Synthesis of Unsymmetrical Polysubstituted Pyridines from β-Sulfonylvinylamines via 1-Aza-Allyl Anion Intermediates

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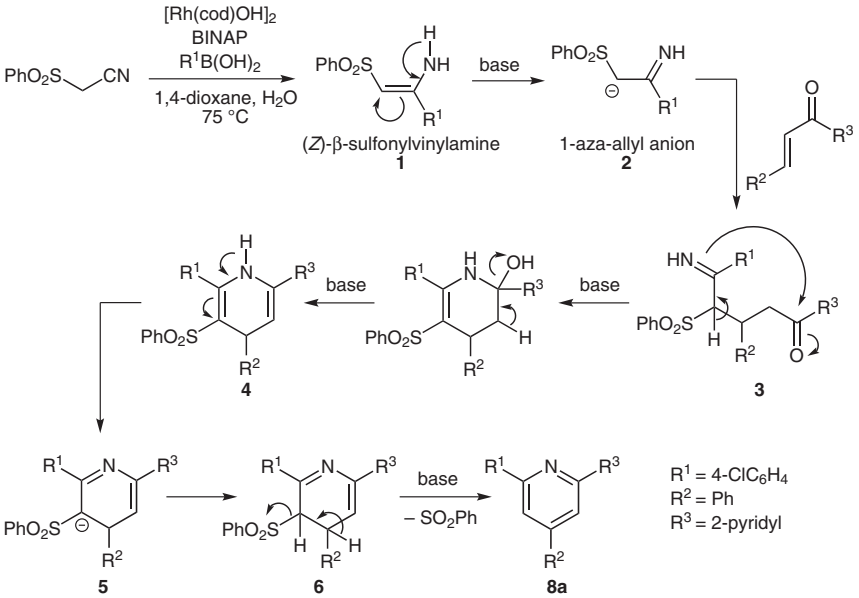
Abstract: A modular synthesis of highly functionalized unsymmetrical pyridines has been developed from reacting β-sulfonylvinylamines with α,β-unsaturated systems in the presence of base via the formation of 1-aza-allyl anion intermediates.

Key words: β-sulfonylvinylamines, 2,4,6-triarylpyridines, 1-aza-allyl anions, α,β-unsaturated ketones, cascade reactions

Pyridines possessing a 2,4,6-triaryl substitution pattern are of immense interest owing to their diverse roles in biology,[1,2] material science,[3,4] and potential in homogeneous catalysis.[5] While there have been many reported protocols[6] to form symmetrical pyridine derivatives, the synthesis of unsymmetrical pyridines is significantly less developed. Existing methods[7] in the construction of unsymmetrical pyridines typically suffer from low yields, limited scope, or poor regioselectivity.

Utilizing (*Z*)-β-sulfonylvinylamine **1** formed from a previously discovered[8] rhodium(I)-catalyzed addition of arylboronic acids to (arylsulfonyl)acetonitriles and inspired by Feringa's dihydropyridine synthesis,[9] we have developed a cascade reaction in which the resulting amines are reacted with various α,β-unsaturated substrates to form unsymmetrical pyridines (Scheme 1). The mechanism proposed for this remarkable transformation can be rationalized by first generating the 1-aza-allyl anion[10] synthon **2** with base followed by Michael addition of the resulting carbanion[11] to chalcone producing imine **3**. Additional base facilitates condensation of this imine to the carbonyl group to form dihydropyridine **4** and upon deprotonation, tautomerization places the resulting anion in a stabilized position adjacent to the electron-withdrawing sulfone moiety. Finally, aromatization of **6**, via elimination of sulfinic acid, results in the formation of pyridine **8a**.

