Copper-Catalyzed Arylation of Alkenyl Aziridines via Three-Component Coupling Reaction involving Alkynes and Benzyne

Francesco Berti, Paolo Crotti, Giulio Cassano, Mauro Pineschi*

Dipartimento di Scienze Farmaceutiche, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy
Fax +39(050)2219660; E-mail: pineschi@farm.unipi.it

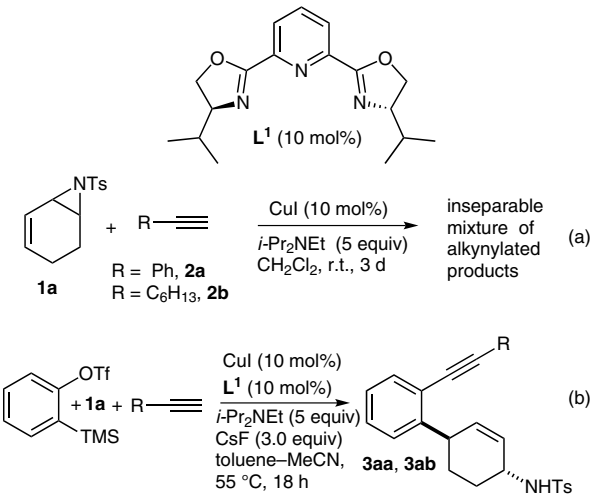
Received: 19.07.2012; Accepted after revision: 27.08.2012

Abstract: Alkenyl aziridines can be successfully arylated in a three-component coupling triggered by in situ generated benzyne with a simple copper catalyst (CuI–PPh_3), without the need of any palladium salts. The corresponding allylic amines can be obtained with good to high regioselectivity in mild reaction conditions with a variety of cyclic and acyclic alkenyl aziridines. A new domino reaction with ethyl propiolate to give tetrahydrophenanthridine was also found.

Key words: arylation, copper catalysis, aziridine, terminal alkyne, benzyne

Aziridines are versatile intermediates for the synthesis of many nitrogen-containing biologically important compounds.[1] The C-arylative ring-opening reaction of aryl aziridines with arene and heteroarenes as π-components in accordance with a Friedel–Crafts-type process has been described in several reports.[2] Very recently, a mild nickel-catalyzed arylative regioselective ring-opening process of styrenyl aziridines making use of organozinc reagents has also been described.[3] On the other hand, the C-arylative ring opening of alkenyl aziridines, otherwise called allylic or vinyl aziridines, has received only scant attention. The Friedel–Crafts arylation of allyl aziridines linked to an ester group was shown to occur exclusively at the allylic position (S_N2 addition).[4] Interestingly, a complete reversal of the regioselectivity (S_N2' addition) was obtained by the use of arylboronic acids in combination with palladium pincer complexes.[5] In the last decade, the use of benzyne as a carbon–carbon π-component for the construction of two different carbon–carbon bonds *ortho* to each other has gained considerable attention.[6] In our ongoing interest for stereoselective alkynylation of small ring heterocycles,[7] we explored the function of some simple copper catalysts, originally developed for the asymmetric alkynylation of pyridinium ions,[8] for the ring opening of alkenyl aziridines. Herein, we report that simple copper complexes catalyze novel regio- and stereoselective arylative ring-opening reactions of alkenyl aziridines via a three-component coupling making use of benzyne and terminal alkynes.

At the outset of this study, the addition of phenylacetylene (**2a**) and 1-octyne (**2b**) to aziridine **1a** using CuI (10 mol%), (*S*,*S*)-PyBox ligand **L**^{1} (10 mol%) in the presence of *i*-Pr_2NEt (5.0 equiv) in CH_2Cl_2,[8a] gave an unseparable mixture of alkynylated adducts with very low conversions (Scheme 1, Equation a). A recently reported cooperative copper- and palladium-catalyzed three-component coupling of benzynes, acyclic allylic epoxides, and terminal alkynes,[9] prompted us to explore the introduction of the low-lying LUMO orbital triple bond of benzyne as a reaction component.



