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

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In this manuscript, phosphine-dependent [3 + 3] and [4 + 3] annulation reactions of allenoate with aziridines were disclosed. The alkyldiphenylphosphine-promoted [4 + 3] annulation of allenoate 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 allenoates 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 allenoates 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 allenoates 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

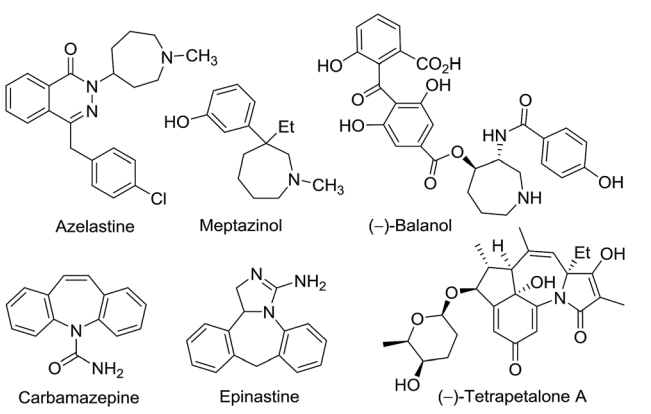

Fig. 1 Selected examples of biologically active azepine-containing heterocyclic compounds.

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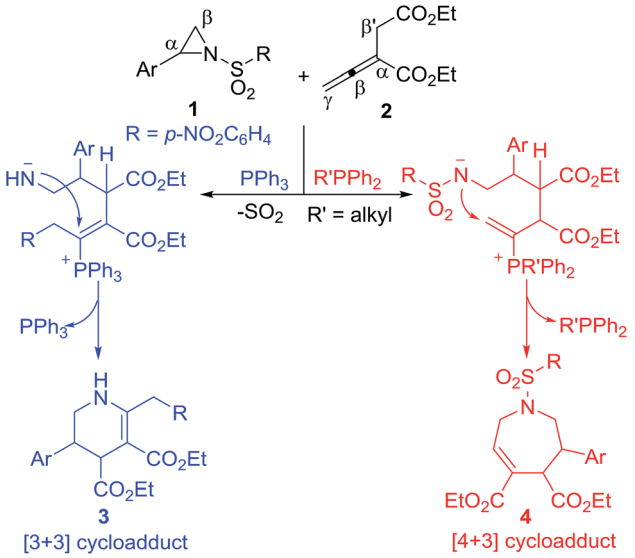
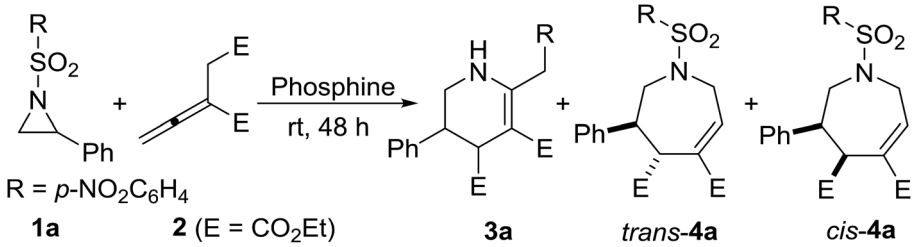


Scheme 1 Phosphine-dependent [3 + 3] and [4 + 3] annulation of allenoate with aziridines.

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 PPh_3-promoted [3 + 3] annulation of aziridines with α-substituted allenoates to generate highly functionalized tetrahydropyridines by release of SO_2.[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 PPh_3 to an allenoate, and the resulting amide anion attacks the β-carbon of the allenoate 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 desulonation could attack the γ-carbon of the allenoates 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 alkyldiphenylphosphine-promoted [4 + 3] annulation of aziridines with an allenoate 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 Ph_3P, aziridines and α-substituted allenoates performed [3 + 3] annulation in dichloromethane at room temperature. Through revisiting the catalyst screening, we found that alkyldiphenyl-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 allenoate **2** was

Table 1 Screening of the reaction conditions[a]