For preliminary studies, variation in the type and equivalents of base, temperature, and solvent were screened in the synthesis of 2,4,6-triphenylpyridine.[12] Sodium hydroxide proved to be the ideal base as higher temperatures were tolerated without a reduction in yield, which allowed for significantly shorter reaction times. With a set of optimized reaction conditions in hand, the scope of unsymmetrical pyridines was subsequently studied (Table 1). We were able to illustrate that a diverse array of these de-



Scheme 1

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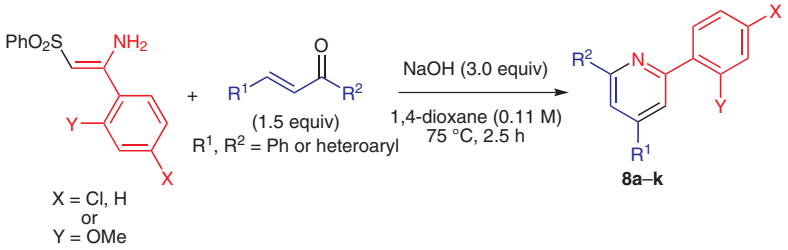
sirable pyridines could be synthesized in moderate to good yields. This reaction provides access to structurally novel bipyridyl derivatives that may serve as tri- and bidentate ligands in homogeneous catalysis. In addition, the presence of halogenated substituents provides synthetically useful handles for construction of increasingly complex pyridines and allows for further functionalization such as the introduction of chiral components for potential applications in asymmetric catalysis.

Table 1 Synthesis of Unsymmetrical Pyridines



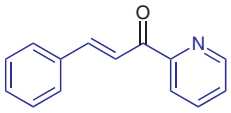
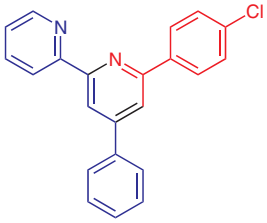
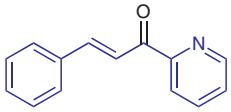
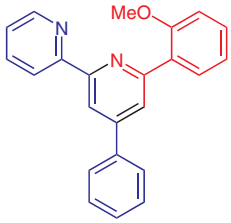
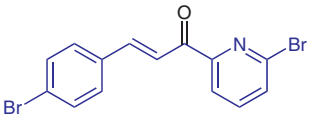
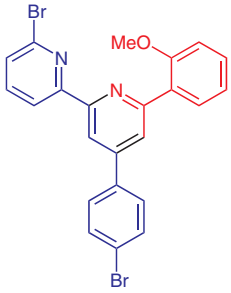
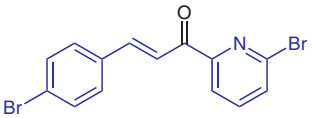
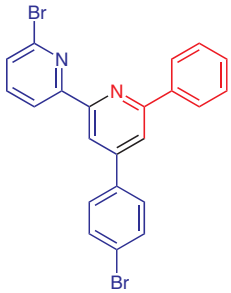
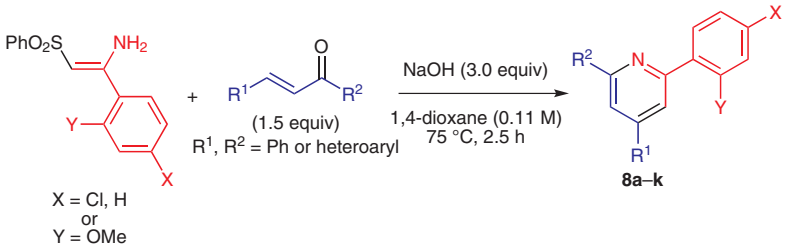
Entry	Substrate	Product	Yield (%)[a]
1	 **7a**	 **8a**	78
2	 **7a**	 **8b**	75[b]
3	 **7b**	 **8c**	73[b]
4	 **7b**	 **8d**	85[b]

Table 1 Synthesis of Unsymmetrical Pyridines (continued)



