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Palladium-catalyzed intramolecular α-arylation of sulfoximines

Carsten Bolm *, Hiroaki Okamura, Marinella Verrucci

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Straße 1, D-52056 Aachen, Germany

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Dedicated to Professor Dr. J. P. Genêt on occasion of his 60th birthday

Abstract

The palladium-catalyzed cyclization of *N*-(2-bromobenzyl)- and *N*-(2-bromobenzoyl)-sulfoximines affords six-membered heterocycles in moderate to good yield. In both cases, the α-arylations of the sulfoximine methyl groups are catalyzed by combination of $Pd(OAc)_2$ and *rac*-BINAP in the presence of a base such as Cs_2CO_3 or K_2CO_3.

Keywords: Arylation; Catalysis; Cyclization; Palladium; Sulfoximine

1. Introduction

The palladium-catalyzed α-arylation of carbonyl compounds was first reported in 1997 [1] and since then it has been developed to an important method for C–C bond formations [2]. The scope of this reaction covers a wide range of substrates such as ketones, esters, amides, nitriles and other compounds having acidic α-hydrogens. Recently, we reported on the first palladium-catalyzed α-arylation of sulfoximines, which allowed the preparation of six- to eight-membered heterocyclic ring systems in a most straighforward manner [3]. A typical example is shown in Scheme 1. In the presence of catalytic amounts of $Pd(OAc)_2$ or $[Pd_2dba_3]$ in combination with *rac*-BINAP as ligand and sodium–*tert*-butoxide as base, 1,9-dibromonaphthaline (**1**) reacts with sulfoximine **2** to give cyclized product **3** in 99% yield. Mechanistic studies (using 2,2′-dibromobiphenyl as substrate) revealed that the transformation involves two steps which occur sequentially. First, the sulfoximine is *N*-arylated to afford intermediate **4**, which then cyclizes to give **3** through activation of the acidic protons of the sulfoximine methyl group. Both steps are palladium-catalyzed and proceed without detectable racemization at the stereogenic sulfur atom.

Thus, the heterocyclization reaction depicted in Scheme 1 relies on the high efficiency of both the palladium-catalyzed *inter*molecular *N*-arylation of the sulfoximine [4,5] and the subsequent *intra*molecular ring close involving a formal CH-activation [6]. We now wondered, if such cyclization reaction would also occur with other substrates that lack the *N*-aryl-sulfoximine nitrogen bond. As starting materials we envisaged the use of benzylated and benzoylated sulfoximines **5** and **6**, respectively. Those compounds are readily available [7,8] and would lead to interesting heterocyclic products **7** and **8**, respectively, which could eventually serve as useful building blocks for the synthesis of biologically active sulfoximines [9,10] and chiral ligands for asymmetric catalysis [5] (Scheme 2).

Here, we report on the realization of this concept.

2. Results and discussion

N-(2-Bromobenzyl)-sulfoximines (**5a**,**c**) and *N*-(2-bromobenzoyl)-sulfoximines (**6a**–**d**) were prepared by derivatization of *NH*-sulfoximine (**2**) with the corresponding 2-bromobenzyl bromide or 2-bromobenzoyl chloride, respectively. Compounds **5b** and **5d** were derived from the reduction of **6b** and **6d**, respectively. A metallation/alkylation sequence using *n*-butyliodide as electrophile afforded **5e** from **5a**. The results of the

* Corresponding author. Fax: +49-241-809-2391.
E-mail address: carsten.bolm@oc.rwth-aachen.de (C. Bolm).

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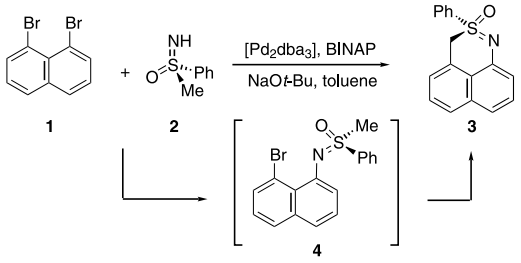
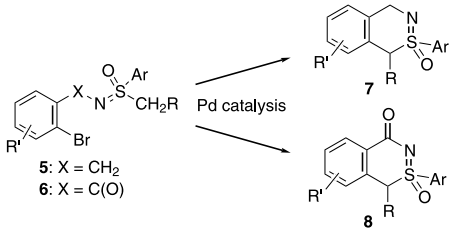


Scheme 1.