Entry	Phosphine (mol%)	Solvent	Yield[b] (%)	4a : 3a[c]	dr (*trans* : *cis*) for 4a[c]
1	PPh_3 (100)	CH_2Cl_2	73	0 : 100	—
2	$MePPh_2$ (100)	CH_2Cl_2	78	90 : 10	54 : 46
3	$EtPPh_2$ (100)	CH_2Cl_2	93	92 : 8	81 : 19
4	*n*-$PrPPh_2$ (100)	CH_2Cl_2	97	80 : 20	91 : 1
5	i-$PrPPh_2$ (100)	CH_2Cl_2	35	63 : 37	100 : 0
6	*n*-$BuPPh_2$ (100)	CH_2Cl_2	56	89 : 11	78 : 22
7	*t*-$BuPPh_2$ (100)	CH_2Cl_2	21	100 : 0	100 : 0
8	$CyPPh_2$ (100)	CH_2Cl_2	83	60 : 40	82 : 18
9	DPPB (100)	CH_2Cl_2	35	66 : 34	100 : 0
10	DPPB (50)	CH_2Cl_2	57	77 : 23	100 : 0
11	DPPP (50)	CH_2Cl_2	48	69 : 31	100 : 0
12	$EtPPh_2$ (100)	$Cl(CH_2)_2Cl$	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

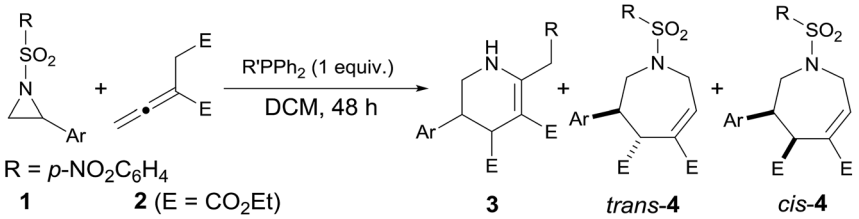
[a] Unless otherwise stated, all reactions were performed using 0.125 mmol of **1a** and 0.150 mmol of **2** in 5 mL of CH_2Cl_2 at room temperature for 48 h. [b] Sum of the isolated yields of **3a** and **4a**. [c] Ratio of isolated yields. [d] React time is 72 h. DPPB: 1,4-bis(diphenylphosphino)butane; DPPP: 1,3-bis(diphenylphosphino)propane.

obtained when 1 equivalent of $EtPPh_2$ was added, with 93% yield of the cycloadducts, 92 : 8 of regioselectivity and 81 : 19 of diastereoselectivity (Table 1, entry 3). *n*-$PrPPh_2$ is also an effective catalyst compared to PPh_3, and gave similar result to that with $EtPPh_2$ (entry 4). $MePPh_2$, i-$PrPPh_2$, *n*-$BuPPh_2$, $CyPPh_2$, DPPB, and DPPP gave good yield of cycloadducts with poor to moderate regioselectivity (entries 2, 5, 6, 8–11). *t*-$BuPPh_2$ 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 $EtPPh_2$ as the catalyst. The results showed that the aprotic CH_2Cl_2 remained to be the best solvent, while MeOH gave excellent reaction selectivity but low yield of cycloadducts (entry 16). Other solvents, such as THF, CH_3Cl, $Cl(CH_2)_2Cl$, and toluene afforded low to moderate yield of cyloadducts and lower reaction selectivity (entries 12–15). As such, CH_2Cl_2 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 $EtPPh_2$ or *n*-$PrPPh_2$ 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-MeC_6H_4 and 2,4,6-$Me_3C_6H_2$ 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.