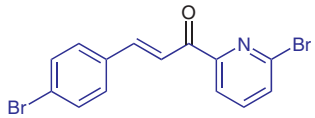
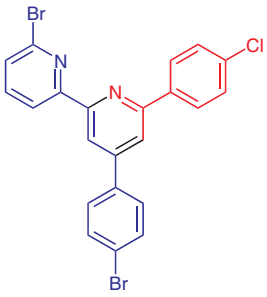
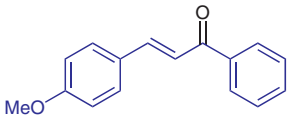
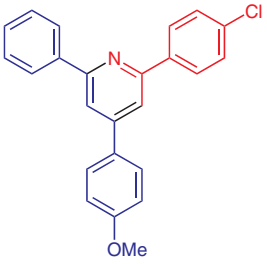
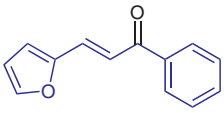
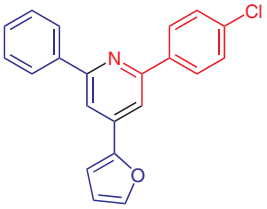
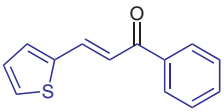
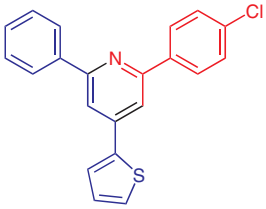
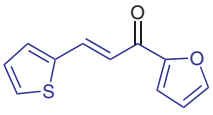
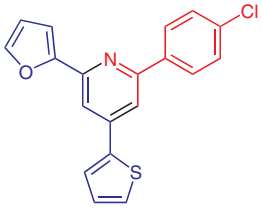
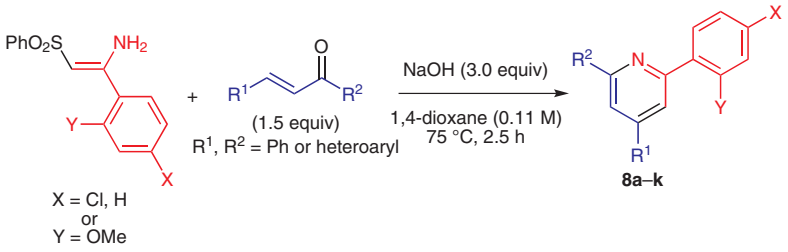
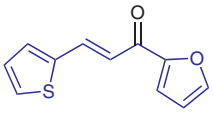
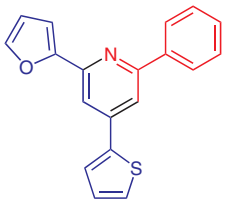
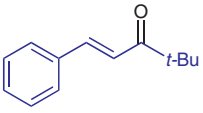
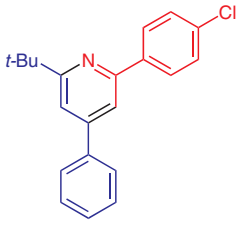
Entry	Substrate	Product	Yield (%)[a]
5	 **7b**	 **8e**	87[b]
6	 **7c**	 **8f**	72
7	 **7d**	 **8g**	72
8	 **7e**	 **8h**	64
9	 **7f**	 **8i**	55

Table 1 Synthesis of Unsymmetrical Pyridines (continued)



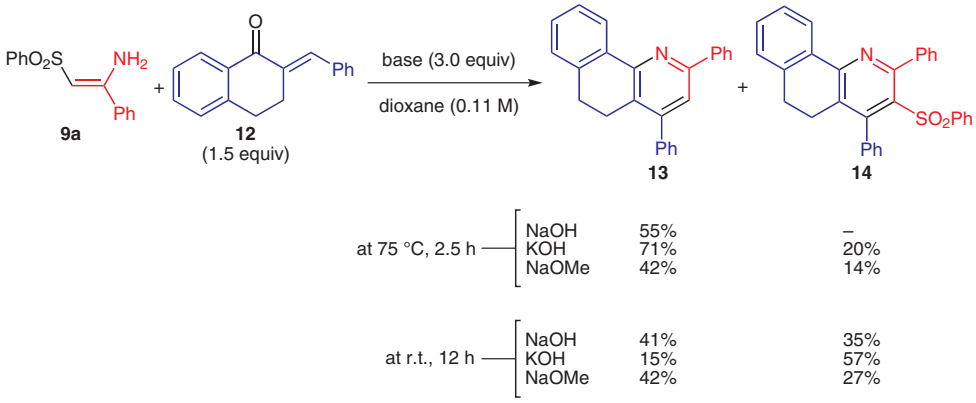
Entry	Substrate	Product	Yield (%)[a]
10	 **7f**	 **8j**	81[b]
11	 **7g**	 **8k**	72[c]

