Synthesis of 3-Aroyl-4-hydroxy-4-arylpiperidine Derivatives by DBU-Catalyzed Reactions of Amines with Vinyl Ketones

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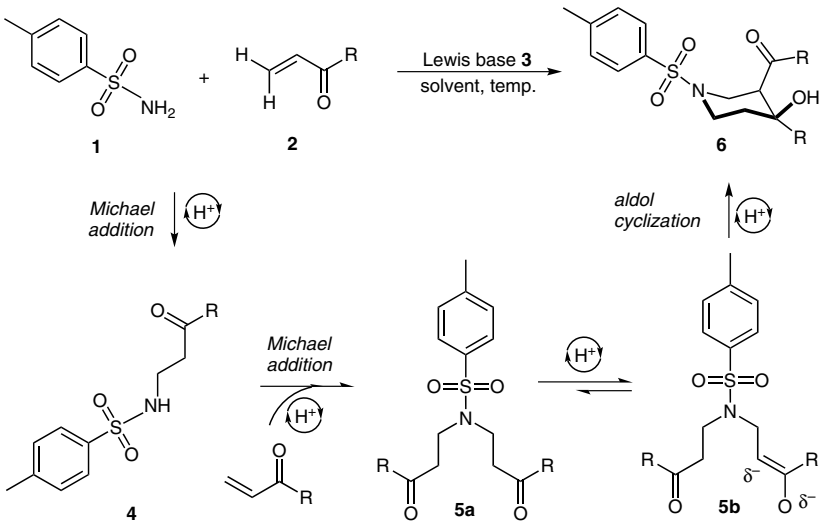
Abstract: In one-pot cascade reaction, a series of functionalized 3-aroyl-4-hydroxy-4-arylpiperidine derivatives were prepared from sulfonamides and vinyl ketones with good to excellent yields and diastereoselectivities. The reaction was catalyzed by the commercially available Lewis base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and could be easily manipulated under mild condition.

Key words: Michael addition, vinyl ketones, cascade reaction, cyclization, stereoselectivity

Piperidine derivatives are key structural components in many biological active compounds and drugs. Such molecules have been investigated as, for instance, cytotoxic agents, dopamine transporter (DAT) inhibitors, and potential anticonvulsant compounds.[1] These core units can also be used as intermediates for the synthesis of important compounds such as the popular antihistaminic agent phenindamine tartrate (Thephorin).[2] Therefore, the development of highly efficient methodologies for the construction of these heterocyclic compounds is a major theme in the modern organic chemistry.[3]

Cascade reactions have become a flourishing area over the past few years. These straightforward routes, which allow two or more reactions to occur in a single operation under the same reaction conditions, avoid time-consuming, costly protecting-group manipulations as well as the isolation of reaction intermediates.[4] In addition, molecular complexities are often achieved quickly in this way, accompanied by high levels of stereoselectivities. There is, however, usually one critical requirement for any cascade reaction: the conditions for the consecutive reactions are compatible with the former reaction.[5] Therefore, the exploration of catalyzed cascade reactions by employing a single catalyst that is capable of promoting each single step is one of the major topics of current research. Considering the benefits of tolerance of numerous functional groups and requirement for mild reaction conditions, we consider that the organic bases have been particularly favorable. Herein, we report a successful Michael–Michael–Aldol cascade reaction in which multiple steps are catalyzed by a Lewis base catalyst and which provides a series of 3-aroyl-4-hydroxy-4-arylpiperidine derivatives in *cis*-form with excellent yields under mild conditions.