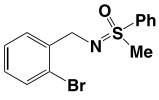
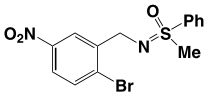
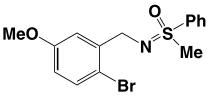
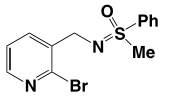
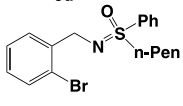


Scheme 2.

palladium-catalyzed cyclization reactions are summarized in Tables 1 and 2.

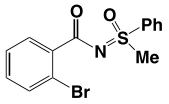
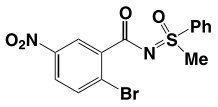
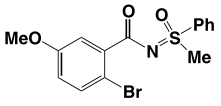
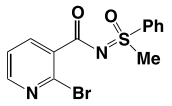
For the optimization of the reaction protocol **5a** was used as substrate. Confirming the overall concept we found that with $Pd(OAc)_2$ as metal source, *rac*-BINAP as ligand, and cesium carbonate as base in toluene under reflux a smooth intramolecular C-arylation of **5a** occurred affording the corresponding sulfoximine-containing heterocycle after 16 h in 93% yield (Table 1, entry 1). Other bases could also be applied, but the yields were lower. For example, potassium carbonate afforded the product in 88% yield, and the stronger base sodium *tert*-butoxide led to decomposition and none of the product was obtained. Nitro-substituted **5b** was also a good substrate for the cyclization reaction (Table 1, entry 4). However in this case and in contrast to the general trend, K_2CO_3 proved to be a better base than Cs_2CO_3. Compound **5c** bearing an electron-donating substituent (Table 1, entries 5–8) was less reactive than the previously mentioned substrates, and in order to

Table 1
Palladium-catalyzed cyclization reactions of benzylated sulfoximines **5** [a]

entry	substrate	Pd source	base	time	yield/%[b]
1		$Pd(OAc)_2$	Cs_2CO_3	16 h	93
2		$Pd(OAc)_2$	K_2CO_3	16 h	88
3	**5a**	$Pd(OAc)_2$	NaO*t*-Bu	16 h	0
4		$Pd(OAc)_2$	K_2CO_3	16 h	83
	5b				
5		$Pd(OAc)_2$	Cs_2CO_3	16 h	78
6		$Pd(OAc)_2$	Cs_2CO_3	3 d	91
7		$PdCl_2$	Cs_2CO_3	3 d	29
8	**5c**	$[Pd_2dba_3]$	Cs_2CO_3	3 d	trace
9		$Pd(OAc)_2$	Cs_2CO_3	16 h	92
	5d				
10		$Pd(OAc)_2$	Cs_2CO_3	16 h	40[c]
	5e				

[a] All the reactions were performed with 5 mol% of [Pd], 10 mol% of *rac*-BINAP, and 4 equiv. of base in refluxing toluene. [b] Products isolated by column chomatography. [c] Ca. 1:1 mixture of diastereomers.

Table 2
Palladium-catalyzed cyclization reactions of benzoylated sulfoximines **6** [a]

entry	substrate	Pd source	base	time	yield/%[b]
1	 **6a**	$Pd(OAc)_2$	K_2CO_3	16 h	62
2		$Pd(OAc)_2$	NaO*t*-Bu	16 h	0
3		$[Pd_2dba_3]$	K_2CO_3	16 h	~10
4	 **6b**	$Pd(OAc)_2$	K_2CO_3	16 h	0
5	 **6c**	$Pd(OAc)_2$	K_2CO_3	16 h	74
6	 **6d**	$Pd(OAc)_2$	Cs_2CO_3	3 days	16

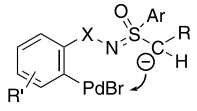
[a] All the reactions were performed with 5 mol% of [Pd], 10 mol% of *rac*-BINAP, and 4 equiv. of base in refluxing toluene. [b] Products isolated by column chomatography.

achieve a high product yield with the $Pd(OAc)_2$-based catalyst an extended reaction time was required (91% after 3 days). The catalyst derived from $PdCl_2$ showed a rather low activity (Table 1, entry 7), and, much to our surprise, use of $[Pd_2dba_3]$, which previously had been applied successfully in α-arylations, gave rise to an ineffective catalyst (Table 1, entry 8). Pyridine-derived **5d** proved to be an excellent substrate for the heterocyclization, and its palladium-catalyzed ring closure afforded the corresponding product in 92% yield. Particularly noteworthy is the conversion of **5e**, since for the first time the cyclization of a methylene carbon α to the sulfoximine was achieved. Even though the yield of the cyclized product was only 40% and a 1:1 mixture of diastereomers was obtained, this transformation sets the basis for further investigations directed towards the synthesis of higher branched and more functionalized derivatives.