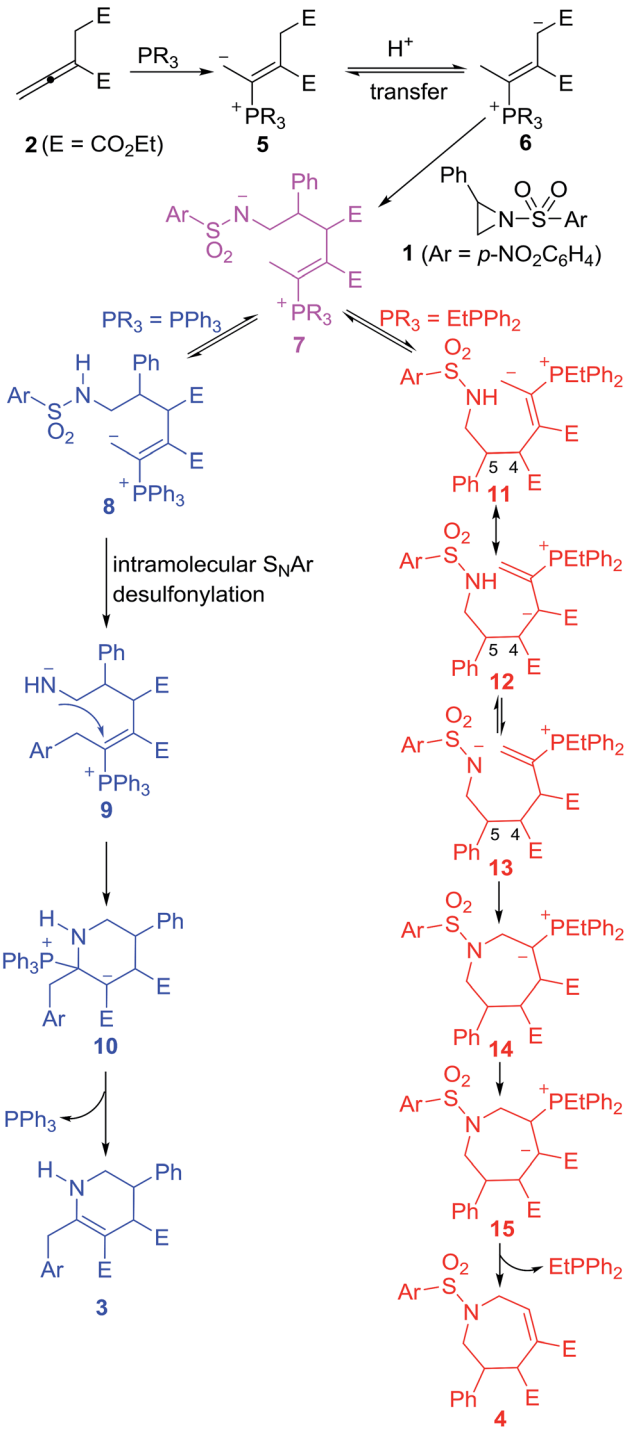
Two plausible pathways for the reactions of the aziridines **1** and the allenoate **2** are presented in Scheme 2. PPh_3 and $EtPPh_2$ or *n*-$PrPPh_2$ were found to mainly lead to [3 + 3] and [4 + 3] annulations, respectively. The reaction starts with a nucleophilic addition of the catalyst to the allenoate **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 PPh_3 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 SO_2 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 PPh_3, when alkyldiphenylphosphine 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*/°C	Yield[b] (%) of **4** + **3**	**4** : **3**[c]	**4**	dr (*trans* : *cis*) for **4**[c]
1	C_6H_5, **1a**	$EtPPh_2$	25	93	92 : 8	**4a**	81 : 19
2	2-MeC_6H_4, **1b**	*n*-$PrPPh_2$	25	65	66 : 34	**4b**	84 : 16
3	3-MeC_6H_4, **1c**	*n*-$PrPPh_2$	25	58	79 : 21	**4c**	71 : 29
4	4-MeC_6H_4, **1d**	*n*-$PrPPh_2$	20	72	88 : 12	**4d**	86 : 14
5	2,4-$Me_2C_6H_3$, **1e**	$EtPPh_2$	25	96	92 : 8	**4e**	61 : 39
6	2,5-$Me_2C_6H_3$, **1f**	*n*-$PrPPh_2$	20	46	93 : 7	**4f**	81 : 19
7	2,4,6-$Me_3C_6H_2$, **1g**	*n*-$PrPPh_2$	25	77	82 : 18	**4g**	62 : 38
8	4-*t*-BuC_6H_4, **1h**	*n*-$PrPPh_2$	25	57	84 : 16	**4h**	78 : 22
9	2-FC_6H_4, **1i**	*n*-$PrPPh_2$	25	60	63 : 37	**4i**	75 : 25
10	3-FC_6H_4, **1j**	*n*-$PrPPh_2$	25	48	75 : 25	**4j**	88 : 12
11	4-FC_6H_4, **1k**	*n*-$PrPPh_2$	20	73	73 : 27	**4k**	70 : 30
12	2-ClC_6H_4, **1l**	*n*-$PrPPh_2$	25	78	77 : 23	**4l**	80 : 20
13	2-BrC_6H_4, **1m**	*n*-$PrPPh_2$	20	42	60 : 40	**4m**	72 : 28
14	2-Naphthyl, **1n**	*n*-$PrPPh_2$	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 CH_2Cl_2 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 C_4 and C_5 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 allenoate 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 N_2 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). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 300 MHz NMR instrument (referenced internally to Me_4Si). Data for ^{13}C 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 allenoate 2

