^a

Received 30th November 2018
Accepted 26th December 2018

DOI: 10.1039/c8ra09852b

rsc.li/rsc-advances

In this manuscript, phosphine-dependent [3 + 3] and [4 + 3] annulation reactions of allenolate with aziridines were disclosed. The alkylidiphenylphosphine-promoted [4 + 3] annulation of allenolate with aziridines has been achieved under mild conditions, providing biologically interesting functionalized tetrahydroazepines in moderate to excellent yield with moderate to excellent regioselectivity and diastereoselectivity.

Nitrogen-containing heterocyclic compounds are widely present in biologically active natural products and synthetic pharmaceuticals. Among them, tetrahydropyridines which can be converted into pyridines and piperidines are intriguing synthetic targets due to their significant biological activities.¹ In addition, azepines are widely found as the core structure in a large number of compounds that possess important pharmaceutical activities. The compounds containing the azepine moiety are important targets in synthetic and medicinal chemistry.² Among these compounds (Fig. 1), azelastine is an effective and safe treatment agent for urticaria.³ Meptazinol is a new opioid-type analgesic with mixed agonist/antagonist properties.⁴ (–)-Balanol is a fungal metabolite with potent protein kinase C inhibitory properties.⁵ An anticonvulsant, carbamazepine, is known to show incidences of cutaneous adverse drug reactions including Stevens–Johnson syndrome, toxic epidermal necrolysis and drug-induced hypersensitivity syndrome.⁶ Epinastine is a potent antiallergic agent that not only has antihistaminic property but also provides antileukotriene, anti-PAF and anti-bradykinin activities.⁷ The tetracyclic natural product, (–)-tetrapetalone A is a novel lipoxygenase inhibitor from *Streptomyces* sp.⁸ Therefore, new synthetic methodologies for the synthesis of azepine derivatives have attracted much attention. Among

various methods, the cycloaddition reactions are practical and efficient methods, and have been extensively investigated.

Nucleophilic phosphine-catalyzed cycloaddition reactions of allenolates have evolved as a very useful tool to access various complex ring systems of organic molecules.^{9,10} Since Lu and coworkers reported the first phosphine-catalyzed [3 + 2] cycloaddition of allenolates with electron-deficient alkenes in 1995,¹¹ various types of cycloaddition reactions have been developed to afford different sizes of carbocycles or heterocycles.⁹ In spite of these advances, developing new cycloaddition reaction of allenolates is still of great significance to construct novel ring frameworks with functional groups.

Aziridines are an important type of versatile building blocks for synthesis of diverse nitrogen-containing heterocyclic compounds and natural products.¹² In the presence of Lewis acid or organocatalyst, aziridines may undergo a ring-opening reaction through C–N bond cleavage and work as a masked

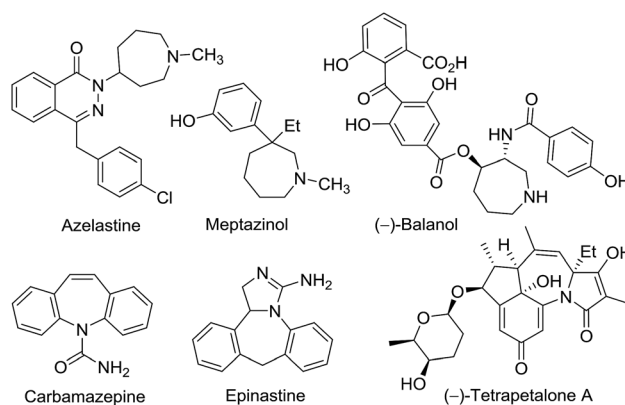


Fig. 1 Selected examples of biologically active azepine-containing heterocyclic compounds.

^aDepartment of Applied Chemistry, China Agricultural University, Beijing 100193, China. E-mail: hchgao@cau.edu.cn

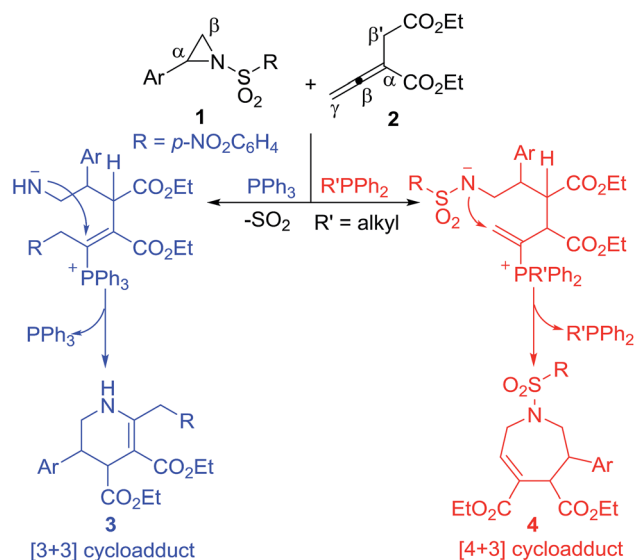
^bInstitute of High Energy Physics, Chinese Academy of Science, 19B Yuquan Lu, Shijingshan District, Beijing 100049, P. R. China

^cDepartment of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, USA. E-mail: ohyun@chem.ucla.edu

† Electronic supplementary information (ESI) available: Experimental procedures, spectral data and crystallographic data. CCDC 1869166. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra09852b

‡ Honglei Liu and Yan Lin contributed equally.





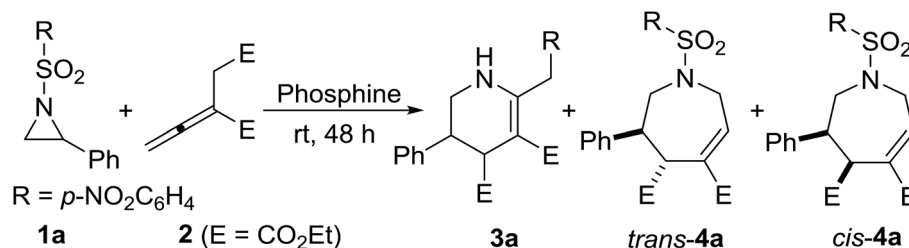
Scheme 1 Phosphine-dependent [3 + 3] and [4 + 3] annulation of allenolate with aziridines.