Scheme 1 Preliminary results

In the presence of benzyne, generated with CsF in toluene–MeCN mixture at 55 °C, the direct ring-opening alkynylation process was completely suppressed, and only *trans*-γ-adducts **3aa** and **3ab** were isolated in 85% and 55% yield, respectively, after chromatographic purification (Scheme 1, Equation b). To our surprise, a three-component coupling was possible also without a palladium catalyst. In the absence of palladium complexes, only the hydroalkynylation product was obtained in a related three-component coupling involving acyclic allylic epoxides.[9] Interestingly, the use of a stoichiometric amount of an inorganic base, such as K_2CO_3, to suppress the two-component coupling product obtained from alkynes and arynes with a related copper catalyst, was also unnecessary.[10] After these preliminary results, different fluoride sources in a range of solvents for benzyne generation were investigated for the model three-component reaction of benzyne, phenylacetylene and aziridine **1a** (Table 1). We found that the use of *i*-Pr_2NEt in the reaction mixture was not essential for the reaction (entry 1). Aiming at an optimization of the three-component coupling without any is-

SYNLETT 2012, 23, 2463–2468
Advanced online publication: 21.09.2012
DOI: 10.1055/s-0031-1290467; Art ID: ST-2012-B0606-L

sues related to kinetic resolution process of the starting aziridine, the chiral PyBox ligand was simplified to the basic 2-oxazoline framework. Unfortunately, the use of 2-ethyl oxazoline (**L²**) as a ligand for copper revealed to be less effective (entry 2). Better results were obtained with phosphorus-based ligands, such as Ph_3P and diphenylphosphinopropane (dppp) (entries 3 and 4).

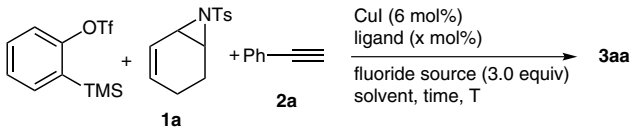
In particular, copper complexes with Ph_3P allowed a complete conversion of the starting aziridine (entry 3). The use of an ethereal solvent such as DME gave an improved solubility of all reaction components, but at the expense of the reaction efficiency (entries 5 and 6). The generation of benzyne with KF in the presence of 18-crown-6 at room temperature, as usually reported for these reaction conditions, afforded compound **3aa** with a low conversion (entry 7). The best results were obtained with the reaction carried out in MeCN. Despite the heterogeneous nature of the reaction, a clean reaction mixture with a complete conversion of starting aziridine **1a** was obtained in five hours at 55 °C using Ph_3P as the ligand (entry 8). Interestingly, in these reaction conditions the hydroalkynylation product was formed in a low amount (<10%) and it was never isolated, unlike the palladium–copper co-catalyzed reaction of allylic epoxides carried out in MeCN as the only reaction solvent.[9]

To explore the scope of the present reaction, the optimized reaction conditions were examined with a variety of alkenyl aziridines and terminal alkynes (Table 2). The reaction was also highly S_N2' regioselective with acyclic alkenyl aziridines (entries 1–5). With 1,3-butadiene-derived aziridine **1b** mixtures of diastereoisomeric *E*/*Z* allylic amines **3ba** and **3bc** were obtained (entries 1 and 2). On the other hand, it was interesting to find that when a *cis*/*trans* mixture of alkenyl aziridines **1c** (*cis*/*trans* = 36:64), **1d** (*cis*/*trans* = 31:69) was used, only the corresponding *E*-allylic amines were obtained with high yields (entries 3–5). As regards to cyclic alkenyl aziridines **1a** and **1e**, the three-component coupling was successful also with enyne **2c** and propargylic acetate **2d** (entries 6–8). However, the five-membered alkenyl aziridine **1e** proved to be less reactive than **1a**, and a lower regioselectivity was observed (entry 8). The *trans* stereochemistry of adduct **3ec** was demonstrated by ^1H NMR analysis and comparison with related 1,4-substituted cyclopentene derivatives.[7b]

It should be noted that the application of the reaction conditions developed by Cheng et al. for 1,3-butadiene monoepoxide (catalytic CuI–[$Pd(dba)_2$/dppp] in toluene–MeCN) to acyclic aziridine **1b**,[9] caused mainly decomposition of the starting aziridine. Curiously, the use of only MeCN in the same reaction afforded the corresponding three-component S_N2' adduct **3ba** with a lower yield (55%) and regioselectivity (S_N2'/S_N2 = 82:18), albeit with an increase in diastereoselectivity (*E*/*Z* = ca. 88:12) with respect to the reaction carried out under exclusive copper catalysis (see entry 1, Table 2). However, the use of palladium is not justified at all when dealing with the benchmark cyclic alkenyl aziridine **1a**. With this substrate, only a complex mixture of products was obtained using the combination of palladium and copper catalysts.