[a] Isolated yields.
[b] Reaction performed at r.t. over 14 h.
[c] KOH was used and the mixture heated at 75 °C over 5 h.

Investigations pertaining to the synthesis of diarylmonoalkyl substituted unsymmetrical pyridines showed that alkylated product **8k** can be formed from α,β-unsaturated substrate **7g** in 72% yield. Variants of **7g** possessing α-hydrogens such as isopropyl and methyl groups resulted in significantly lower yields, and occurrence of aldol condensations was observed especially at room temperature.

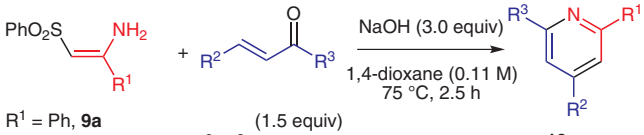
We also investigated the effects of the aryl substituent groups on (*Z*)-β-sulfonylvinylamine **9** and chalcone derivatives (Table 2). In general, electron-rich and chloride substituents resulted in good yields (Table 2, entries 1, 3, 4, and 6) whereas nitro substituents led to low yields (entries 2 and 5). On the other hand, electron-donating, electron-withdrawing, and chloride substituents on **9** were all tolerated to afford the desired product in good yields (entries 7–9).

Heteroaryl containing pyridines were also successfully synthesized in good yields. In addition to the incorporation of typical heteroaryl groups (furyl, thienyl, and pyridyl), the reaction also allows introduction of two furyl substituents in the final product (entry 13) as well as an unprotected pyrrole group (entry 12).



Scheme 2

Table 2 Scope of Chalcones and β-Sulfonylvinylamines



R^1 = Ph, **9a**
= 4-$MeOC_6H_4$, **9b**
= 4-$F_3CC_6H_4$, **9c**
= 4-ClC_6H_4, **9d**

R^2, R^3 = aryl or heteroaryl

Entry	R^1	R^2	R^3	Yield (%)[a]
1	Ph	4-$MeOC_6H_4$	Ph	**10a**, 86
2	Ph	4-$O_2NC_6H_4$	Ph	**10b**, 34[b]
3	Ph	4-ClC_6H_4	Ph	**10c**, 93
4	Ph	Ph	4-$MeOC_6H_4$	**10d**, 85
5	Ph	Ph	4-$O_2NC_6H_4$	**10e**, 20
6	Ph	Ph	4-ClC_6H_4	**10f**, 95
7	4-$MeOC_6H_4$	Ph	Ph	**10g**, 80
8	4-$F_3CC_6H_4$	Ph	Ph	**10h**, 70
9	4-ClC_6H_4	Ph	Ph	**10i**, 90
10	Ph	2-furyl	Ph	**10j**, 77
11	Ph	2-thienyl	Ph	**10k**, 87
12	Ph	2-pyrrolyl	Ph	**10l**, 81
13	Ph	2-furyl	2-furyl	**10m**, 88
14	Ph	Ph	2-pyridyl	**10n**, 75

[a] Isolated yields.
[b] Obtained in 57% yield with KOH.

When a tetralone-based α,β-unsaturated system **12** (a 'fused' chalcone substrate) was reacted with β-sulfonylvinylamine **9a** under the previously optimized reactions conditions, the expected polycyclic product **13** was obtained in 55% yield (Scheme 2).