Next, reactions with *N*-benzoylated sulfoximines **6** as starting materials were investigated. In general, the reactivity of these substrates was lower than those of **5**, and the reaction scope was rather limited. Table 2 summarizes the results. The best catalysis was observed with a mixture of $Pd(OAc)_2$, *rac*-BINAP, and K_2CO_3 and gave the cyclized product stemming from **6a** in 62% yield (Table 2, entry 1). Changing the base to NaO*t*-Bu, KHMDS or LHMDS, as well as using $[Pd_2dba_3]$ as metal source or phosphines such as PPh_3 or P(*t*-Bu)$_3$ as ligands, afforded the product in very low yield at best. *N*-Benzoyl sulfoximine **6b** bearing an electron-withdrawing nitro group on the arene did not undergo cyclization at all, whereas **6c** having a more electron-rich aromatic ring led to the heterocyclic product in 74% yield (Table 2, entries 4 and 5, respectively). In the light of the reaction behavior of pyridine **5d**, which underwent smooth cyclization under standard reaction conditions (Table 1, entry 9), the low reactivity of **6d** was surprising. The yield of the desired product **7d** was only 16%, and prolonged reaction time decreased the yield, probably due to the decomposition of the product under the reaction conditions.

A comparison of the data presented in Tables 1 and 2 reveals that structural details of the substrates have a major impact on their reactivity. As found previously, acylated sulfoximines are prone to undergo cleavage reactions at the carbonyl imine bond [11]. Thus in

reactions with **6**, this cleavage could result in loss of starting material and decomposition of the corresponding product. Tables 1 and 2 also suggest that *N*-benzoylated sulfoximines **6** are less reactive towards cyclization reaction than their *N*-benzylated counterparts **5**. This observation can be attributed to two factors: The presence of an sp^2-hydridized carbon as linking unit between the sulfoximine and the arene part of **6**, which hampers the cyclization for steric reasons, and the electron-withdrawing capability of the carbonyl group in **6**, which reduces the nucleophilicity of the intermediate carbanion. The requirement of fine-tuned electronic properties has also been observed in intermolecular α-arylations of sulfones, where highly nucleophilic carbanions were found to be unreactive [12]. Entirely unsuccessful were direct palladium-catalyzed arylations of sulfoxides with haloarenes [13]. In our study, the importance of electronic factors was further apparent when comparing the cyclizations of **6b** and **6c**. For the former compound a smooth palladium insertion into the aryl halide bond can be expected due to the presence of the electron-withdrawing nitro substituent on the arene. The same group, however, slows down the subsequent cyclization step (of intermediate **9**), which requires a most nucleophilic carbanion at the sulfoximine methyl group. In this particular case, the second factor is so dominate that no heterocycle formation occurs (Table 2, entry 4).



9: X = CH_2 or C(O)

Apparently, the electronic factors are more balanced in **6c**. There, the palladium insertion reaction is more difficult, but the electron-donating capability of the methoxy substituent increases the nucleophilicity of intermediate carbanion, and the cyclization reaction affords the product in good yield (Table 2, entry 5).

3. Conclusion

A new synthesis of sulfoximine-based heterocycles by palladium catalyzed intramolecular α-arylations has been developed. The reaction scope has been investigated, and the relevant factors for an efficient catalytic process have been identified. Since sulfoximines have widely been recognized as most interesting reagents, auxiliaries and ligands in organic synthesis, the newly developed protocol expands the currently existing application repertoire of this highly useful heteroatomic molecular fragment by novel facettes.

4. Experimental

4.1. General

^{1}H- and ^{13}C-NMR (400 and 100 MHz, respectively) spectra were recorded in $CDCl_3$ using TMS as an internal standard on an Inova 400 spectrometer (or a Gemini 300 for ^{13}C-NMR only). Chemical shifts are given in ppm and spin–spin coupling constants, J, are given in Hz. IR spectra were recorded on a Perkin Elmer FTIR as KBr pellets. MS spectra were measured on a Varian MAT 212 and HRMS as well as SIMS-FAB spectra on a Finnigan MAT 95 mass spectrometer.

Sulfoximine **2** was prepared according to literature protocols [14].

4.2. Preparation of *5a* and *5c*

To a suspension of KH (48 mg, 1.2 mmol) in DME (10 ml), methylphenylsulfoximine (2, 155 mg, 1.0 mmol), Bn_4NBr (16 mg, 0.05 mmol), and 2-bromobenzylbromide (375 mg, 1.5 mmol) or 2-bromo-5-methoxybenzylbromide (420 mg, 1.5 mmol) were added at room temperature (r.t.). After stirring for ca. 16 h, water (20 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the resulting product was purified by chromatography using silica gel as stationary phase.