In our reaction design we anticipated that exposure of a mixture of α,β-unsaturated ketone **2** and *p*-toluenesulfonamide **1** to catalytic amounts of a Lewis base should lead to the formation of the corresponding 1,4-addition products **4** (Scheme 1). The α,β-unsaturated carbonyl compounds are an important class of reaction partners for cyclization reactions and a large number of the examples



Scheme 1 Lewis base catalyzed multiple reaction cascade

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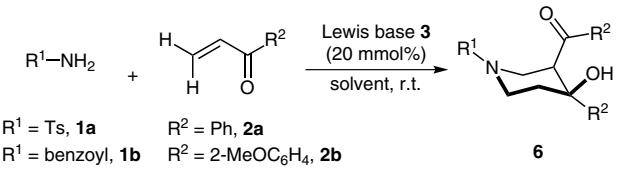
Table 1 Initial Attempts for the Base-Mediated Cascade Reaction[a]



R^1 = Ts, **1a** R^2 = Ph, **2a**
R^1 = benzoyl, **1b** R^2 = 2-$MeOC_6H_4$, **2b**

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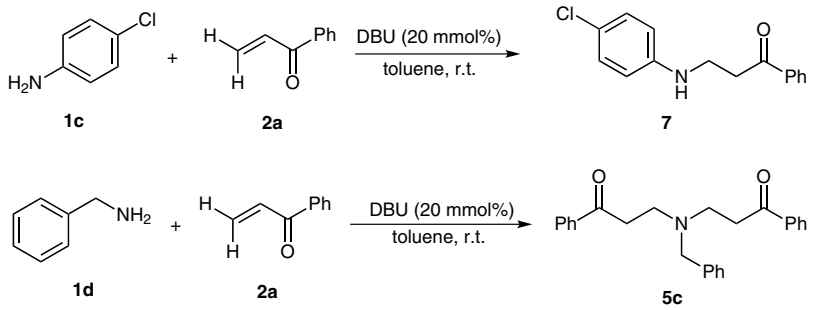
Entry	**1**, **2**	Lewis base	Solvent	Time (h)	Yield (%)[b] (*cis*/*trans*)[c]
1	**1a**, **2a**	Et_3N	Toluene	24	**6a**, trace
2	**1a**, **2a**	K_2CO_3	Toluene	24	**6a**, trace
3	**1a**, **2a**	DABCO	Toluene	24	**6a**, trace
4	**1a**, **2a**	DBU	Toluene	8	**6a**, 74 (*cis*)
5	**1a**, **2a**	DBU	Et_2O	8	**6a**, 60 (*cis*)
6	**1a**, **2a**	DBU	MeCN	8	**6a**, 51 (*cis*)
7	**1a**, **2a**	DBU	THF	8	**6a**, 73 (*cis*)
8	**1a**, **2a**	DBU	CH_2Cl_2	8	**6a**, 51 (*cis*)
9	**1b**, **2a**	DBU	Toluene	24	trace
10	**1a**, **2b**	DBU	Toluene	8	**6b**, 91 (*cis*)

[a] Reaction conditions: **1** (1.0 equiv), **2** (2.5 equiv), DBU, r.t.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopic analysis.

have been described for carbon–carbon bond formation with these substrates.[6] Subsequent action of the Lewis base catalyzed another Michael addition to afford adduct **5a**. The following Lewis base catalyzed deprotonation should effect the generation of **5b**, which was activated to give the desired product **6** through an intramolecular Aldol cyclization. The last cyclization step was expected to be the key to stereochemical control of adduct formation. Compared with the hydroxyl group, both aryl moieties derived from α,β-unsaturated ketone were bulkier groups. The steric hindrance in the reaction would force these groups to remain on the different sides of the ring. In addition, hydrogen bonding between the hydroxyl and carbonyl groups would lead these groups to remain on the same side, thus adding to the stability of adduct.

At the beginning of the reaction optimization, we used *p*-toluenesulfonamide (**1a**) and 2.5 equiv of phenyl vinyl ketone (**2a**) as the starting materials and Et_3N as the base in toluene at room temperature. However, only starting material and none of the desired adduct **6a** was observed (Table 1, entry 1). The same result was found when 1,4-diazobicyclo[2.2.2]octane ((DABCO) was used. These results may due to the weakly basic conditions provided by Et_3N and DABCO. Use of the stronger inorganic base K_2CO_3 was also ineffective in this reaction. In view of these results, we tried to use a stronger organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). To our delight, this base delivered an excellent performance in the reaction, and adduct **6a** was obtained in an all *cis*-form with yields up to 74% yield. The effects of solvents were then investigated in the presence of DBU (Table 1, entries 5–8), and toluene proved to be optimal. Subsequently, changes to the protecting groups on the amines was tested. Unfortunately, when benzamide was used to react with phenyl vinyl ketone, only traces of the desired product was found after 24 hours reaction. The employment of *p*-