1,3-dipole to react with various dipolarophiles, giving diverse cycloadducts. Many Lewis acid or organocatalyst-mediated cycloaddition reactions such as [3 + 2],¹³ [3 + 3],¹⁴ [6 + 3]¹⁵ and [8 + 3]¹⁶ cycloaddition reactions involving aziridines have been reported. In 2009, Kwon reported the first PPh₃-promoted [3 + 3]

annulation of aziridines with α -substituted allenates to generate highly functionalized tetrahydropyridines by release of SO₂.^{17a} During the process, aziridines undergo a ring-opening reaction through the breakage of the C–N bond upon the attack of the zwitterionic adduct formed by the addition of PPh₃ to an allenolate, and the resulting amide anion attacks the β -carbon of the allenolate after an intramolecular desulfonation to realize the [3 + 3] annulation (Scheme 1).¹⁷ The reaction is operationally simple and produces highly functionalized tetrahydropyridines in good to excellent yields with high levels of diastereoselectivity. In theory, however, the amide anion without the desulfonation could attack the γ -carbon of the allenates to result in a [4 + 3] annulation (Scheme 1).¹⁸ With this query in mind and our continuing interest in phosphine-catalyzed cycloaddition reactions,¹⁹ we herein report the first alkylidiphenylphosphine-promoted [4 + 3] annulation of aziridines with an allenolate to afford functionalized tetrahydroazepines under simple and mild reaction conditions (Scheme 1).

As shown in Scheme 1, in our previous work, in the presence of Ph₃P, aziridines and α -substituted allenates performed [3 + 3] annulation in dichloromethane at room temperature. Through revisiting the catalyst screening, we found that alkylidiphenyl-phosphines can reverse the regioselectivity, leading to [4 + 3] annulation, as shown in Table 1. The best result for [4 + 3] annulation of aziridine **1a** and allenolate **2** was

Table 1 Screening of the reaction conditions^a



| Entry | Phosphine (mol%) | Solvent | Yield ^b (%) | 4a : 3a ^c | dr (<i>trans</i> : <i>cis</i>) for 4a ^c |
|-----------------|------------------------------------|--------------------------------------|------------------------|----------------------|------------------------------------------------------|
| 1 | PPh ₃ (100) | CH ₂ Cl ₂ | 73 | 0 : 100 | — |
| 2 | MePPh ₂ (100) | CH ₂ Cl ₂ | 78 | 90 : 10 | 54 : 46 |
| 3 | EtPPh ₂ (100) | CH ₂ Cl ₂ | 93 | 92 : 8 | 81 : 19 |
| 4 | <i>n</i> -PrPPh ₂ (100) | CH ₂ Cl ₂ | 97 | 80 : 20 | 91 : 1 |
| 5 | <i>i</i> -PrPPh ₂ (100) | CH ₂ Cl ₂ | 35 | 63 : 37 | 100 : 0 |
| 6 | <i>n</i> -BuPPh ₂ (100) | CH ₂ Cl ₂ | 56 | 89 : 11 | 78 : 22 |
| 7 | <i>t</i> -BuPPh ₂ (100) | CH ₂ Cl ₂ | 21 | 100 : 0 | 100 : 0 |
| 8 | CyPPh ₂ (100) | CH ₂ Cl ₂ | 83 | 60 : 40 | 82 : 18 |
| 9 | DPPB (100) | CH ₂ Cl ₂ | 35 | 66 : 34 | 100 : 0 |
| 10 | DPPB (50) | CH ₂ Cl ₂ | 57 | 77 : 23 | 100 : 0 |
| 11 | DPPP (50) | CH ₂ Cl ₂ | 48 | 69 : 31 | 100 : 0 |
| 12 | EtPPh ₂ (100) | Cl(CH ₂) ₂ Cl | 43 | 70 : 30 | 30 : 70 |
| 13 | EtPPh ₂ (100) | CHCl ₃ | 44 | 73 : 27 | 62 : 38 |
| 14 ^d | EtPPh ₂ (100) | Toluene | 42 | 60 : 40 | 84 : 16 |
| 15 ^d | EtPPh ₂ (100) | THF | 66 | 85 : 15 | 80 : 20 |
| 16 ^d | EtPPh ₂ (100) | MeOH | 32 | 100 : 0 | 100 : 0 |

^a Unless otherwise stated, all reactions were performed using 0.125 mmol of **1a** and 0.150 mmol of **2** in 5 mL of CH₂Cl₂ at room temperature for 48 h. ^b Sum of the isolated yields of **3a** and **4a**. ^c Ratio of isolated yields. ^d React time is 72 h. DPPB: 1,4-bis(diphenylphosphino)butane; DPPP: 1,3-bis(diphenylphosphino)propane.

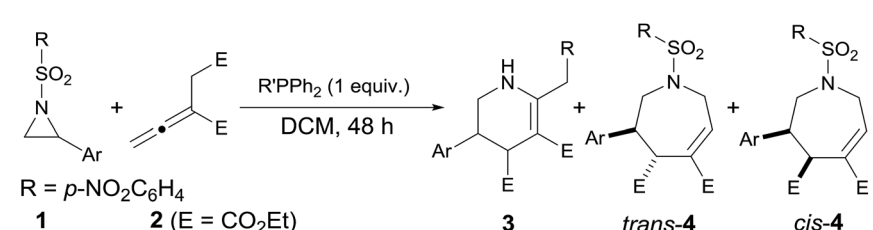
obtained when 1 equivalent of EtPPh₂ was added, with 93% yield of the cycloadducts, 92 : 8 of regioselectivity and 81 : 19 of diastereoselectivity (Table 1, entry 3). *n*-PrPPh₂ is also an effective catalyst compared to PPh₃, and gave similar result to that with EtPPh₂ (entry 4). MePPh₂, *i*-PrPPh₂, *n*-BuPPh₂, CyPPh₂, DPPB, and DPPP gave good yield of cycloadducts with poor to moderate regioselectivity (entries 2, 5, 6, 8–11). *t*-BuPPh₂ afforded much lower yield of cycloadducts although with excellent regio- and diastereoselectivity (100 : 0) (entry 7). Subsequently, the effect of solvents was evaluated with the model reaction using EtPPh₂ as the catalyst. The results showed that the aprotic CH₂Cl₂ remained to be the best solvent, while MeOH gave excellent reaction selectivity but low yield of cycloadducts (entry 16). Other solvents, such as THF, CH₃Cl, Cl(CH₂)₂Cl, and toluene afforded low to moderate yield of cycloadducts and lower reaction selectivity (entries 12–15). As such, CH₂Cl₂ was selected as the best solvent for the reaction. The relative configuration of the product **4a** was determined by single-crystal X-ray analysis.²⁰

Under the optimized conditions, the annulation reactions of different aryl substituted aziridines with diethyl 2-vinylidenesuccinate were evaluated (Table 2). In most cases, regardless of the electronic nature of the substituent of the aryl group, using EtPPh₂ or *n*-PrPPh₂ as the catalyst, moderate to good yield and moderate to good selectivity of cycloadducts were obtained, and the yields are usually lower than that having the simple phenyl ring. The position of substituents on the benzene ring seems to have no significant influence on reactivity and selectivity. For example, substituents such as 4-MeC₆H₄ and 2,4,6-Me₃C₆H₂ gave the desired products **4d** and **4g** in similar yields (entries 4 and 7).