4.2.1. Compound *5a*

Colorless oil, 91% yield; R_f 0.46 (pentane: AcOEt = 1:2); ^{1}H-NMR ($CDCl_3$): δ 7.99–7.96 (m, 2H, Ar), 7.75 (d, J = 7.7 Hz, 1H, Ar), 7.68–7.56 (m, 3H, Ar), 7.50 (d, J = 8.0 Hz, Ar), 7.34 (t, J = 7.7 Hz, Ar), 7.11 (t, J = 8.0 Hz, 1H, Ar), 4.28 (d, J = 15.7 Hz, 1H, CH_2), 4.12 (d, J = 15.7 Hz, CH_2), 3.21 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 140.2 (C), 139.4 (C), 133.0 (C), 132.2 (CH), 129.5 (CH × 3), 128.6 (CH × 2), 128.0 (CH), 127.4 (CH), 123.1 (C), 47.5 (CH_2), 45.5 (CH_3); IR (neat): ν 1443, 1227, 1144, 980, 747 cm^{-1}; MS (EI), m/z (relative intensity): 325 ($[M+2]^+$, 13), 323 ($[M]^+$, 12); HRMS for $C_{14}H_{14}NOSBr$, Calc. $[M]^+$ 322.9980. Found $[M]^+$ 322.9978.

4.2.2. Compound *5c*

White powder, 94% yield; m.p. 96–98 °C; R_f 0.65 (pentane: AcOEt = 1:1); ^{1}H-NMR ($CDCl_3$): δ 7.96–7.90 (m, 2H, Ar), 7.63–7.50 (m, 3H, Ar), 7.35–7.32 (m, 2H, Ar), 6.62 (dd, J = 3.2, 8.7 Hz, 1H, Ar), 4.19 (d, J = 15.8 Hz, 1H, CH_2), 4.03 (d, J = 15.8 Hz, 1H, CH_2), 3,79 (s, 3H, CH_3), 3.17 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 159.1 (C), 141.3 (C), 139.3 (C), 133.1 (CH), 132.7 (CH), 129.5 (CH × 2), 128.6 (CH × 2), 115.2 (CH), 113.7 (CH), 113.3 (C), 55.5 (CH_3), 47.5 (CH_2), 45.3 (CH_3); IR (KBr): ν 1470, 1439, 1296, 1225,

1142, 743 cm^{-1}; MS (EI), *m/z* (relative intensity): 355 ($[M+2]^+$, 33), 353 ($[M]^+$, 29); Calc. for $C_{13}H_{13}N_2OSBr$: C, 50.86; H, 4.55; N, 3.95. Found C, 51.18; H, 4.92; N, 3.87%.

4.3. Preparation of **5b** and **5d**

$BH_3 \cdot SMe_2$ (890 μl, 2.0 mmol) was added to a solution of **6b** (383 mg, 1.0 mmol) or 6d (339 mg, 1.0 mmol) in THF (10 ml) at 0 °C, and the reaction temperature was allowed to rise to r.t. After stirring for ca. 16 h, an aqueous solution of NaOH (0.1 N, 10 ml) was added and the whole mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the resulting product was purified by chromatography using silica gel as stationary phase.

4.3.1. Compound **5b**

Pale brown powder, 91% yield; m.p. 131–133 °C; R_f 0.47 (ether); ^{1}H-NMR ($CDCl_3$): δ 8.66 (m, 1H, Ar), 8.00–7.91 (m, 3H, Ar), 7.70–7.56 (m, 4H, Ar), 4.28 (d, $J = 16.7$ Hz, 1H, CH_2), 4.06 (d, $J = 16.7$ Hz, 1H, CH_2), 3.27 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 147.4 (C), 142.7 (C), 138.9 (C), 133.4 (CH), 133.0 (CH), 129.9 (C), 129.7 (CH × 2), 128.5 (CH × 2), 124.1 (CH), 122.6 (CH), 47.0 (CH_2), 45.4 (CH_3); IR (KBr): *v* 1517, 1344, 1260, 1224, calcd. $[M]^+$ 323.9932. Found $[M]^+$ 323.9932.