Scheme 2 The reactions of *p*-chloroaniline and benzylamine with phenyl vinyl ketone (**2a**)

chloroaniline (**1c**) afforded the Michael addition product after 12 hours reaction, and the double Michael addition adduct **5c** was gained by the use of benzylamine (Scheme 2).[7] When the vinylketone with an *o*-methoxyphenyl group was used to react with *p*-toluenesulfonamide, the cascade adduct **6b** was afforded with an excellent yield of 91%.

With the optimized conditions established, we explored the reactions of a variety of substituted amides with *o*-methoxyphenyl vinylketone (**2b**) and 2,5-dimethoxyphenyl vinylketone (**2c**) by using 20 mmol% DBU at room temperature (Figure 1).[8] In general, a range of benzene sulfonamides could be applied successfully to this multiple-cascade reaction, providing a diverse set of 3-aroyl-4-hydroxy-4-arylpiperidine derivatives **6b**–**h** with different aromatic and aliphatic substituents in *cis*-form with good yields. Especially, up to 99% yield was obtained when *p*-chlorobenzene sulfonamide (**1h**) and 2,5-dimethoxyphenyl vinylketone (**2c**) were used. The propylamine also proved to be a suitable substrate, affording the corresponding adduct **6i** in high yield.

Furthermore, consistently good to excellent yields and high stereoselectivities (all *cis*-form) were observed for *p*-methylbenzene sulfonamide with a range of aryl vinyl ketones (Figure 2).[9] Phenyl vinyl ketone tolerated substitutions at any position of the aromatic ring, and both electron-donating and electron-withdrawing functionalities were compatible. The additions of more sterically hindered phenyl vinyl ketone with a 2-naphthyl group proceeded equally well, with a high yield of the *cis*-form, and the vinyl ketone derived from cinnamic aldehyde also performed efficiently. Except for somewhat longer reaction time, the additions of aryl vinyl ketones with alkyl