However, at room temperature, we observed formation of sulfonylated product **14**. In order to determine if the sulfonylated compound is a potential intermediate along the mechanistic pathway leading to formation of **13**, pure **14** was subjected to the optimized conditions, and only starting material was recovered. This observation shows that **14** is not an intermediate of **13** and implies that **14** could possibly be a kinetic product formed from an oxidation process formally removing hydrogen leading to its aromatization. Potassium hydroxide afforded the highest yield of either the desired product **13** (71%) or the sulfonylated product **14** (57%) when the appropriate reaction conditions were applied.

In summary, we have developed a modular synthesis of unsymmetrical polysubstituted pyridines, which tolerates a wide variety of functionality. This has led to the synthesis of novel pyridine products, which are potentially useful building blocks in the design of more complex heterocycles as well as ligands for catalysis. The utility of these compounds are currently under investigation.

TLC was performed with Silicycle normal phase glass plates (0.25 mm, 60-A pore size, 230–400 mesh). Purification of reaction products was generally done by flash chromatography with Silicycle Ultra-Pure 230–400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 23 °C with a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe. IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. High-resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected.

Polysubstituted Pyridine Derivatives 8; General Procedure

To a 2-dram vial equipped with a magnetic stir bar was added the β-sulfonylvinylamine (0.20 mmol) followed by the α,β-unsaturated substrate (0.30 mmol) and 1,4-dioxane (1.8 mL). The reaction was allowed to stir for 5 min before adding the appropriate base (0.60 mmol) as a solid and heated in a 75 °C oil bath for 2.5 h. The solvent was removed in vacuo and the crude was purified by flash column chromatography on silica gel (hexanes–EtOAc, 9:1) (Table 1).

8a

Yellow solid; yield: 54 mg (78%); mp 135–136 °C.

IR (film): 3085, 3058, 3036, 2962, 2928, 1601, 1567, 1550, 1474, 1442, 1402, 1383, 1102, 1091, 1013, 824, 795, 744, 695, 671, 619, 496 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (m, 1 H), 8.62–8.66 (m, 2 H), 8.14 (d, *J* = 8.0 Hz, 2 H), 7.93 (d, *J* = 2.0 Hz, 1 H), 7.77–7.87 (m, 3 H), 7.45–7.54 (m, 5 H), 7.33 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.60, 156.37, 156.08, 150.67, 149.33, 138.82, 138.11, 137.10, 135.39, 129.31, 129.26, 129.13, 128.55, 127.46, 124.12, 121.67, 118.43, 118.01.

HRMS (ESI): *m/z* calcd for $C_{22}H_{15}ClN_2$ [MH^+]: 343.0924; found: 343.1002.

8b

Colorless oil; yield: 51 mg (75%).

IR (film): 3059, 3032, 3008, 2960, 2936, 2835, 1603, 1584, 1550, 1492, 1394, 1246, 1119, 761, 620 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (m, 1 H), 8.62 (m, 2 H), 8.14 (d, *J* = 1.6 Hz, 1 H), 8.03 (dd, *J* = 9.2, 1.6 Hz, 1 H), 7.78–7.85 (m, 3 H), 7.36–7.55 (m, 4 H), 7.30 (m, 1 H), 7.14 (dt, *J* = 7.2, 0.8 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.51, 156.80, 156.32, 155.95, 149.23, 149.21, 139.27, 137.02, 131.73, 130.25, 129.50, 129.15, 128.98, 127.58, 123.83, 123.50, 121.73, 121.31, 117.34, 111.83, 56.00.

HRMS (ESI): *m/z* calcd for $C_{23}H_{18}N_2O$ [MH^+]: 339.1419; found: 339.1499.

8c

White solid; yield: 72 mg (73%); mp 161–162 °C.