4.4. Preparation of **5e**

To a solution of LDA (1.2 mmol) in THF (10 ml), a solution of **5a** (324 mg, 1.0 mmol) in THF (5 ml) was added at −78 °C. After stirring for 30 min at this temperature, *n*-BuI (138 μl, 1.2 mmol) was added and the reaction temperature was allowed to rise to r.t. After stirring for ca. 16 h, H_2O (20 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the resulting product was purified by chromatography using silica gel as stationary phase.

4.4.1. Compound **5e**

Yellowish powder, 82% yield; m.p. 68–70 °C; R_f 0.73 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 7.87 (bd, $J = 7.1$ Hz, 2H, Ar), 7.75 (br d, $J = 7.7$ Hz, 1H, Ar), 7.64–7.52 (m, 3H, Ar), 7.46 (dd, $J = 1.2$, 7.8 Hz, 1H, Ar), 7.31 (dt, $J = 1.2$, 7.4 Hz, 1H, Ar), 7.07 (br t, $J = 7.7$ Hz, 1H, Ar), 4.25 (d, $J = 15.9$ Hz, 1H, CH_2), 4.10 (d, $J = 15.9$ Hz, 1H, CH_2), 3.36–3.16 (m, 2H, CH_2), 1.88–1.77 (m, 1H, CH_2), 1.73–1.61 (m, 1H, CH_2), 1.38–1.23 (m, 4H, CH_2–CH_2–), 0.85 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 132.8 (CH), 131.9 (CH), 129.2 (CH × 2), 129.1 (CH × 2), 127.7 (CH), 127.1 (CH), 122.8 (CH), 56.8 (CH_2), 47.0 (CH_2), 30.3 (CH_2), 22.3 (CH_2), 22.1 (CH_2), 13.7 (CH_3); IR ($CHCl_3$): *v* 2956, 1443, 1263, 1227, 1142, 750 cm^{-1}; MS (EI) *m/z* (relative intensity): 338 ($[M - C_3H_7 + 2]^+$, 6), 336 ($[M - C_3H_7]^+$, 6); HRMS for $C_{18}H_{22}NOSBr$, Calc. $[M]^+$ 379.0605. Found $[M]^+$ 379.0605.

4.5. Preparation of **6a–d**

Et_3N (167 μl, 1.2 mmol), and a catalytic amount of DMAP, the aromatic acid chloride (1.1 mmol) were added to a CH_2Cl_2 (10 ml) solution of methylphenylsulfoximine (2, 155 mg, 1.0 mmol) at r.t. The reaction mixture was stirred for 5 h, and poured into water (20 ml). The mixture was extracted with CH_2Cl_2 (3 × 20 ml), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting product was purified by chromatography using silica gel as stationary phase.

4.5.1. Compound **6a**

White powder, 84% yield; m.p. 88.5–90.5 °C; R_f 0.58 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.15–8.10 (m, 2H, Ar), 7.81 (dd, $J = 1.7$, 7.7 Hz, 1H, Ar), 7.74–7.59 (m, 4H, Ar), 7.34 (dt, $J = 1.4$, 7.7 Hz, 1H, Ar), 7.25 (dt $J = 1.7$, 7.7 Hz, 1H, Ar), 3.50 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 174.7 (C), 138.1 (C × 2), 133.8 (CH), 133.5 (CH), 131.0 (CH), 130.4 (CH), 129.5 (CH × 2), 127.1 (CH × 2), 126.9 (CH), 120.1 (C), 44.3; IR (KBr): *v* 1635, 1297, 1256, 1216, 1144, 979, 744 cm^{-1}; MS (EI), *m/z* (relative intensity): 324 ($[M-CH_3+2]^+$, 1), 322 ($[M - CH_3]^+$, 1); Calc. for $C_{14}H_{12}NO_2SBr$: C, 49.72; H, 3.58; N, 4.14. Found C, 49.78; H, 3.53; N, 4.00%.

4.5.2. Compound **6b**

Yellowish powder, 89% yield; m.p. 167.5–168.5 °C; R_f 0.32 (Hexane: AcOEt = 1:1); ^{1}H-NMR ($CDCl_3$): δ 8.69 (d, $J = 2.7$ Hz, 1H, Ar), 8.13–8.07 (m, 3H, Ar), 7.83–7.60 (m, 4H, Ar), 3.52 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 172.5 (C), 146.8 (C), 139.3 (C), 137.8 (C), 135.1 (CH), 134.4 (CH), 129.9 (CH × 2), 128.1 (C), 127.2 (CH × 2), 125.6 (CH), 125.3 (CH), 44.3 (CH_3); IR ($CHCl_3$): *v* 1635, 1515, 1344, 1300, 1217, 1153, 972 cm^{-1}; MS (EI), *m/z* (relative intensity): 369 ($[M - CH_3 + 2]^+$, 0.7), 367 ($[M - CH_3]^+$, 0.6); Calc. for $C_{14}H_{11}N_2O_4SBr$: C, 43.88; H, 2.89; N, 7.31. Found C, 43.77; H, 3.00; N, 7.25%.