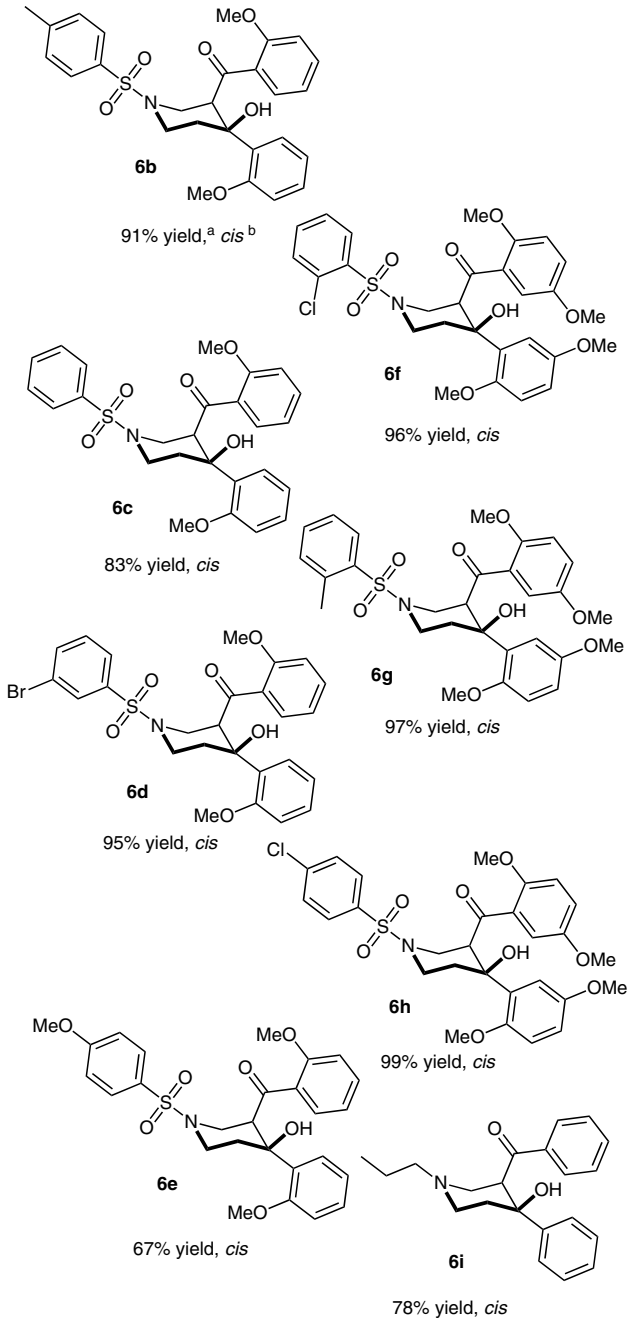


Figure 1 The cascade reactions with different substituted benzene sulfonamides. *Reagents and conditions*: **1**, **2** (2.5 equiv), DBU(20 mmol%), r.t., toluene, 4–8 h. [a] Yields were determined after column chromatography. [b] Determined by NMR spectroscopic analysis.

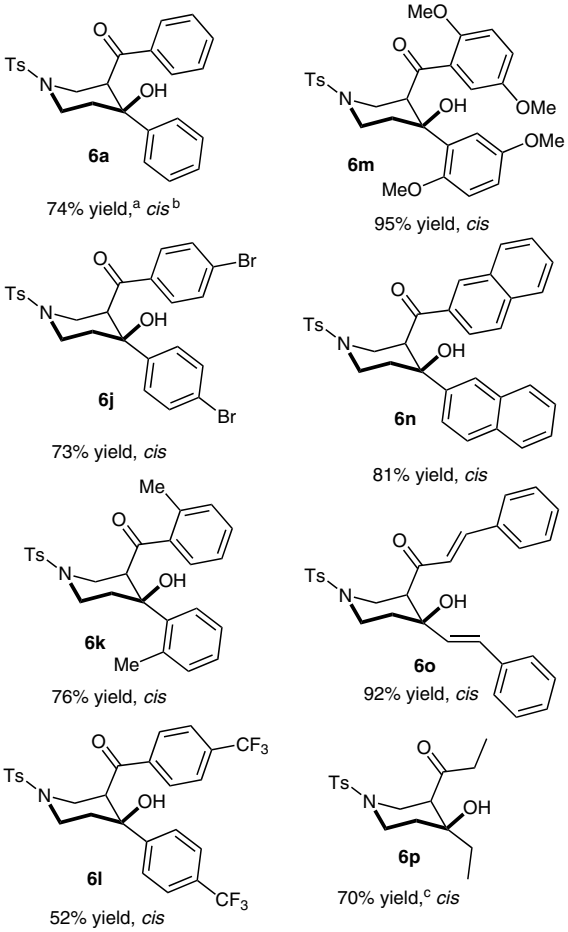


Figure 2 Scope of the vinyl ketones in the cascade reaction. *Reagents and conditions*: **1**, **2** (2.5 equiv), DBU(20 mmol%), r.t., toluene, 4–8 h. [a] Yields were determined after column chromatography. [b] Determined by NMR spectroscopic analysis. [c] The reaction was performed for 48 h with 100 mmol% DBU.

groups proceeded smoothly to furnish the corresponding products.