IR (film): 3050, 3006, 2960, 2935, 2909, 2856, 2834, 1649, 1635, 1604, 1575, 1553, 1543, 1492, 1407, 1383, 1245, 1125, 1073, 1010, 800, 672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (dd, *J* = 7.6, 0.8 Hz, 1 H), 8.51 (d, *J* = 1.6 Hz, 1 H), 8.10 (d, *J* = 1.6 Hz, 1 H), 7.99 (dd, *J* = 6.0, 1.6 Hz, 1 H), 7.60–7.69 (m, 5 H), 7.49 (dd, *J* = 8.0, 0.8 Hz, 1 H),

7.38–7.45 (m, 1 H), 7.14 (dt, *J* = 7.6, 0.8 Hz, 1 H), 7.04 (d, *J* = 8 Hz, 1 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.81, 157.45, 156.16, 154.82, 148.16, 141.70, 139.34, 137.99, 132.37, 131.65, 130.50, 129.16, 128.96, 128.18, 123.71, 123.52, 121.32, 120.38, 117.30, 111.80, 55.98.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{16}Br_2N_2O$ [MH$^+$]: 494.9629; found: 494.9717.

8d

White solid; yield: 79 mg (85%); mp 177–180 °C.

IR (film): 3100, 3050, 3015, 2980, 2962, 2925, 2854, 1604, 1598, 1574, 1551, 1490, 1408, 1383, 1123, 1074, 1009, 822, 799, 773, 692, 642 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 7.6, 0.4 Hz, 1 H), 8.51 (d, *J* = 1.2 Hz, 1 H), 8.15 (m, 2 H), 7.9 (d, *J* = 1.6 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.64 (s, 4 H), 7.42–7.55 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.37, 154.81, 149.22, 141.56, 139.21, 139.03, 137.47, 132.26, 129.36, 128.86, 128.83, 128.20, 127.08, 123.59, 120.23, 118.67, 117.53.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{14}Br_2N_2$ [MH$^+$]: 464.9524; found: 464.9615.

8e

White solid; yield: 87 mg (87%); mp 210–213 °C.

IR (film): 3099, 3054, 3020, 2991, 2943, 2915, 2888, 1654, 1635, 1623, 1616, 1604, 834, 817, 798, 729, 694, 579 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (dd, *J* = 7.6, 0.8 Hz, 1 H), 8.52 (d, *J* = 1.2 Hz, 1 H), 8.09 (m, 2 H), 7.86 (d, *J* = 1.6 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.64 (s, 4 H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.34, 156.31, 155.09, 149.60, 141.79, 139.40, 137.61, 137.47, 135.68, 132.49, 129.18, 129.01, 128.50, 123.91, 120.35, 118.56, 117.96.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{13}Br_2ClN_2$ [MH$^+$]: 498.9134; found: 498.9213.

8f

Yellow solid; yield: 54 mg (72%); mp 164–166 °C.

IR (film): 3084, 3063, 3039, 3004, 2958, 2932, 2836, 1700, 1583, 1428, 1291, 1237, 1180, 1090, 1031, 1013, 776, 755, 693, 570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.20 (m, 4 H), 7.85 (d, *J* = 1.6 Hz, 1 H), 7.79 (d, *J* = 1.6 Hz, 1 H), 7.68 (m, 2 H), 7.41–7.54 (m, 5 H), 7.01–7.07 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.77, 157.77, 156.39, 150.03, 139.74, 138.33, 135.28, 131.31, 129.31, 129.06, 128.94, 128.59, 128.54, 127.32, 117.06, 116.54, 114.79, 55.66.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{18}ClNO$ [MH$^+$]: 372.1077; found: 372.1155.

8g

Orange solid; yield: 48 mg (72%); mp 135–137 °C.