4.5.3. Compound **6c**

White powder, 91% yield; m.p. 95–97 °C; R_f 0.54 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.14–8.10 (m, 2H, Ar), 7.74–7.60 (m, 3H, Ar), 7.48 (d, $J = 8.7$ Hz, 1H, Ar), 7.33 (d, $J = 3.0$ Hz, 1H, Ar), 6.82 (dd, $J = 3.0$, 8.7 Hz, 1H, Ar), 3.80 (s, 3H, CH_3), 3.48 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 174.9 (C), 158.6 (C), 139.1 (C), 138.3 (C), 134.4 (CH), 134.1 (CH), 129.7 (CH × 2), 127.3 (CH × 2), 117.7 (CH), 115.4 (CH), 110.6 (C), 55.6 (CH_3), 44.2 (CH_3); IR (KBr): *v* 1627, 1573, 1469, 1403, 1317, 1260, 1217, 1116, 975 cm^{-1}; MS (EI), *m/z* (relative intensity):

369 ([M+2]$^+$, 22), 367 ([M]$^+$, 18); Calc. for $C_{15}H_{14}NO_3SBr$: C, 48.92; H, 3.83; N, 3.81. Found C, 48.97; H, 3.92; N, 3.81%.

4.5.4. Compound **6d**

White powder, 71% yield; m.p. 73.5–74.5 °C; R_f 0.39 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.44 (dd, $J = 1.9$, 4.7 Hz, 1H, Ar), 8.17 (dd, $J = 1.9$, 7.7 Hz, 1H, Ar), 8.13–8.08 (m, 2H, Ar), 7.76–7.62 (m, 3H, Ar), 7.30 (dd, $J = 4.7$, 7.7 Hz, 1H, Ar), 3.50 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 172.6 (C), 150.3 (CH), 148.5 (C), 139.4 (CH), 137.8 (C), 134.0 (CH), 132.7 (C), 129.6 (CH × 2), 127.1 (CH × 2), 122.0 (CH), 44.2 (CH_3); IR (KBr): ν 1636, 1396, 1276, 1216, 1154, 1056, 975 cm^{-1}; MS (EI), m/z (relative intensity): 325 ([M − CH_3 + 2]$^+$, 0.7), 323 ([M − CH_3]$^+$, 0.7); HRMS for $C_{13}H_{11}N_2O_2SBr$, Calc. [M − CH_3 + 2]$^+$ 324.9470. Found [M − CH_3 + 2]$^+$ 324.9480.

4.6. Typical reaction procedure for the palladium-catalyzed cyclization reaction

rac-BINAP (33 mg, 0.05 mmol), K_2CO_3 (276 mg, 2.0 mmol) or Cs_2CO_3 (652 mg, 2.0 mmol), and the substrate (0.5 mmol) were added toluene (5 ml) to the mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and the resulting suspension was stirred and heated to 100 °C. After the reaction time indicated in Tables 1 and 2, the reaction mixture was cooled to r.t., and water (10 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 ml), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting product was purified by chromatography using silica gel as stationary phase.

4.6.1. Compound **7a**

White powder; m.p. 88–90 °C; R_f 0.43 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 7.81 (m, 1H, Ar), 7.78 (m, 1H, Ar), 7.58 (br t, $J = 7.4$ Hz, 1H, Ar), 7.46 (br t, $J = 7.4$ Hz, 2H, Ar), 7.34 (br d, $J = 4.0$ Hz, 2H, Ar), 7.25 (m, 1H, Ar), 7.06 (br d, $J = 7.4$ Hz, 1H, Ar), 4.77 (d, $J = 15.8$ Hz, 1H, CH_2), 4.68 (d, $J = 15.8$ Hz, 1H, CH_2), 4.41 (d, $J = 15.3$ Hz, 1H, CH_2), 4.13 (d, $J = 15.3$ Hz, 1H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 140.3 (C), 138.2 (C), 133.4 (CH), 129.9 (CH × 5), 128.6 (C), 128.1 (CH), 127.0 (CH), 126.7 (CH), 54.0 (CH_2), 49.1 (CH_2); IR ($CHCl_3$) 1652, 1241, 1190, 1120, 753 cm^{-1}; MS (EI), m/z (relative intensity): 243 ([M]$^+$, 25); HRMS for $C_{14}H_{13}NOS$, Cacl. [M]$^+$ 243.0718. Found [M]$^+$ 243.0717.