The annulation reaction also worked well with 2-naphthyl substituted aziridine (**1n**), affording the corresponding product in 58% yield (entry 14). Unfortunately, the alkyl substituent gave no desired product, due to the weak electrophilic properties of alkyl aziridines. All these products (**4**) are new compounds.

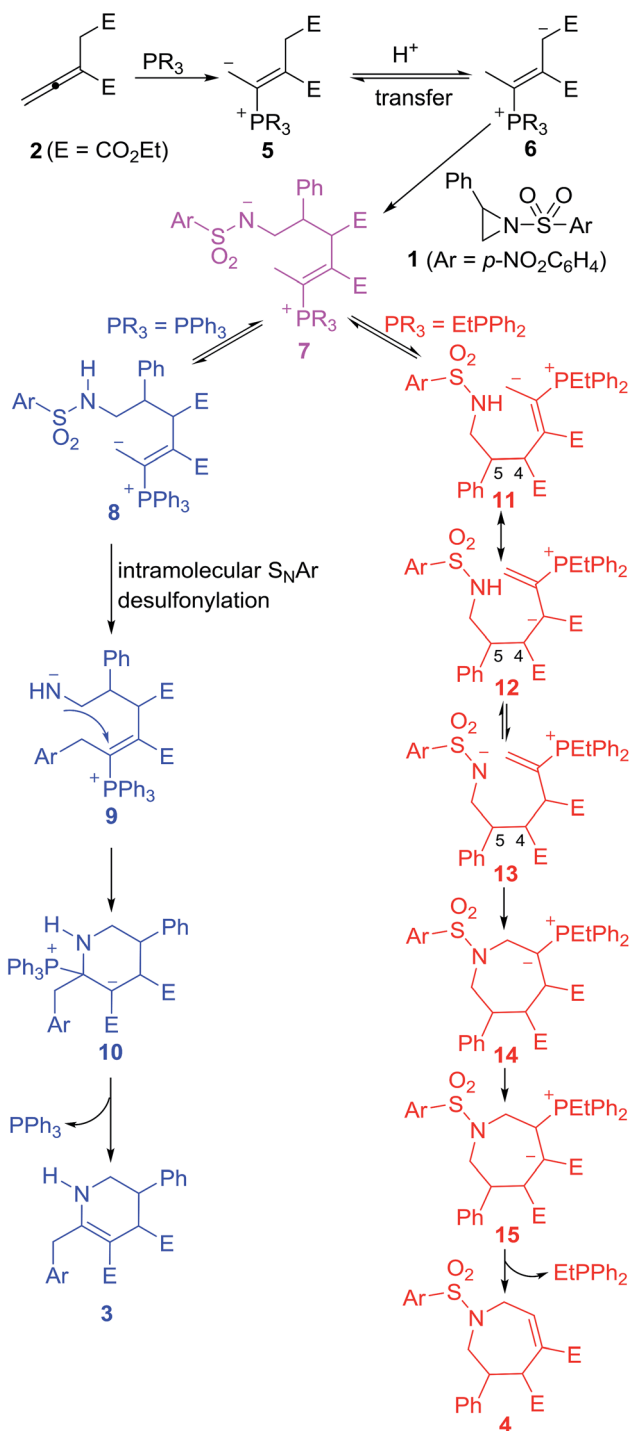
Two plausible pathways for the reactions of the aziridines **1** and the allenolate **2** are presented in Scheme 2. PPh₃ and EtPPh₂ or *n*-PrPPh₂ were found to mainly lead to [3 + 3] and [4 + 3] annulations, respectively. The reaction starts with a nucleophilic addition of the catalyst to the allenolate **2**. A subsequent proton transfer then occurs to neutralize the negative charge on the terminal γ -carbon atom of **5**. The newly formed secondary carboanion **6** is nucleophilic, and may attack the electron-deficient C atom of the aziridine to give a zwitterionic intermediate **7**. When PPh₃ is used as catalyst, a proton transfer ensues to neutralize the negative charge on N atom and results in a primary carboanion **8**. The formation of **8** may be followed by a desulfonylation step and the *p*-nitrophenyl group is migrated to the terminal γ -carbon, releasing a molecule of SO₂ and leaving the negative charge on the N atom. A nucleophilic step then occurs to close the six-membered ring and the elimination of triphenylphosphine gives the [3 + 3] annulation product **3** with the catalyst being regenerated. Compared with PPh₃, when alkyl(diphenyl)phosphine is used as catalyst, the primary carboanion **11** isomerizes into intermediate **12**, which performs a proton transfer from N atom to C atom to give the intermediate **13**. The cyclization of **13** furnished the ylide **14**, which undergoes a proton transfer to produce the intermediate **15**. Through elimination of the phosphine, the β -phosphonium ester **15** was converted to the

Table 2 Substrate scope with respect to aziridines^a



| Entry | Ar in 1 | R'PPh ₂ | T/ ^o C | Yield ^b (%) of 4 + 3 | 4 : 3 ^c | 4 | dr (<i>trans</i> : <i>cis</i>) for 4 ^c |
|-------|-----------------------------------------------------------------|------------------------------|-------------------|-----------------------------------------------|----------------------------------|-----------|------------------------------------------------------------|
| 1 | C ₆ H ₅ , 1a | EtPPh ₂ | 25 | 93 | 92 : 8 | 4a | 81 : 19 |
| 2 | 2-MeC ₆ H ₄ , 1b | <i>n</i> -PrPPh ₂ | 25 | 65 | 66 : 34 | 4b | 84 : 16 |
| 3 | 3-MeC ₆ H ₄ , 1c | <i>n</i> -PrPPh ₂ | 25 | 58 | 79 : 21 | 4c | 71 : 29 |
| 4 | 4-MeC ₆ H ₄ , 1d | <i>n</i> -PrPPh ₂ | 20 | 72 | 88 : 12 | 4d | 86 : 14 |
| 5 | 2,4-Me ₂ C ₆ H ₃ , 1e | EtPPh ₂ | 25 | 96 | 92 : 8 | 4e | 61 : 39 |
| 6 | 2,5-Me ₂ C ₆ H ₃ , 1f | <i>n</i> -PrPPh ₂ | 20 | 46 | 93 : 7 | 4f | 81 : 19 |
| 7 | 2,4,6-Me ₃ C ₆ H ₂ , 1g | <i>n</i> -PrPPh ₂ | 25 | 77 | 82 : 18 | 4g | 62 : 38 |
| 8 | 4- <i>t</i> -BuC ₆ H ₄ , 1h | <i>n</i> -PrPPh ₂ | 25 | 57 | 84 : 16 | 4h | 78 : 22 |
| 9 | 2-FC ₆ H ₄ , 1i | <i>n</i> -PrPPh ₂ | 25 | 60 | 63 : 37 | 4i | 75 : 25 |
| 10 | 3-FC ₆ H ₄ , 1j | <i>n</i> -PrPPh ₂ | 25 | 48 | 75 : 25 | 4j | 88 : 12 |
| 11 | 4-FC ₆ H ₄ , 1k | <i>n</i> -PrPPh ₂ | 20 | 73 | 73 : 27 | 4k | 70 : 30 |
| 12 | 2-ClC ₆ H ₄ , 1l | <i>n</i> -PrPPh ₂ | 25 | 78 | 77 : 23 | 4l | 80 : 20 |
| 13 | 2-BrC ₆ H ₄ , 1m | <i>n</i> -PrPPh ₂ | 20 | 42 | 60 : 40 | 4m | 72 : 28 |
| 14 | 2-Naphthyl, 1n | <i>n</i> -PrPPh ₂ | 25 | 58 | 81 : 19 | 4n | 78 : 22 |