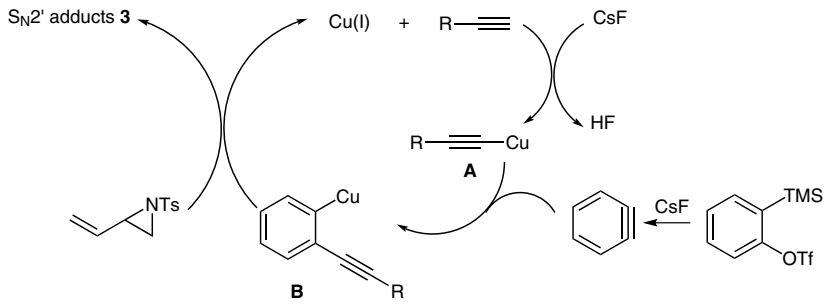
It is plausible that CsF efficiently promoted both the formation of benzyne and copper acetylide (species **A**, Scheme 2), that after the addition to the benzyne nucleus give the key reactive aryl cuprous species **B**. At this point, unlike allylic epoxides, the key oxidative addition step occurs also without the aid of palladium salts. Attack of **B** at the γ-position of the double bond (S_N2'-addition) followed by a fast reductive elimination, with only marginal isomerization to the corresponding α-adduct (S_N2-addition),[11] gives the corresponding arylated allylic amines in a highly

Table 1 Results of the Screening of Different Reaction Conditions[a]



Entry	Fluoride source	Solvent	Ligand (mol%)	Time (h), temp (°C)	Conv. (%)[b]
1	CsF	toluene–MeCN (1:1)	**L¹** (6)	16 h, 55	80
2	CsF	toluene–MeCN (1:1)	**L²** (12)	16 h, 55	44
3	CsF	toluene–MeCN (1:1)	Ph_3P (12)	16 h, 55	100
4	CsF	toluene–MeCN (1:1)	dppp (6)	16 h, 55	52
5	CsF	DME	Ph_3P (12)	16 h, 55	59
6	CsF	DME	dppp (6)	16 h, 55	55
7	KF/18-crown-6	THF	Ph_3P (12)	16 h, r.t.	30
8	CsF	MeCN	Ph_3P (12)	5 h, 55	100

[a] General reaction conditions: benzyne precursor (1.1 equiv), phenylacetylene (1.0 equiv), aziridine **1a** (0.9 equiv), fluoride salt (3.0 equiv), CuI (0.06 equiv), ligand (x equiv). **L²** = 2-ethyl oxazoline.
[b] Conversion of the starting aziridine **1a** was determined by ^1H NMR of the crude mixture.



Scheme 2 Plausible mechanism for copper-catalyzed arylation

regioselective fashion. The results obtained indicate the increased susceptibility of allylic aziridines to undergo ring opening via S_N2' displacement catalyzed by copper–phosphine complexes with respect to the corresponding allylic epoxides, in which the palladium catalysis is mandatory.[9]

Table 2 Examination of the Scope of the Three-Component Reaction[a]