4.6.2. Compound **7b**

White powder: m.p. 165–166 °C; R_f 0.30 (pentane: AcOEt = 1:1); ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, $J = 2.4$ Hz, 1H, Ar), 8.12 (dd, $J = 2.4$, 8.4 Hz, 1H, Ar), 7.86–7.80 (m, 2H, Ar), 7.64 (tt, $J = 1.2$, 7.4 Hz, 1H, Ar), 7.55–7.47 (m, 2H, Ar), 7.20 (d, $J = 8.4$ Hz, 1H, Ar), 4.83 (s, 2H, CH_2), 4.50 (d, $J = 15.8$ Hz, 1H, CH_2), 4.20 (d, $J = 15.8$ Hz, 1H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 147.5 (C), 139.8 (C), 139.4 (C), 135.9 (C), 133.9 (CH), 130.2 (CH), 129.4 (CH × 2), 129.1 (CH × 2), 122.1 (CH), 121.7 (CH), 53.9 (CH_2), 48.8 (CH_2); IR (KBr) 1521, 1345, 1228, 1189, 1124, 733 cm^{-1}; MS (EI), m/z (relative intensity): 288 ([M]$^+$, 15); HRMS of $C_{14}H_{12}N_2O_3S$, Calc. [M]$^+$ 288.0569. Found [M]$^+$ 288.0569.

4.6.3. Compound **7c**

Pale brown powder; m.p. 120–121 °C; R_f 0.28 (pentane: AcOEt = 1:1); ^{1}H-NMR ($CDCl_3$): δ 7.72–7.67 (m, 2H, Ar), 7.48 (tt, $J = 1.2$, 7.4 Hz, 1H, Ar), 7.40–7.35 (m, 2H, Ar), 6.88 (d, $J = 8.2$ Hz, 1H, Ar), 6.80 (d, $J = 2.7$ Hz, 1H, Ar), 6.68 (dd, $J = 2.7$, 8.2 Hz, 1H, Ar), 4.63 (d, $J = 15.6$ Hz, 1H, CH_2), 4.53 (d, $J = 15.6$ Hz, 1H, CH_2), 4.26 (d, $J = 15.1$ Hz, 1H, CH_2), 3.97 (d, $J = 15.1$ Hz, 1H, CH_2), 3.74 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 159.5 (C), 140.3 (C), 139.7 (C), 133.3 (CH), 130.0 (CH), 129.0 (CH × 4), 120.5 (C), 112.7 (CH), 112.2 (CH), 55.4 (CH_3), 53.6 (CH_2), 49.5 (CH_2); IR (KBr) 1604, 1498, 1445, 1262, 1231, 1118, 841, 797 cm^{-1};MS (EI), m/z (relative intensity): 273 ([M]$^+$, 3); Calc. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found C, 66.18; H, 5.52; N, 5.00%.

4.6.4. Compound **7d**

Colorless oil; R_f 0.22 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.45 (dd, $J = 1.6$, 4.8 Hz, 1H, Ar), 7.91–7.87 (m, 2H, Ar), 7.64–7.46 (m, 4H, Ar), 7.27 (dd, $J = 4.8$, 7.7 Hz, 1H, Ar), 4.80 (d, $J = 16.6$ Hz, 1H, CH_2), 4.70 (d, $J = 16.6$ Hz, 1H, CH_2), 4.58 (d, $J = 16.0$ Hz, 1H, CH_2), 4.32 (d, $J = 16.0$ Hz, 1H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 148.4 (C), 148.1 (CH), 139.7 (C), 134.3 (CH), 133.7 (CH), 132.9 (C), 129.3 (CH × 2), 128.8 (CH × 2), 123.1 (CH), 56.2 (CH_2), 47.6 (CH_2); IR ($CHCl_3$) 1440, 1234, 1139, 1119, 752 cm^{-1}; MS (EI), m/z (relative intensity): 244 ([M]$^+$, 63%); HRMS for $C_{13}H_{12}N_2OS$, Calc. [M]$^+$ 244.0670, Found 244.0671.