^a All of the reactions were performed using 0.125 mmol of **1a**, 0.150 mmol of **2**, and 0.125 mmol of catalyst in 5 mL of CH₂Cl₂ for 48 h. ^b Sum of the isolated yields of **3** and **4**. ^c Ratio of isolated yields.



Scheme 2 The stepwise pathways of the [3 + 3] and [4 + 3] annulation reactions.

[4 + 3] annulation product **4**. The carbon–carbon single bond between C₄ and C₅ in the intermediates **11**, **12** and **13** might rotate, thus resulting in moderate diastereoselectivity.

Conclusions

In conclusion, we disclosed phosphine-dependent [3 + 3] and [4 + 3] annulations of allenolate with aziridines and developed the

first phosphine-promoted [4 + 3] annulation involving aziridines. The reaction works efficiently under mild conditions to give functionalized tetrahydroazepines in moderate to excellent yield with moderate to excellent diastereoselectivity.

Experimental

General methods

All reactions were performed under N₂ atmospheres in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents were purified and dried according to standard methods prior to use. Organic solutions were concentrated under reduced pressure on a rotary evaporator or an oil pump. Reactions were monitored through thin layer chromatography (TLC) on silica gel-precoated glass plates (0.25 mm thickness, silica gel). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using flash silica gel (200–300 mesh). ¹H and ¹³C NMR spectra were recorded in CDCl₃ using a 300 MHz NMR instrument (referenced internally to Me₄Si). Data for ¹³C NMR spectra are reported in terms of chemical shift. Melting points were determined on a melting point apparatus.

Preparation of aziridines **1**

The 2-aryl-1-(4-nitrobenzenesulfonyl) aziridines were prepared according to procedures described previously in the literature.^{17a}

Preparation of allenolate **2**

The diethyl 2-vinylidene-1,4-dicarboxylate **2** was prepared according to procedures described previously in the literature.^{17a,c}

General procedure for the annulation of aziridines **1** and allenolate **2**

An oven-dried 10 mL flask was charged with diphenyl-ethylphosphine or diphenyl-*n*-propylphosphine (0.125 mmol), the *N*-4-nitrobenzenesulfonyl-protected aziridine (0.125 mmol), and CH₂Cl₂ (5 mL) at room temperature. After adding diethyl 2-vinylidene-1,4-dicarboxylate (0.15 mmol) to this solution, the mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated and the residue purified through flash column chromatography (EtOAc/hexane, 1 : 5) to afford the corresponding tetrahydroazepine product.

Diethyl *trans*-1-(4-nitrophenylsulfonyl)-3-phenyl-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4a**)**. Prepared according to the general procedure as described above catalyzed by EtPPh₂ in 69% yield (43.3 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 132–133 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.40–8.32 (m, 2H), 7.99–7.92 (m, 2H), 7.31–7.22 (m, 3H), 7.16 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.08 (dd, *J* = 5.0, 2.7 Hz, 1H), 4.58–4.50 (m, 1H), 4.41–4.08 (m, 6H), 3.89–3.78 (m, 1H), 3.59 (dd, *J* = 5.0, 17.9 Hz, 1H), 2.90 (dd, *J* = 11.0, 14.3 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 166.2, 150.3,

143.2, 140.4, 136.7, 130.3, 128.8, 128.5, 127.6, 127.4, 124.5, 61.9, 61.5, 51.3, 50.5, 46.9, 46.6, 14.12, 14.06; IR (film) ν_{\max} 3106, 2983, 2934, 2872, 1715, 1654, 1606, 1532, 1497, 1455, 1401, 1352, 1311, 1245.75, 1166, 1095, 1074, 1048, 1030, 978, 945, 908, 855, 766, 744, 702, 687, 617, 604, 590, 502, 463 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 503.1483, found 503.1480.

Diethyl trans-1-(4-nitrophenylsulfonyl)-3-*o*-tolyl-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4b). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 36% yield (23.2 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 148–149 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.44–8.28 (m, 2H), 8.04–7.84 (m, 2H), 7.23–7.16 (m, 1H), 7.16–7.08 (m, 2H), 7.07–7.04 (m, 1H), 6.91–6.88 (m, 1H), 4.70–4.64 (m, 1H), 4.62–4.54 (m, 1H), 4.34–4.21 (m, 2H), 4.21–4.05 (m, 3H), 3.75–3.68 (m, 1H), 3.64–3.57 (m, 1H), 2.93–2.85 (m, 1H), 2.50 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 166.1, 150.2, 143.3, 138.7, 136.8, 136.0, 130.9, 130.1, 128.4, 127.3, 126.3, 125.6, 124.5, 61.8, 61.5, 50.4, 50.3, 46.3, 42.2, 19.7, 14.1, 14.0; IR (film) ν_{\max} 3105, 2923, 2851, 1716, 1652, 1606, 1531, 1447, 1401, 1351, 1310, 1247, 1166, 1092, 1073, 1047, 1029, 978, 947, 913, 855, 757, 742, 686 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 517.1639, found 517.1634.

Diethyl trans-1-(4-nitrophenylsulfonyl)-3-*m*-tolyl-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4c). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 33% yield (21.3 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 125–126 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.40–8.30 (m, 2H), 8.07–7.92 (m, 2H), 7.17–7.12 (m, 1H), 7.10–7.01 (m, 2H), 7.00–6.90 (m, 2H), 4.58–4.51 (m, 1H), 4.36–4.01 (m, 6H), 3.85–3.78 (m, 1H), 3.58 (dd, *J* = 5.0, 17.9 Hz, 1H), 2.88 (dd, *J* = 11.1, 14.3 Hz, 1H), 2.28 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 166.2, 150.2, 143.2, 140.4, 138.4, 136.6, 130.4, 128.7, 128.5, 128.34, 128.30, 128.2, 124.5, 124.2, 61.9, 61.5, 51.3, 50.5, 46.9, 46.6, 21.3, 14.11, 14.09; IR (film) ν_{\max} 3106, 2982, 2932, 1715, 1653, 1607, 1532, 1447, 1401, 1351, 1311, 1253, 1166, 1093, 1074, 1049, 1029, 978, 947, 913, 856, 821, 795, 765, 742, 703, 686, 607, 463 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 517.1639, found 517.1631.