The constitution and configuration of the new products were proven by X-ray crystal structure analysis of 3-aroyl-4-hydroxy-4-arylpiperidine derivative **6a** (Figure 3).[10]

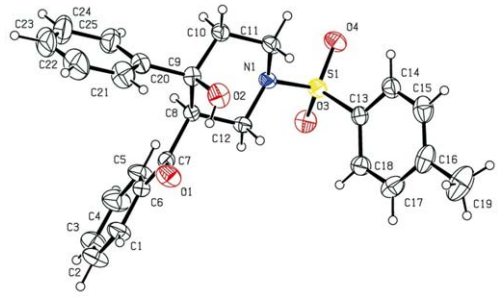
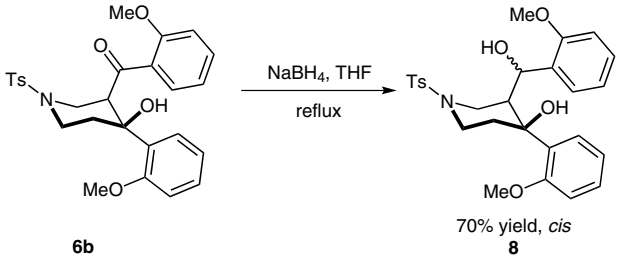


Figure 3 Molecular structure of 3-aroyl-4-hydroxy-4-arylpiperidine derivative **6a**

In addition, we attempted the conversion of compound **6b** into other functionalized compounds (Scheme 3). It was found that compound **8** could be easily obtained by hydrogenation reduction with $NaBH_4$.



Scheme 3 The transforms of adduct **6b**

In conclusion, a highly efficient and easily manipulated one-pot cascade reaction of sulfonamides and aryl vinyl ketones was developed. Catalyzed by DBU, functional 3-aroyl-4-hydroxy-4-arylpiperidine derivatives were obtained under mild reaction conditions in good to excellent yields as well as the highest levels of diastereoselectivities. An asymmetric version and application of this approach to natural product total synthesis are under investigation.

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Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0030th.