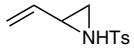
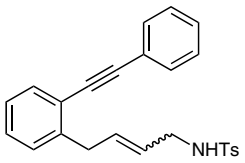
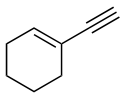
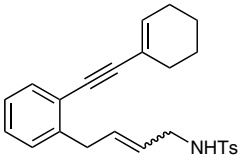
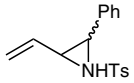
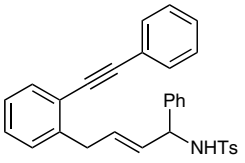
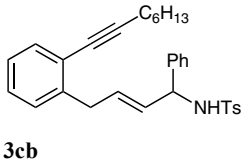
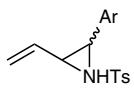
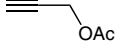
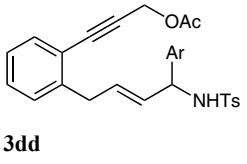
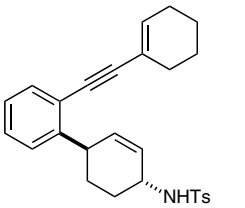
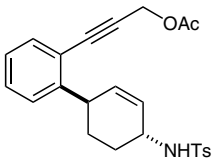
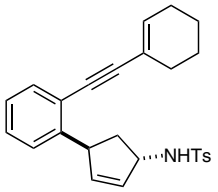
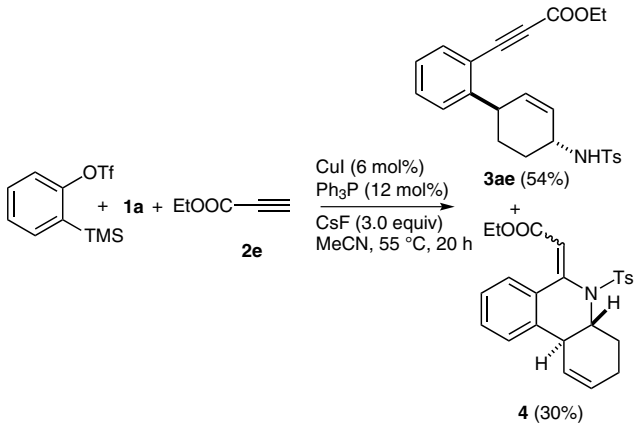
Entry	Aziridine	Alkyne	Time	Conversion	S_N2'/S_N2[b]	Main product	Yield (%)[c]
1[d]	 **1b**	 **2a**	16 h	92	91:9	 **3ba** *E*/*Z* = 60:40[e]	70[e]
2	**1b**	 **2c**	16 h	>95	76:24	 **3bc** *E*/*Z* = 63:37[e]	75[e]
3	 **1c**	**2a**	5 h	>95	>95:<5	 **3ca**	82
4	**1c**	**2b**	16 h	72	>95:<5	 **3cb**	45
5	 **1d** Ar = 4-MeOC$_6$H$_4$	 **2d**	16 h	66	90:10	 **3dd**	60
6	**1a**	**2c**	16 h	95	>95:<5	 **3ac**	74

Table 2 Examination of the Scope of the Three-Component Reaction[a] (continued)

Entry	Aziridine	Alkyne	Time	Conversion	S_N2'/S_N2[b]	Main product	Yield (%)[c]
7	**1a**	**2d**	16 h	100	92:8	 **3ad**	84
8	 **1e**	**2c**	16 h	85	88:12	 **3ec**	57

[a] Unless stated otherwise, all reactions were carried out with benzyne precursor (1.1 equiv), terminal alkyne (1.0 equiv), aziridine (0.9 equiv), CsF (3.0 equiv), CuI (0.06 equiv), Ph_3P (0.12 equiv) in MeCN at 55 °C.
[b] Determined by ^1H NMR of the crude mixture.
[c] Isolated yield after chromatographic purification.
[d] Reaction was carried out at 65 °C with CuI (0.1 equiv) and Ph_3P (0.2 equiv).
[e] An unseparable diastereoisomeric mixture was obtained.

Interestingly, a particular result was obtained when ethyl propiolate was used as the alkyne component. The initial formation of consistent amount (ca. 37% of the crude mixture) of the S_N2 adduct allowed a novel domino intramolecular amination of the conjugated triple bond of ethyl propiolate to give tetrahydrophenanthridine **4**, which was isolated with 30% yield after chromatographic purification (Scheme 3).



Scheme 3 New domino reaction pathway with ethyl propiolate

In conclusion, a novel regioselective and *anti*-stereoselective arylation of alkenyl aziridines by means of a three-component reaction involving benzyne and alkynes catalyzed by simple copper complexes has been developed.[12] The use of a conjugated alkyne allows the consecutive one-pot formation of two carbon–carbon bonds followed by an intramolecular carbon–nitrogen bond formation. The reaction occurs in mild conditions to afford functionalized allylic amines with good to high levels of regio- and stereoselectivity. Unlike related allylic epoxides, the use of a cooperative palladium catalysis is not necessary, and in most cases it was detrimental to the reaction efficiency.

Acknowledgment

This work was supported by the Ministero dell'Università e della Ricerca (PRIN 2008) and by the University of Pisa.