4.6.5. Compound **7e**

Colorless oil; R_f 0.26 (pentane: AcOEt = 1:1); ^{1}H-NMR ($CDCl_3$): δ 7.90–6.90 (m, 18H, Ar), 4.90 (d, $J = 15.9$ Hz, 1H, CH_2), 4.77 (d, $J = 16.8$ Hz, 1H, CH_2), 4.72 (d, $J = 16.8$ Hz, 1H, CH_2), 4.65 (d, $J = 15.9$ Hz, 1H, CH_2), 4.10–4.00 (m, 2H, CH × 2), 2.50 (m, 1H, CH_2), 1.80–1.18 (m, 11H, CH_2), 0.84 (t, $J = 7.2$ Hz, 3H, CH_3), 0.78 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ137.8 (C), 137.7 (C), 133.3–125.8 (C × 4, CH × 18), 63.3 (CH), 62.7 (CH), 50.2 (CH_2), 49.1 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.2 (CH_2), 14.0 (CH_3), 13.9 (CH_3); IR ($CHCl_3$) 2957, 1446, 1236, 1126, 752, 695 cm^{-1}; MS (EI), m/z (relative intensity): 299 ([M]$^+$, 6%); HRMS of $C_{13}H_{12}N_2OS$, Calc. [M]$^+$ 299.1344. Found 299.1343.

4.6.6. Compound **8a**

White powder, m.p. 148–149 °C; R_f 0.43 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.31 (m, 1H, Ar), 8.17–8.13 (m, 2H, Ar), 7.77 (t, $J = 7.6$ Hz, 1H, Ar), 7.66 (t, $J = 7.6$ Hz, 2H, Ar), 7.58–7.53 (m, 2H, Ar), 7.25 (m, 1H, Ar), 4.60 (d, $J = 15.4$ Hz, 1H, CH_2), 4.50 (d, $J = 15.4$ Hz, 1H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 167.5 (C), 136.6 (C), 135.2 (CH), 132.9 (CH), 130.2 (CH), 130.0 (CH × 3), 129.3 (CH), 128.8 (CH × 2), 128.8 (C), 127.3 (C), 53.4 (CH_2); IR (KBr) 1639, 1311, 1279, 1148, 1131, 982 cm^{-1}; MS (EI), *m*/*z* (relative intensity): 257 ([M]$^+$, 83%); Calc. for $C_{14}H_{11}NO_2S$: C, 65.36; H, 4.31; N, 5.44. Found C, 65.36; H, 4.40; N, 5.30%.

4.6.7. Compound **8c**

Yellow powder, m.p. 192.5–194 °C; R_f 0.41 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.20–8.10 (m, 2H, Ar), 7.81–7.60 (m, 4H, Ar), 7.15 (d, $J = 8.4$ Hz, 1H, Ar), 7.06 (dd, $J =$ 2.7, 8.4 Hz, 1H, Ar), 4.55 (d, $J = 15.1$ Hz, 1H, CH_2), 4.44 (d, $J = 15.1$ Hz, 1H, CH_2), 3,87 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 167.6 (C), 160.5 (C), 136.3 (C), 134.9 (CH), 130.3 (CH), 129.8 (C), 129.7 (CH × 2), 128.6 (CH × 2), 120.2 (CH), 118.9 (C), 113.2 (CH), 55.7 (CH_3), 52.6 (CH_2); IR (KBr) 1655, 1603, 1493, 1323, 1281, 1236 cm^{-1}; MS (EI), *m*/*z* (relative intensity): 287 ([M]$^+$, 41%); Calc. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found C, 62.62; H, 4.80; N, 4.62%.

4.6.8. Compound **8d**

Yellow oil; R_f 0.23 (AcOEt); ^{1}H-NMR ($CDCl_3$): δ 8.72 (dd, $J = 1.7$, 4.7 Hz, 1H, Ar), 8.59 (dd, $J = 1.7$, 7.9 Hz, 1H, Ar), 8.20–8.16 (m, 2H, Ar), 7.81 (t, $J = 7.4$ Hz, 1H, Ar), 7.69 (t, $J = 7.4$ Hz, 2H, Ar), 7.53 (dd, $J = 4.7$, 7.9 Hz, 1H, Ar), 4.83 (d, $J = 15.8$ Hz, 1H, CH_2), 4.59 (d, $J = 15.8$ Hz, 1H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 167.0 (C), 153.0 (CH), 138.6 (C), 137.6 (CH), 136.2 (C), 135.2 (CH), 130.0 (CH × 2), 128.6 (CH × 2), 125.0 (CH), 125.3 (C), 55.3 (CH_2); IR ($CHCl_3$) 1656, 1302, 1235, 1146, 982, 752 cm^{-1}; MS (EI), *m*/*z* (relative intensity): 258 ([M]$^+$, 62); HRMS for $C_{13}H_{11}N_2O_2S$, calcd. [M]$^+$ 258.0463. Found 258.0463.

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