Diethyl trans-1-(4-nitrophenylsulfonyl)-3-*p*-tolyl-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4d). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 54% yield (34.9 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 118–119 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.38–8.33 (m, 2H), 8.05–7.87 (m, 2H), 7.19–6.91 (m, 5H), 4.60–4.46 (m, 1H), 4.39–4.06 (m, 6H), 3.84–3.77 (m, 1H), 3.62–3.54 (m, 1H), 2.92–2.83 (m, 11.0 Hz, 1H), 2.29 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 166.2, 150.2, 143.2, 137.4, 137.3, 136.6, 130.4, 129.4, 128.5, 127.2, 124.5, 61.8, 61.5, 51.4, 50.5, 46.7, 46.5, 21.0, 14.11, 14.06; IR (film) ν_{\max} 3105, 3057, 2984, 2960, 2927, 2853, 2307, 1715, 1655, 1607, 1533, 1516, 1464, 1447, 1402, 1351, 1310, 1266, 1167, 1093, 1074, 1049, 1029, 978, 946, 911, 880, 856, 819, 801, 742, 704, 687, 609, 590, 556, 522, 463 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 517.1639, found 517.1630.

Diethyl trans-3-(2,4-dimethylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4e). Prepared according to the general procedure as described above catalyzed by EtPPh₂ in 54% yield (35.8 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 121–122 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.39–8.33 (m, 2H), 7.98–7.92 (m, 2H), 7.11–7.08 (m, 1H), 7.01–7.00 (m, 1H), 6.87–6.84 (m, 1H), 6.79–6.76 (m, 1H), 4.67–4.50 (m, 2H), 4.31–4.21 (m, 2H), 4.20–4.09 (m, 2H), 4.07–4.06 (m, 1H), 3.73–3.55 (m, 2H), 2.87 (dd, *J* = 11.4, 14.2 Hz, 1H), 2.46 (s, 3H), 2.25 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.7, 166.2, 150.2, 143.3, 136.9, 136.8, 135.8, 135.7, 131.6, 130.1, 128.4, 126.9, 125.5, 124.5, 61.8, 61.5, 50.44, 50.36, 46.5, 41.9, 20.8, 19.6, 14.1, 14.0; IR (film) ν_{\max} 2963, 2926, 2854, 1719, 1606, 1532, 1448, 1401, 1351, 1310, 1260, 1167, 1092, 1028, 978, 913, 855, 801, 754, 744, 686, 610, 463 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 531.1796, found 531.1789.

Diethyl trans-3-(2,5-dimethylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4f). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 35% yield (23.2 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 130–131 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.40–8.32 (m, 2H), 7.99–7.92 (m, 2H), 7.14–7.03 (m, 2H), 6.94–6.91 (m, 1H), 6.69–6.68 (m, 1H), 4.68–4.52 (m, 2H), 4.31–4.21 (m, 2H), 4.19–4.12 (m, 2H), 4.07–4.06 (m, 1H), 3.75–3.55 (m, 2H), 2.89 (dd, *J* = 11.5, 14.2 Hz, 1H), 2.45 (s, 3H), 2.17 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 166.2, 150.1, 143.2, 138.5, 136.8, 135.5, 132.7, 130.7, 130.1, 128.4, 127.9, 126.3, 124.4, 61.7, 61.4, 50.3, 46.3, 42.1, 20.9, 19.1, 14.02, 14.01; IR (film) ν_{\max} 2981, 2928, 1714, 1651, 1606, 1531, 1504, 1447, 1401, 1351, 1311, 1249, 1165, 1092, 1073, 1047, 977, 947, 913, 856, 831, 754, 739, 714, 686, 607 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 531.1796, found 531.1790.

Diethyl trans-3-mesityl-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4g). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 39% yield (26.6 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 130–131 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.44–8.24 (m, 2H), 8.03–7.86 (m, 2H), 7.05–7.02 (m, 1H), 6.84–6.81 (m, 2H), 4.47–4.39 (m, 1H), 4.33–4.05 (m, 5H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.56–3.44 (m, 1H), 3.40–3.33 (m, 1H), 2.38 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.5, 166.7, 150.2, 144.2, 136.9, 135.8, 134.0, 133.3, 131.0, 129.4, 128.3, 124.5, 61.5, 61.3, 49.2, 47.1, 46.9, 42.1, 21.2, 21.1, 20.6, 14.1, 13.8; IR (film) ν_{\max} 3105, 2982, 2936, 2872, 1730, 1655, 1608, 1532, 1448, 1401, 1350, 1310, 1246, 1165, 1096, 1030, 957, 928, 855, 754, 740, 686, 612, 579, 463 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_8\text{S}^+ [\text{M} + \text{H}]^+$ 545.1952, found 545.1929.

Diethyl trans-3-(4-*tert*-butylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (trans-4h). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 37% yield (25.8 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR

(300 MHz, CDCl₃) δ 8.42–8.26 (m, 2H), 8.00–7.86 (m, 2H), 7.37–7.19 (m, 2H), 7.10–7.07 (m, 3H), 4.57–4.51 (m, 1H), 4.38–4.06 (m, 6H), 3.85–3.78 (m, 1H), 3.62–3.54 (m, 1H), 2.92–2.84 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.27 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.4, 166.2, 150.2, 143.2, 137.7, 136.8, 133.3, 132.7, 130.3, 128.6, 128.4, 127.7, 127.6, 126.4, 126.2, 126.0, 125.3, 124.5, 61.9, 61.6, 51.1, 50.5, 46.9, 46.6, 14.1, 14.0; IR (film) ν_{\max} 3105, 3061, 2982, 2936, 2872, 1715, 1654, 1604, 1531, 1446, 1401, 1351, 1310, 1249, 1166, 1093, 1074, 1048, 1029, 977, 946, 915, 900, 856, 822, 741, 686, 624, 607, 589, 479, 463 cm⁻¹; HRMS (ESI) calcd for C₂₈H₃₅N₂O₈S⁺ [M + H]⁺ 559.2109, found 559.2106.