References

(1) For a recent review, see: Lu, P. *Tetrahedron* **2010**, *66*, 2549.
(2) For a comprehensive review, see: Krake, S.; Bergmeier, S. C. *Tetrahedron* **2010**, *66*, 7337.
(3) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541.
(4) Takada, H.; Yasui, E.; Sahara, Y.; Chinen, Y.; Tanaka, H.; Morita, Y.; Kobiki, C.; Narisawa, D.; Mizukami, M.; Miyashita, M.; Nagumo, S. *Heterocycles* **2011**, *83*, 555.
(5) Kjellgren, J.; Aydin, J.; Wallner, O. A.; Saltanova, I. V.; Szabó, K. J. *Chem.–Eur. J.* **2005**, *11*, 5260.
(6) For recent reviews, see: (a) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214. (b) Yoshida, H.; Takaki, K. *Heterocycles* **2012**, *85*, 1333. (c) Okuma, K. *Heterocycles* **2012**, *85*, 515. (d) Bhunia, A.; Reddy Yetra, S.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (e) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *122*, 3550. (f) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766.
(7) (a) Crotti, S.; Bertolini, F.; Macchia, F.; Pineschi, M. *Chem. Commun.* **2008**, 3127. (b) Bertolini, F.; Woodward, S.; Crotti, S.; Pineschi, M. *Tetrahedron Lett.* **2009**, *50*, 4515; and references therein.
(8) (a) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (b) Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1906.
(9) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 391.

(10) (a) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393. (b) See also: Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2008**, 5013.
(11) For a review, see: Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339.
(12) The following reagents were purchased from Aldrich and used as received: CuI (99.999%); 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (97%); CsF (99.9%); Ph_3P (≥99%); phenylacetylene (98%); propargyl acetate (98%); 1-octyne (97%); ethyl propiolate (99%).

Typical Procedure for the Three-Component Coupling with Alkenyl Aziridines (Table 1, Entry 8): In a dried Schlenk tube flushed with argon, CuI (1.5 mg, 8.1 μmol), and Ph_3P (4.2 mg, 16.2 μmol) were placed in anhyd MeCN (1.2 mL). The solution was stirred for 10 min at r.t. and then CsF (68.4 mg, 0.45 mmol), *o*-trimethylsilylphenyl triflate (41.3 μL, 0.17 mmol), phenylacetylene (16.5 μL, 0.15 mmol) and aziridine **1a** (0.135 mmol) were sequentially added. After stirring at 55 °C for 5 h, the suspension was filtered on Celite through a glass sintered Buchner funnel washing with CH_2Cl_2. The crude residue was purified by flash chromatography eluting with hexanes–EtOAc (8:2; R_f 0.10) to afford 46 mg (80%) of (1*R**,4*R**)-4-{[2-(phenylethynyl)phenyl]cyclohex-2-enyl}benzenesulfonamide (**3aa**), as an oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.60–2.22 (m, 4 H), 2.43 (s, 3 H), 4.00 (br, 2 H), 4.78 (br, 1 H, N*H*Ts), 5.62 (d, 1 H, *J* = 10.1 Hz), 5.81 (d, 1 H, *J* = 10.1 Hz), 7.08–7.52 (m, 11 H), 7.81 (d, 2 H, *J* = 8.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.53, 28.9, 29.8, 39.2, 49.7, 87.5, 93.6, 122.3, 123.2, 126.3, 127.0, 128.4 (2 × C), 128.6, 129.0, 129.8, 131.4, 132.4, 133.7, 138.3, 143.4, 146.2. MS (ESI): *m*/*z* = 450 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{25}NO_2S$: C, 75.85; H, 5.89; N, 3.28. Found: C, 76.04; H, 5.68; N, 3.13.

Compound 3ca (Table 2, Entry 3): Following the typical procedure, the crude residue was purified by flash chromatography eluting with hexanes–EtOAc (8:2; R_f 0.27), to afford compound **3ca** (53 mg, 82%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.50 (d, 2 H, *J* = 6.1 Hz), 4.73 (d, 1 H, *J* = 7.1 Hz, N*H*Ts), 4.92 (t, 1 H, *J* = 6.2 Hz), 5.52 (dd, 1 H, *J* = 15.3, 6.1 Hz), 5.60–5.77 (m, 1 H), 7.05–7.28 (m, 10 H), 7.30–7.39 (m, 3 H), 7.41–7.53 (m, 3 H), 7.57 (d, 2 H, *J* = 7.9 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.4, 37.1, 59.3, 87.8, 93.4, 122.7, 123.2, 126.2, 127.0, 127.1, 127.5, 128.3, 128.4 (2 × C), 128.5, 128.8, 129.3, 130.5, 131.2, 131.4, 132.2, 137.6, 139.9, 141.3, 143.0. MS (ESI): *m*/*z* = 500 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{27}NO_2S$: C, 77.96; H, 5.70; N, 3.28. Found: C, 78.02; H, 5.68; N, 3.14.