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(7) CCDC 857042 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) **General Procedure for the Cascade Reaction:** To a mixture of amines **1** (0.2 mmol) and vinyl ketones **2** (0.45 mmol) in toluene (1.0 mL) was added DBU (0.04 mmol) at room temperature. After 6–8 h the reaction was complete (as determined by TLC). The reaction mixture was concentrated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to afford the product **6**. The analytical data of some typical compounds:
Compound 6b: White solid; m.p.179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 2 H), 7.57 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.36 (dd, *J* = 13.7, 5.1 Hz, 3 H), 7.09 (t, *J* = 7.1 Hz, 1 H), 6.98–6.81 (m, 2 H), 6.78–6.63 (m, 2 H), 6.50 (d, *J* = 8.1 Hz, 1 H), 5.08 (dd, *J* = 11.4, 3.7 Hz, 1 H), 4.47 (d, *J* = 2.4 Hz, 1 H), 4.14 (dd, *J* = 10.6, 2.3 Hz, 1 H), 4.02 (s, 3 H), 3.76–3.67 (m, 1 H), 3.42 (s, 3 H), 2.92 (ddd, *J* = 11.0, 7.4, 3.2 Hz, 2 H), 2.74–2.52 (m, 1 H), 2.44 (s, 3 H), 1.57 (d, *J* = 13.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6, 158.6, 155.6, 143.5, 133.9, 133.5, 132.4, 129.8, 129.2, 129.0, 128.7, 127.6, 127.5, 120.7, 120.5, 111.0, 110.7, 72.5, 55.8, 54.5, 51.9, 44.0, 42.3, 34.7, 21.6. IR ($CDCl_3$): 3459, 2926, 1648, 1592, 1456, 1319, 1160, 913, 729, 573 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{29}NO_6S+Na^+$: 518.1608; found: 518.1587.
Compound 6d: White solid; m.p. 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (t, *J* = 1.6 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 2 H), 7.58 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.51–7.31 (m, 2 H), 7.15–7.04 (m, 1 H), 6.91 (t, *J* = 8.4 Hz, 2 H), 6.80–6.62 (m, 2 H), 6.51 (d, *J* = 8.1 Hz, 1 H), 5.08 (dd, *J* = 11.4, 3.8 Hz, 1 H), 4.50 (d, *J* = 2.7 Hz, 1 H), 4.15 (dd, *J* = 11.0, 2.4 Hz, 1 H), 4.04 (s, 3 H), 3.82–3.66 (m, 1 H), 3.42 (s, 3 H), 3.00 (td, *J* = 11.1, 4.8 Hz, 2 H), 2.70–2.51 (m, 1 H), 1.60 (d, *J* = 13.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.4, 158.6, 155.5, 138.7, 135.8, 133.9, 132.2, 130.7, 130.3, 129.2, 128.9, 128.7, 127.5, 126.0, 123.3, 120.7, 120.5, 111.0, 110.7, 72.5, 55.8, 54.6, 51.8, 43.9, 42.3, 34.6. IR ($CDCl_3$): 3432, 2934, 1655, 1597, 1462, 1245, 1166, 1022, 757, 580 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}BrNO_6S+H^+$: 560.0737; found: 560.0738.
Compound 6e: White solid; m.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.69 (m, 2 H), 7.57 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.41–7.31 (m, 1 H), 7.09 (td, *J* = 8.1, 1.7 Hz, 1 H), 7.05–6.98 (m, 2 H), 6.94–6.83 (m, 2 H), 6.72 (qd, *J* = 7.6, 1.4 Hz, 2 H), 6.55–6.41 (m, 1 H), 5.08 (dd, *J* = 11.4, 3.8 Hz, 1 H), 4.47 (d, *J* = 2.7 Hz, 1 H), 4.17–4.11 (m, 1 H), 4.02 (s, 3 H), 3.88 (s, 3 H), 3.75–3.65 (m, 1 H), 3.42 (s, 3 H), 3.01–2.81 (m, 2 H), 2.63 (tdd, *J* = 13.1, 4.8, 2.8 Hz, 1 H), 1.57 (dd, *J* = 11.2, 2.3 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6, 162.9, 158.6, 155.5, 133.9, 132.4, 129.6, 129.2, 129.0, 128.7, 128.0, 127.4, 120.6, 120.5, 114.3, 111.0, 110.7, 72.5, 55.8, 55.6, 54.5, 51.8, 44.0, 42.3, 34.7. IR ($CDCl_3$): 3454, 2936, 1656, 1597, 1254, 1159, 1023, 756, 559 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{29}NO_7S+Na^+$: 534.1557; found: 534.1568.
Compound 6i: White solid; m.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.81 (m, 2 H), 7.59–7.46 (m, 3 H), 7.41 (dd, *J* = 10.5, 4.7 Hz, 2 H), 7.27–7.21 (m, 2 H), 7.13 (ddd, *J* = 7.3, 3.8, 1.2 Hz, 1 H), 5.16 (d, *J* = 2.7 Hz, 1 H), 4.40 (d, *J* = 8.0 Hz, 1 H), 3.04–2.83 (m, 2 H), 2.69 (t, *J* = 11.4 Hz, 2 H), 2.44 (dd, *J* = 8.6, 7.2 Hz, 2 H), 2.07 (t, *J* = 12.8 Hz, 1 H), 1.82 (dt, *J* = 13.9, 2.6 Hz, 1 H), 1.64–1.46 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.46, 147.21, 137.03, 135.90, 133.93, 133.05, 128.81, 128.60, 128.34, 128.28, 128.08, 126.76, 124.57, 73.16, 60.46, 52.83, 50.51, 49.17, 39.86, 20.15, 12.03. IR ($CDCl_3$): 3458, 2959, 2929, 2818, 1663, 1448, 1377, 1205, 1070, 701 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}NO_2+H$: 324.1958; found: 324.1959.