Diethyl *trans*-3-(2-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4i). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 29% yield (18.9 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.42–8.32 (m, 2H), 8.00–7.92 (m, 2H), 7.25–7.18 (m, 1H), 7.18–6.96 (m, 4H), 4.66–4.58 (m, 1H), 4.53–4.47 (m, 1H), 4.28–4.13 (m, 5H), 3.84–3.77 (m, 1H), 3.70–3.62 (m, 1H), 3.05–2.96 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 166.2, 160.6 (d, J = 246.7 Hz), 150.3, 143.3, 136.6, 130.5, 129.2 (d, J = 8.5 Hz), 128.7 (d, J = 4.4 Hz), 128.5, 127.2 (d, J = 14.4 Hz), 124.5, 124.4 (d, J = 3.5 Hz), 115.9 (d, J = 22.7 Hz), 61.9, 61.6, 49.93, 49.90, 45.9, 40.6, 14.1; IR (film) ν_{\max} 3106, 2983, 2931, 1716, 1606, 1586, 1532, 1492, 1455, 1401, 1351, 1310, 1248, 1167, 1094, 1048, 1029, 979, 946, 913, 856, 818, 757, 744, 686 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆FN₂O₈S⁺ [M + H]⁺ 521.1388, found 521.1389.

Diethyl *trans*-3-(3-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4j). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 32% yield (20.8 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.39–8.35 (m, 2H), 8.02–7.91 (m, 2H), 7.30–6.82 (m, 5H), 4.59–4.51 (m, 1H), 4.42–4.09 (m, 6H), 3.88–3.81 (m, 1H), 3.58 (dd, J = 18.0, 5.0 Hz, 1H), 2.90–2.82 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 166.0, 162.8 (d, J = 246.8 Hz), 150.3, 143.1, 142.9 (d, J = 7.0 Hz), 136.9, 130.3 (d, J = 8.3 Hz), 129.9, 128.4, 124.5, 123.1 (d, J = 2.8 Hz), 114.5 (d, J = 16.0 Hz), 114.2 (d, J = 16.8 Hz), 62.0, 61.6, 50.9, 50.6, 46.5, 46.2, 14.1, 14.0; IR (film) ν_{\max} 2983, 1719, 1590, 1532, 1449, 1351, 1253, 1167, 1095, 857, 742, 596 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆FN₂O₈S⁺ [M + H]⁺ 521.1388, found 521.1384.

Diethyl *trans*-3-(4-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4k). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 37% yield (24.1 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.46–8.26 (m, 2H), 8.08–7.87 (m, 2H), 7.39–7.06 (m, 3H), 7.06–6.89 (m, 2H), 4.61–4.48 (m, 1H), 4.43–4.09 (m, 6H), 3.92–3.74 (m, 1H), 3.63–3.56 (m, 1H), 2.90–2.82 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 166.1, 162.1 (d, J = 246.5 Hz), 150.3, 143.1, 136.9, 136.2 (d, J = 3.3 Hz), 130.0,

129.0 (d, J = 8.0 Hz), 128.4, 124.54, 124.51, 115.6 (d, J = 21.3 Hz), 61.9, 61.6, 51.2, 50.5, 46.6, 46.1, 14.1, 14.0; IR (film) ν_{\max} 2983, 1717, 1606, 1532, 1511, 1352, 1244, 1166, 1092, 1048, 856, 743, 608 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆FN₂O₈S⁺ [M + H]⁺ 521.1388, found 521.1388.

Diethyl *trans*-3-(2-chlorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4l). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 48% yield (32.2 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.46–8.26 (m, 2H), 8.08–7.87 (m, 2H), 7.39–7.06 (m, 3H), 7.06–6.89 (m, 2H), 4.61–4.48 (m, 1H), 4.43–4.09 (m, 6H), 3.92–3.74 (m, 1H), 3.63–3.56 (m, 1H), 2.90–2.82 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.2, 166.1, 150.3, 143.3, 138.0, 137.1, 133.9, 130.8, 130.2, 130.1, 128.8, 128.6, 128.5, 127.6, 127.1, 124.5, 61.9, 61.6, 50.2, 49.8, 45.7, 42.5, 14.0, 13.7; IR (film) ν_{\max} 2983, 1717, 1606, 1532, 1511, 1352, 1244, 1166, 1092, 1048, 856, 743, 608 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆ClN₂O₈S⁺ [M + H]⁺ 537.1093, found 537.1093.

Diethyl *trans*-3-(2-bromophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4m). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 18% yield (13.1 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.48–8.22 (m, 2H), 8.10–7.86 (m, 2H), 7.60–7.57 (m, 1H), 7.22–6.93 (m, 4H), 4.97–4.91 (m, 1H), 4.57–4.51 (m, 1H), 4.38–4.02 (m, 5H), 3.90–3.83 (m, 1H), 3.68–3.61 (m, 1H), 2.85–2.77 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 166.1, 150.2, 143.2, 139.6, 137.3, 133.4, 129.9, 128.9, 128.5, 127.7, 127.6, 124.6, 124.5, 61.9, 61.6, 50.3, 49.9, 45.7, 45.2, 14.0; IR (film) ν_{\max} 3105, 2962, 2928, 2872, 1720, 1654, 1606, 1531, 1471, 1445, 1401, 1351, 1310, 1257, 1167, 1093, 1075, 1049, 1024, 979, 947, 913, 855, 763, 745, 734, 686, 666 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆BrN₂O₈S⁺ [M + H]⁺ 581.0588, found 581.0593.

Diethyl *trans*-3-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate (*trans*-4n). Prepared according to the general procedure as described above catalyzed by *n*-PrPPH₂ in 36% yield (24.9 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ¹H NMR (300 MHz, CDCl₃) δ 8.43–8.23 (m, 2H), 8.03–7.88 (m, 2H), 7.84–7.67 (m, 3H), 7.62 (s, 1H), 7.50–7.39 (m, 2H), 7.31–7.22 (m, 1H), 7.14–7.12 (m, 1H), 4.60–4.50 (m, 2H), 4.32–4.25 (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.94–3.87 (m, 1H), 3.68–3.61 (m, 1H), 3.09–3.00 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.4, 166.2, 150.2, 143.2, 137.7, 136.8, 133.3, 132.7, 130.3, 128.6, 128.4, 127.7, 127.6, 126.4, 126.2, 126.0, 125.3, 124.5, 61.9, 61.6, 51.1, 50.5, 46.9, 46.6, 14.1, 14.0; IR (film) ν_{\max} 3105, 3061, 2982, 2936, 2872, 1715, 1654, 1604, 1531, 1446, 1401, 1351, 1310, 1249, 1166, 1093, 1074, 1048, 1029, 977, 946, 915, 900, 856, 822, 741, 686, 624, 607, 589, 479, 463 cm⁻¹; HRMS (ESI) calcd for C₂₈H₂₉N₂O₈S⁺ [M + H]⁺ 553.1639, found 553.1631.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is supported by the NSFC (No. 21172253, 21372256, 21572264 and 21871293 to H. G, 21473206 to D. W.), Chinese Universities Scientific Fund (No. 2018TC052 and 2018TC055), the National Key R&D Plan of China (2016YFD0200208) and the NIH (R01GM071779 to O. K.)