IR (film): 3117, 3086, 3063, 3038, 2922, 2850, 1611, 1546, 1490, 1012, 832, 736, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.20 (m, 4 H), 7.91 (d, *J* = 1.6 Hz, 1 H), 7.88 (d, *J* = 1.6 Hz, 1 H), 7.57–7.59 (m, 1 H), 7.42–7.54 (m, 5 H), 6.97 (dd, *J* = 4.0, 1.6 Hz, 1 H), 6.57 (dd, *J* = 4.0, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.81, 156.45, 151.99, 143.93, 139.48, 139.39, 138.07, 135.40, 129.42, 129.05, 128.93, 128.53, 127.25, 113.43, 112.92, 112.38, 108.86.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{14}ClNO$ [MH$^+$]: 332.0764; found: 332.0842.

8h

White solid; yield: 47 mg (64%); mp 145–147 °C.

IR (film): 3106, 3085, 3065, 3039, 2953, 2923, 2851, 1580, 1574, 1527, 1436, 1424, 1102, 1092, 1014 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.16 (m, 4 H), 7.86 (d, *J* = 1.6 Hz, 1 H), 7.81 (d, *J* = 1.6 Hz, 1 H), 7.60 (dd, *J* = 2.4, 1.6 Hz, 1 H), 7.42–7.55 (m, 6 H), 7.17 (dd, *J* = 4.0, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.04, 156.65, 143.37, 141.95, 139.40, 137.99, 135.47, 129.49, 129.09, 128.97, 128.65, 128.58, 127.30, 127.29, 125.58, 115.76, 115.25.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{14}ClNS$ [MH$^+$]: 348.0535; found: 348.0608.

8i

Orange solid; yield: 39 mg (55%); mp 122–123 °C.

IR (film): 3112, 3073, 2955, 2924, 2853, 1608, 1577, 1572, 1548, 1424, 1405, 1221, 1093, 1013, 828, 754, 744, 703, 592, 556 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (m, 2 H), 7.84 (d, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.60 (dd, *J* = 2.6, 1.2 Hz, 1 H), 7.57 (dd, *J* = 2.6, 1.0 Hz, 1 H), 7.42–7.48 (m, 3 H), 7.22 (dd, *J* = 2.6, 0.8 Hz, 1 H), 7.16 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.57 (dd, *J* = 2.0, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.61, 153.78, 149.94, 143.43, 143.04, 141.53, 137.57, 135.34, 128.90, 128.44, 128.37, 127.18, 125.52, 114.81, 113.40, 112.17, 109.32.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{12}ClNOS$ [MH$^+$]: 338.0328; found: 338.0400.

8j

Orange solid; yield: 49 mg (81%); mp 96–97 °C.

IR (film): 3108, 3087, 3066, 3040, 3012, 2957, 2924, 2853, 1612, 1549, 1538, 1525, 1016, 742, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (m, 2 H), 7.84 (s, 1 H), 7.77 (s, 1 H), 7.61 (d, *J* = 4.0 Hz, 1 H), 7.56 (s, 1 H), 7.40–7.53 (m, 4 H), 7.24 (m, 1 H), 7.16 (m, 1 H), 6.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.91, 154.00, 149.91, 143.31, 142.89, 141.78, 139.20, 129.23, 128.74, 128.40, 127.12, 127.03, 125.41, 115.15, 113.21, 112.15, 109.21.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{13}NOS$ [MH$^+$]: 304.0718; found: 304.0790.

8k

Colorless oil; yield: 46 mg (72%).

IR (film): 3075, 3053, 2962, 2924, 2899, 1656, 1635, 1604, 1595, 1551, 1492, 1403, 1091, 1012, 877, 734, 697, 616, 588, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (m, 2 H), 7.71 (d, *J* = 1.6 Hz, 1 H), 7.66 (m, 2 H), 7.41–7.53 (m, 6 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.92, 155.06, 149.89, 139.73, 138.60, 135.00, 129.25, 128.97, 128.96, 128.46, 127.42, 116.29, 115.50, 38.09, 30.53.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}ClN$ [MH$^+$]: 322.1284; found: 322.1354.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(11) Initial C-alkylation at the β-carbon of 1-aza-allyl anions is typically observed over N-alkylation; see ref. 10c.

(12) See Supporting Information for additional details relating to the optimization process.