Compound 3cb (Table 2, Entry 4): Following the typical procedure, the title compound was purified by semipreparative TLC plates eluting with hexanes–EtOAc (9:1; R_f 0.16, two runs), to afford compound **3cb** (29 mg, 45%) as a yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 6.0 Hz), 1.25–1.72 (m, 10 H), 2.37 (s, 3 H), 3.41 (d, 2 H, *J* = 6.3 Hz), 4.67 (d, 1 H, *J* = 6.5 Hz, N*H*Ts), 4.92 (app. t, 1 H, *J* = 6.5 Hz), 5.49 (dd, 1 H, *J* = 6.3, 15.5 Hz), 5.59–5.71 (m, 1 H), 6.95–7.42 (m, 11 H), 7.58 (d, 2 H, *J* = 7.8 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.0, 19.5, 21.5, 22.5, 28.6, 28.8, 31.3, 37.0, 59.3, 79.1, 94.6, 123.6, 126.1, 127.0, 127.2, 127.6, 127.6, 128.5, 129.3, 130.3, 131.6, 132.2, 137.7, 140.0, 141.1, 143.1. MS (ESI): *m*/*z* = 508 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{35}NO_2S$: C, 76.66; H, 7.26; N, 2.88. Found: C, 76.85; H, 7.13; N, 2.80.

Compound 3dd (Table 2, Entry 5): Following the typical procedure, the crude residue was purified by flash chromatography eluting with hexanes–EtOAc (8:2; R_f 0.05) to afford compound **3dd** (41 mg, 60%) as a brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.37 (s, 3 H), 3.30–3.50 (m, 2 H), 3.75 (s, 3 H), 4.80–4.90 (m, 3 H), 5.18 (d, 1 H, *J* = 7.1 Hz), 5.49–5.56 (m, 2 H), 6.67–6.87 (m, 2 H), 6.97–7.43 (m, 8 H), 7.57 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.7, 21.4, 37.1, 52.8, 55.2, 58.7, 84.8, 86.9, 113.7, 121.6, 127.1, 128.2, 128.9, 129.0, 129.2, 130.5, 130.7, 132.2, 132.6, 137.7, 141.8, 142.8, 158.9, 170.7. MS (ESI): *m*/*z* = 530 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{29}NO_5S$: C, 69.16; H, 5.80; N, 2.78. Found: C, 70.04; H, 5.76; N, 2.65.

Compound 3ac (Table 2, Entry 6): Following the typical procedure the chromatographic purification was performed with hexanes–EtOAc (9:1) containing 4% of Et_3N (R_f 0.12) to afford compound **3ac** (43 mg, 74%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.46–1.75 (m, 7 H), 2.09–2.25 (m, 5 H), 2.43 (s, 3 H), 3.91–4.03 (m, 2 H), 4.68 (br, 1 H, N*H*Ts), 5.57 (dt, 1 H, *J* = 10.1, 2.3 Hz), 5.76 (dt, 1 H, *J* = 10.1, 0.8 Hz), 6.13–6.20 (m, 1 H), 7.03–7.38 (m, 6 H), 7.80 (d, 2 H, *J* = 8.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.4, 21.5, 22.2, 25.7, 28.7, 29.1, 29.7, 39.0, 49.6, 84.4, 95.5, 120.7, 122.8, 126.1, 126.8, 127.0, 127.9, 128.8, 129.7, 132.1, 133.8, 135.0, 138.2, 143.3, 145.8. MS (ESI): *m*/*z* = 454 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{29}NO_5S$: C, 75.14; H, 6.77; N, 3.25. Found: C, 75.25; H, 6.60; N, 3.20.