Notes and references

- (a) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435; (b) J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 625.
- For selected reviews, see: (a) D. O'hagan, *Nat. Prod. Rep.*, 1997, **14**, 637; (b) S. Singh, J. Goo, V. Gajulapati, T.-S. Chang, K. Lee and Y. Choi, *Anti-Cancer Agents Med. Chem.*, 2016, **16**, 539.
- For selected examples, see: (a) W. E. Berger, S. Shah, P. Lieberman, J. Hadley, D. Price, U. Munzel and S. Bhatia, *Journal of Allergy and Clinical Immunology: In Practice*, 2014, **2**, 179; (b) O. O. Daramola and R. C. Kern, *Curr. Opin. Otolaryngol. Head Neck Surg.*, 2016, **24**, 10.
- B. Holmes and A. Ward, *Drugs*, 1985, **30**, 285.
- For selected reviews, see: (a) M. Gassel, C. Breitenlechner, S. Herrero, R. Engh and D. Bossemeyer, *Handb. Exp. Pharmacol.*, 2005, **167**, 85; (b) I. Collins, *Anti-Cancer Agents Med. Chem.*, 2009, **9**, 32.
- For selected recent reviews, see: (a) Z. Li, Q. Guo, L. Wang, S. Wang, X. Zhang, Y. Wang, Z. Gao and C. Jin, *Iran. J. Public Health*, 2014, **43**, 1616; (b) N. Djordjevic, S. M. Jankovic and J. R. Milovanovic, *Eur. J. Drug Metab. Pharmacokinet.*, 2017, **42**, 729.
- For selected reviews, see: (a) K. Tasaka, *Drugs Today*, 2000, **36**, 735; (b) F. W. Fraunfelder, *Drugs Today*, 2004, **40**, 677.
- (a) T. Komoda, Y. Sugiyama, N. Abe, M. Imachi, H. Hirota and A. Hirota, *Tetrahedron Lett.*, 2003, **44**, 1659; (b) T. Komoda, K. Yoshida, N. Abe, Y. Sugiyama, M. Imachi, H. Hirota, H. Koshino and A. Hirota, *Biosci., Biotechnol., Biochem.*, 2004, **68**, 104.
- For recent reviews, see: (a) Q.-Y. Zhao, Z. Lian, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 1724; (b) Y. C. Fan and O. Kwon, *Chem. Commun.*, 2013, **49**, 11588; (c) Z. Wang, X. Xu and O. Kwon, *Chem. Soc. Rev.*, 2014, **43**, 2927; (d) Y. M. Xiao, Z. H. Sun, H. C. Guo and O. Kwon, *Beilstein J. Org. Chem.*, 2014, **10**, 2089; (e) Y. Xiao, H. Guo and O. Kwon, *Aldrichimica Acta*, 2016, **49**, 3; (f) T. Wang, X. Han, F. Zhong, W. Yao and Y. Lu, *Acc. Chem. Res.*, 2016, **49**, 1369; (g) W. Li and J. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 1657; (h) Y. Wei and M. Shi, *Org. Chem. Front.*, 2017, **4**, 1876; (i) H. Chan, W.-L. Ni and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344; (j) H. Guo, Y. C. Fan, Z. Sun, Y. Wu and O. Kwon, *Chem. Rev.*, 2018, **118**, 10049.
- For application in synthesis of natural products, see: (a) J. C. Wang and M. J. Krische, *Angew. Chem., Int. Ed.*, 2003, **42**, 5855; (b) K. Agapiou and M. J. Krische, *Org. Lett.*, 2003, **5**, 1737; (c) Y. S. Tran and O. Kwon, *Org. Lett.*, 2005, **7**, 4289; (d) R. A. Jones and M. J. Krische, *Org. Lett.*, 2009, **11**, 1849; (e) M. Sampath, P.-Y. B. Lee and T. P. Loh, *Chem. Sci.*, 2011, **2**, 1988; (f) I. P. Andrews and O. Kwon, *Chem. Sci.*, 2012, **3**, 2510; (g) R. A. Villa, Q. H. Xu and O. Kwon, *Org. Lett.*, 2012, **14**, 4634; (h) G. A. Barcan, A. Patel, K. N. Houk and O. Kwon, *Org. Lett.*, 2012, **14**, 5388; (i) L. Cai, K. Zhang and O. Kwon, *J. Am. Chem. Soc.*, 2016, **138**, 3298.
- C. Zhang and X. Lu, *J. Org. Chem.*, 1995, **60**, 2906.
- For some reviews, see: (a) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (b) P. Müller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905; (c) Y. Tang, S. Ye and X.-L. Sun, *Synlett*, 2005, 2720; (d) I. D. G. Watson, L. Yu and A. K. Yudin, *Acc. Chem. Res.*, 2006, **39**, 194; (e) G. S. Singh, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2007, **107**, 2080; (f) G. Callebaut, T. Meiresonne, N. De Kimpe and S. Mangelinckx, *Chem. Rev.*, 2014, **114**, 7954.
- For selected examples, see: (a) I. Ungureanu, P. Klotz and A. Mann, *Angew. Chem., Int. Ed.*, 2000, **39**, 4615; (b) M. Nakagawa and M. Kawahara, *Org. Lett.*, 2000, **2**, 953; (c) R. J. Madhushaw, C.-C. Hu and R.-S. Liu, *Org. Lett.*, 2002, **4**, 4151; (d) V. K. Yadav and V. Sriramurthy, *J. Am. Chem. Soc.*, 2005, **127**, 16366; (e) T. Munegumi, I. Azumaya, T. Kato, H. Masu and S. Saito, *Org. Lett.*, 2006, **8**, 379; (f) P. A. Wender and D. Strand, *J. Am. Chem. Soc.*, 2009, **131**, 7528; (g) B. Kang, A. W. Miller, S. Goyal and S. T. Nguyen, *Chem. Commun.*, 2009, 3928; (h) J. Fan, L. Gao and Z. Wang, *Chem. Commun.*, 2009, 5021; (i) F. Fontana, C. C. Chen and V. K. Aggarwal, *Org. Lett.*, 2011, **13**, 3454; (j) R. Maeda, R. Ishibashi, R. Kamaishi, K. Hirotaki, H. Furuno and T. Hanamoto, *Org. Lett.*, 2011, **13**, 6240; (k) G. Arena, C. C. Chen, D. Leonori and V. K. Aggarwal, *Org. Lett.*, 2013, **15**, 4250; (l) R. A. Craig, N. R. O'Connor, A. F. G. Goldberg and B. M. Stoltz, *Chem.-Eur. J.*, 2014, **20**, 4806; (m) M. Yoshiki, R. Ishibashi, Y. Yamada and T. Hanamoto, *Org. Lett.*, 2014, **16**, 5509; (n) J. A. Johnson, B. M. Petersen, A. Kormos, E. Echeverría, Y.-S. Chen and J. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 10293.
- (a) K. M. Goodenough, P. Raubo and J. P. A. Harrity, *Org. Lett.*, 2005, **7**, 2993; (b) L. C. Pattenden, R. A. J. Wybrow, S. A. Smith and J. P. A. Harrity, *Org. Lett.*, 2006, **8**, 3089; (c) S. Wang, Z. Chai, S. Zhou, S. Wang, X. Zhu and Y. Wei, *Org. Lett.*, 2013, **15**, 2628; (d) S. R. Pathipati, V. Singh, L. Eriksson and N. Selander, *Org. Lett.*, 2015, **17**, 4506.
- R. Shintani, K. Ikehata and T. Hayashi, *J. Org. Chem.*, 2011, **76**, 4776.
- H. Liu, H. Jia, W. Shi, C. Wang, C. Zhang and H. Guo, *Org. Lett.*, 2018, **20**, 3570.
- (a) H. Guo, Q. Xu and O. Kwon, *J. Am. Chem. Soc.*, 2009, **131**, 6318; for other phosphine-catalyzed [3 + 3] cycloaddition, see: (b) S. Zheng and X. Lu, *Tetrahedron Lett.*, 2009, **50**, 4532; (c) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, Y. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard III, H. Guo and O. Kwon, *J. Am. Chem. Soc.*, 2011, **133**, 13337; (d) J. Liu, H. Liu, R. Na, G. Wang, Z. Li,