(9) The analytical data of some typical compounds: **Compound 6k**: White solid; m.p. 197–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.56 (m, 4 H), 7.43–7.29 (m, 4 H), 7.23 (s, 1 H), 7.18–7.02 (m, 2 H), 6.93 (d, *J* = 7.1 Hz, 1 H), 4.95 (d, *J* = 2.6 Hz, 1 H), 4.38 (dd, *J* = 11.5, 3.8 Hz, 1 H), 3.94 (dd, *J* = 11.6, 2.3 Hz, 1 H), 3.85–3.66 (m, 1 H), 3.04–2.79 (m, 2 H), 2.44 (s, 3 H), 2.38 (s, 3 H), 2.25 (s, 3 H), 2.18–2.06 (m, 1 H), 1.82 (d, *J* = 14.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4, 145.8, 143.9, 138.9, 138.0, 135.6, 135.3, 133.4, 129.9, 128.9, 128.9, 128.3, 127.9, 127.6, 125.7, 125.3, 121.4, 72.7, 49.5, 45.3, 42.5, 39.1, 21.6, 21.4. IR ($CDCl_3$): 3443, 2925, 1654, 1584, 1387, 1341, 1280, 1163, 924, 545 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{29}NO_4S+Na^+$: 486.1710; found: 486.1689.
Compound 6n: White solid; m.p. 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 7.96 (d, *J* = 6.6 Hz, 2 H), 7.83–7.63 (m, 8 H), 7.55 (p, *J* = 6.7 Hz, 3 H), 7.40–7.27 (m, 4 H), 5.27 (d, *J* = 2.3 Hz, 1 H), 4.74 (dd, *J* = 11.4, 3.6 Hz, 1 H), 4.18–4.03 (m, 1 H), 3.88 (d, *J* = 11.2 Hz, 1 H), 3.08 (ddd, *J* = 16.1, 8.0, 4.0 Hz, 2 H), 2.41 (s, 3 H), 2.35–2.21 (m, 1 H), 1.92 (d, *J* = 14.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 143.9, 143.3, 136.1, 133.4, 133.1, 132.7, 132.4, 132.4, 131.0, 130.0, 129.9, 129.4, 129.0, 128.4, 128.2, 127.8, 127.7, 127.4, 127.2, 126.2, 126.0, 123.7, 123.4, 122.6, 73.1, 49.4, 45.6, 42.6, 39.2, 21.6. IR ($CDCl_3$): 3443, 3058, 2924, 1655, 1345, 1163, 922, 730, 549 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{33}H_{29}NO_4S+Na^+$: 558.1710; found: 558.1716.
Compound 6o: White solid; m.p. 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 12.1, 3.9 Hz, 3 H), 7.60–7.52 (m, 2 H), 7.46–7.36 (m, 3 H), 7.24 (m, 7 H), 6.69 (dd, *J* = 30.5, 16.0 Hz, 2 H), 6.15 (d, *J* = 15.9 Hz, 1 H), 4.54 (d, *J* = 2.4 Hz, 1 H), 3.86 (dd, *J* = 11.5, 2.6 Hz, 1 H), 3.73 (dd, *J* = 9.4, 2.0 Hz, 1 H), 3.48 (dd, *J* = 11.6, 3.9 Hz, 1 H), 2.88–2.71 (m, 2 H), 2.44 (s, 3 H), 2.00–1.84 (m, 1 H), 1.75 (d, *J* = 15.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3, 146.1, 143.9, 136.3, 133.8, 133.6, 133.0, 131.6, 129.9, 129.5, 129.1, 128.9, 128.5, 127.7, 127.6, 126.6, 125.4, 71.0, 52.0, 44.4, 41.9, 36.6, 21.6. IR ($CDCl_3$): 3451, 3029, 2926, 2253, 1598, 1339, 1160, 1091, 919, 733 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{29}NO_4S+Na^+$: 510.1735; found: 510.1713.
Compound 6p: White solid; m.p. 83–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 3.75–3.50 (m, 3 H), 2.97 (dd, *J* = 11.6, 3.8 Hz, 1 H), 2.80–2.47 (m, 4 H), 2.43 (s, 3 H), 1.68 (dd, *J* = 11.2, 2.5 Hz, 1 H), 1.60–1.51 (m, 1 H), 1.41 (dtd, *J* = 28.6, 14.2, 7.2 Hz, 2 H), 1.05 (t, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.9, 143.8, 132.9, 129.8, 127.6, 70.5, 53.6, 44.2, 41.9, 38.3, 33.7, 33.3, 21.5, 7.6, 7.1. IR ($CDCl_3$): 3488, 2971, 2930, 1696, 1343, 1161, 921, 744, 548 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}NO_4S+H^+$: 340.1577; found: 340.1587.

(10) CCDC 857043 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.