Compound 3ad (Table 2, Entry 7): Following the typical procedure, the title compound was purified by semipreparative TLC plates eluting with toluene–hexanes–Et_2O (4:2:1, 2 runs; R_f 0.18), to afford **3ad** (48 mg, 84%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39–1.99 (m, 3 H), 2.01–2.19 (m, 4 H), 2.44 (s, 3 H), 3.79–3.89 (m, 1 H), 3.90–4.04 (m, 1 H), 4.50 (d, 1 H, *J* = 8.9 Hz, N*H*Ts), 4.89 (s, 2 H), 5.58 (dt, 1 H, *J* = 10.1, 2.4 Hz), 5.73 (dt, 1 H, *J* = 10.1, 0.8 Hz), 7.06–7.45 (m, 7 H), 7.80 (d, 2 H, *J* = 6.7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.8, 21.5, 29.0, 29.8, 39.0, 49.7, 52.8, 84.6, 87.0, 121.2, 126.2, 126.9, 127.0, 129.0, 129.1, 129.7, 132.7, 133.4, 138.3, 143.3, 146.7, 170.3. MS (ESI): *m*/*z* = 446 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.60; H, 5.70; N, 3.30.

Compound 3ec (Table 2, Entry 8): Following the typical procedure, the crude residue was purified by flash chromatography eluting with hexanes–EtOAc (9:1) containing 4% Et_3N (R_f 0.07) to afford compound **3ec** (32 mg, 57%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.57–1.75 (m, 4 H), 1.94–2.24 (m, 6 H), 2.42 (s, 3 H), 4.41–4.65 (m, 3 H), 5.65–5.71 (m, 1 H), 5.90–5.96 (m, 1 H), 6.13–6.20 (m, 1 H), 6.94–7.21 (m, 3 H), 7.25–7.40 (m, 3 H), 7.77 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.4, 21.5, 22.3, 25.7, 40.5, 46.0, 47.4, 59.7, 85.0, 97.2, 120.1, 123.0, 125.4, 126.3, 127.0, 128.1, 129.7, 131.9, 132.1, 135.1, 138.1, 143.1, 145.0, 145.5. MS (ESI): *m*/*z* = 440 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{27}NO_2S$: C, 74.79; H, 6.52; N, 3.35. Found: C, 75.10; H, 6.45; N, 3.32.

Compound 3ae: Purified by flash chromatography eluting with hexanes–EtOAc (8:2; R_f 0.12); yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, *J* = 7.0 Hz), 1.45–1.65 (m, 2 H), 1.85–2.00 (m, 1 H), 2.05–2.20 (m, 1 H), 2.43 (s, 3 H), 3.83–3.94 (m, 1 H), 3.93–4.05 (m, 1 H), 4.28 (q, 2 H, *J* = 7.0 Hz), 4.71 (d, 1 H, *J* = 9.0 Hz, N*H*Ts), 5.60–5.67 (m, 2 H), 7.10–7.41 (m, 5 H), 7.53 (d, 1 H, *J* = 7.8 Hz), 7.80 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.1, 21.5, 29.4, 29.8, 39.2, 49.6, 62.1, 84.3, 84.7, 118.7, 126.5, 127.0, 127.3, 129.6, 129.8, 130.9, 132.8, 133.9, 138.3, 143.4, 148.4, 174.9. MS (ESI): *m*/*z* = 446 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.22; H, 5.88; N, 3.24.

Compound 4: Purified by flash chromatography eluting with hexanes–EtOAc (8:2; R_f 0.28); yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.0 Hz), 1.30–1.42 (m, 1 H), 1.82–2.02 (m, 1 H), 2.32 (s, 3 H), 2.28–2.38 (m, 1

H), 2.86 (br dd, 1 H, J = 2.8, 12.3 Hz), 3.14–3.32 (m, 2 H), 4.16 (q, 2 H, J = 7.0 Hz), 5.88–6.00 (m, 1 H), 6.11 (br d, 1 H, J = 11.5 Hz), 6.49 (s, 1 H), 6.81–7.42 (m, 8 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.3, 21.6, 25.7, 31.6, 40.6, 60.5, 60.6, 120.3, 121.2, 123.0, 124.9, 128.0, 128.7, 129.3, 129.6, 130.0, 132.7, 134.9, 137.6, 143.9, 147.0, 165.3. MS (ESI): m/z = 446 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.45; H, 5.78; N, 3.28.