- H. Yu, M. Wang, J. Zhong and H. Guo, *Chem. Lett.*, 2012, **41**, 218; (e) J. Hu, W. Dong, X.-Y. Wu and X. Tong, *Org. Lett.*, 2012, **14**, 5530; (f) L. Zhang, H. Liu, G. Qiao, Z. Hou, Y. Liu, Y. Xiao and H. Guo, *J. Am. Chem. Soc.*, 2015, **137**, 4316; (g) Z. Li, H. Yu, Y. Liu, L. Zhou, Z. Sun and H. Guo, *Adv. Synth. Catal.*, 2016, **358**, 1880; (h) L. Liang and Y. Huang, *Org. Lett.*, 2016, **18**, 2604; (i) L. Zhou, C. Yuan, C. Zhang, L. Zhang, Z. Gao, C. Wang, H. Liu, Y. Wu and H. Guo, *Adv. Synth. Catal.*, 2017, **359**, 2316; (j) W. Yang, W. Sun, C. Zhang, Q. Wang, Z. Guo, B. Mao, J. Liao and H. Guo, *ACS Catal.*, 2017, **7**, 3142; (k) L. Zhang, W. Yang, L. Zhou, H. Liu, J. Huang, Y. Xiao and H. Guo, *J. Heterocycl. Chem.*, 2017, **54**, 3377.
- 18 For phosphine-catalyzed [4 + 3] annulation, see: (a) K. Kumar, R. Kapoor, A. Kapur and M. P. S. Ishaq, *Org. Lett.*, 2000, **2**, 2023; (b) S. Zheng and X. Lu, *Org. Lett.*, 2009, **11**, 3978; (c) C. Jing, R. Na, B. Wang, H. Liu, L. Zhang, J. Liu, M. Wang, J. Zhong, O. Kwon and H. Guo, *Adv. Synth. Catal.*, 2012, **354**, 1023; (d) R. Zhou, J. Wang, C. Duan and Z. He, *Org. Lett.*, 2012, **14**, 6134; (e) G. Zhan, M. L. Shi, Q. He, W. Du and Y. C. Chen, *Org. Lett.*, 2015, **17**, 4750; (f) Z. Li, H. Yu, Y. Feng, Z. Hou, L. Zhang, W. Yang, Y. Wu, Y. Xiao and H. Guo, *RSC Adv.*, 2015, **5**, 34481; (g) C. Yuan, L. Zhou, M. Xia, Z. Sun, D. Wang and H. Guo, *Org. Lett.*, 2016, **18**, 5644; (h) J. Chen and Y. Huang, *Org. Lett.*, 2017, **19**, 5609.
- 19 (a) Z. Li, H. Yu, H. Liu, L. Zhang, H. Jiang, B. Wang and H. Guo, *Chem.-Eur. J.*, 2014, **20**, 1731; (b) H. Yu, L. Zhang, Z. Li, H. Liu, B. Wang, Y. Xiao and H. Guo, *Tetrahedron*, 2014, **70**, 340; (c) Z. Gao, C. Wang, C. Yuan, L. Zhou, Y. Xiao and H. Guo, *Chem. Commun.*, 2015, **51**, 12653; (d) C. Wang, Z. Gao, L. Zhou, C. Yuan, Z. Sun, Y. Xiao and H. Guo, *Org. Lett.*, 2016, **18**, 3418; (e) H. Liu, Y. Liu, C. Yuan, G.-P. Wang, S.-F. Zhu, Y. Wu, B. Wang, Z. Sun, Y. Xiao, Q. Zhou and H. Guo, *Org. Lett.*, 2016, **18**, 1302; (f) Y. Liu, W. Yang, Y. Wu, B. Mao, X. Gao, H. Liu, Z. Sun, Y. Xiao and H. Guo, *Adv. Synth. Catal.*, 2016, **358**, 2867; (g) Y. Wu, Y. Liu, W. Yang, H. Liu, L. Zhou, Z. Sun and H. Guo, *Adv. Synth. Catal.*, 2016, **358**, 3517; (h) B. Mao, W. Shi, J. Liao, H. Liu, C. Zhang and H. Guo, *Org. Lett.*, 2017, **19**, 6340; (i) H. Liu, Y. Zhao, Z. Li, H. Jia, C. Zhang, Y. Xiao and H. Guo, *RSC Adv.*, 2017, **7**, 29515; (j) X. Gao, Z. Li, W. Yang, Y. Liu, W. Chen, C. Zhang, L. Zheng and H. Guo, *Org. Biomol. Chem.*, 2017, **15**, 5298; (k) L. Zhou, C. Yuan, Y. Zeng, H. Liu, C. Wang, X. Gao, Q. Wang, C. Zhang and H. Guo, *Chem. Sci.*, 2018, **9**, 1831; (l) C. Wang, Z. Gao, L. Zhou, Q. Wang, Y. Wu, C. Yuan, J. Liao, Y. Xiao and H. Guo, *Chem. Commun.*, 2018, **54**, 279; (m) Z. Gao, C. Wang, L. Zhou, C. Yuan, Y. Xiao and H. Guo, *Org. Lett.*, 2018, **20**, 4302; (n) L. Zhou, C. Wang, C. Yuan, H. Liu, C. Zhang and H. Guo, *Org. Lett.*, 2018, **20**, 6591.
- 20 Crystallographic data for **4a** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1869166.†