The diethyl 2-vinylidenesuccinate **2** was prepared according to procedures described previously in the literature.[17a,c]

General procedure for the annulation of aziridines 1 and allenoate 2

An oven-dried 10 mL flask was charged with diphenylethylphosphine or diphenyl-*n*-propylphosphine (0.125 mmol), the *N*-4-nitrobenzenesulfonyl-protected aziridine (0.125 mmol), and CH_2Cl_2 (5 mL) at room temperature. After adding diethyl 2-vinylidenesuccinate (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 $EtPPh_2$ in 69% yield (43.3 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow solid. Mp = 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{27}N_2O_8S^+$ $[M + H]^+$ 503.1483, found 503.1480.

Diethyl *trans*-1-(4-nitrophenylsulfonyl)-3-*o*-tolyl-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4b). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{25}H_{29}N_2O_8S^+$ $[M + H]^+$ 517.1639, found 517.1634.

Diethyl *trans*-1-(4-nitrophenylsulfonyl)-3-*m*-tolyl-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4c). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{25}H_{29}N_2O_8S^+$ $[M + H]^+$ 517.1639, found 517.1631.

Diethyl *trans*-1-(4-nitrophenylsulfonyl)-3-*p*-tolyl-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4d). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{25}H_{29}N_2O_8S^+$ $[M + H]^+$ 517.1639, found 517.1630.

Diethyl *trans*-3-(2,4-dimethylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4e). Prepared according to the general procedure as described above catalyzed by $EtPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{26}H_{31}N_2O_8S^+$ $[M + H]^+$ 531.1796, found 531.1789.

Diethyl *trans*-3-(2,5-dimethylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4f). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{26}H_{31}N_2O_8S^+$ $[M + H]^+$ 531.1796, found 531.1790.

Diethyl *trans*-3-mesityl-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahy-dro-1*H*-azepine-4,5-dicarboxylate (*trans*-4g). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{33}N_2O_8S^+$ $[M + H]^+$ 545.1952, found 545.1929.

Diethyl *trans*-3-(4-*tert*-butylphenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4h). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{35}N_2O_8S^+$ $[M + H]^+$ 559.2109, found 559.2106.

Diethyl *trans*-3-(2-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4i). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 29% yield (18.9 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{26}FN_2O_8S^+$ $[M + H]^+$ 521.1388, found 521.1389.

Diethyl *trans*-3-(3-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4j). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 32% yield (20.8 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{26}FN_2O_8S^+$ $[M + H]^+$ 521.1388, found 521.1384.

Diethyl *trans*-3-(4-fluorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4k). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 37% yield (24.1 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{26}FN_2O_8S^+$ $[M + H]^+$ 521.1388, found 521.1388.

Diethyl *trans*-3-(2-chlorophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4l). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 48% yield (32.2 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{26}ClN_2O_8S^+$ $[M + H]^+$ 537.1093, found 537.1093.

Diethyl *trans*-3-(2-bromophenyl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4m). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 18% yield (13.1 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{26}BrN_2O_8S^+$ $[M + H]^+$ 581.0588, found 581.0593.

Diethyl *trans*-3-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine-4,5-dicarboxylate (*trans*-4n). Prepared according to the general procedure as described above catalyzed by *n*-$PrPPh_2$ in 36% yield (24.9 mg). It was purified by flash chromatography (20% EtOAc/PE) to afford pale-yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{29}N_2O_8S^+$ $[M + H]^+$ 553.1639, found 553.1631.

Conflicts of interest

There are no conflicts to declare.

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