PdI_2/I_2-Catalyzed Thiolation-Annulation of 2-Alkynylbenzyl Azides with Disulfides: Selective Synthesis of 4-Sulfenylisoquinolines

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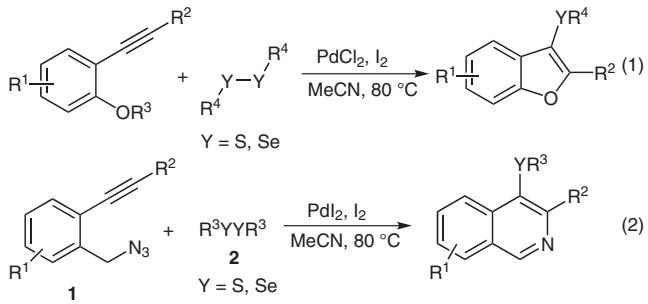
Abstract: A PdI_2/I_2-catalyzed thiolation-annulation route of alkynes with azides and disulfides for the synthesis of 4-sulfenylisoquinolines is described. This route allows numerous 2-alkynylbenzyl azides to react with disulfides or 1,2-diphenyldiselane leading to the corresponding 4-chalcogen-substituted isoquinolines in moderate to good yields.

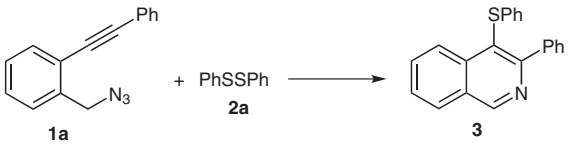
Key words: palladium, iodine, thiolation, annulation, 2-alkynylbenzyl azides, disulfides, isoquinolines

Intramolecular annulation of alkynes, particularly electrophilic annulation of alkynes, has become one of the most important methods in organic synthesis because it provides excellent opportunities for the construction of carbocycles and heterocycles from readily accessible substrates by simple initiation with excellent selectivity.[1–5] This intramolecular annulation method is also applied in the synthesis of the isoquinoline nucleus,[1–6] which is widely present in many natural products and biologically active molecules.[6] For example, Larock's group have reported that a wide range of 3,4-disubstituted isoquinolines were synthesized by Pd-catalyzed annulation of alkynes (or allenes) with aldehydes and *tert*-butylamine.[2] Interestingly, recent results have demonstrated that 2-alkynylbenzyl azides were suitable substrates for the synthesis of isoquinoline derivatives by either Lewis acid catalyzed intramolecular annulation[3c,g] or electrophilic iodocyclization transformations.[4] Liang's group[3c] and Yamamoto's group[3g] independently have reported Ag or Au/Ag-catalyzed cyclization of 2-alkynylbenzyl azides leading to 1,3-disubstituted isoquinolines. Yamamoto's group have employed 2-alkynylbenzyl azides to construct the 1,3-disubstituted 4-haloisoquinoline skeleton via an electrophilic



Scheme 1 Synthesis of chalcogen-substituted compounds

Table 1 Screening of Optimal Conditions in the Reaction of **1a** with **2a**[a]



Entry	[Pd] (mol%)	Additive (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	$PdCl_2$ (5)	–	MeCN	80	trace
2	$PdCl_2$ (5)	I_2 (2)	MeCN	80	35
3	–	I_2 (2)	MeCN	80	12
4	PdI_2 (5)	I_2 (2)	MeCN	80	73
5	PdI_2 (5)	–	MeCN	80	6
6	$PdBr_2$ (5)	I_2 (2)	MeCN	80	40
7	PdI_2 (5)	I_2 (3)	MeCN	80	70
8	PdI_2 (5)	I_2 (1)	MeCN	80	53
9	PdI_2 (5)	NIS (2)	MeCN	80	50
10	PdI_2 (5)	ICl (2)	MeCN	80	43
11	PdI_2 (5)	*n*-Bu_4NI (2)	MeCN	80	trace
12	PdI_2 (5)	I_2 (2)	MeCN	60	64
13	PdI_2 (5)	I_2 (2)	MeCN	100	61
14	PdI_2 (5)	I_2 (2)	DMSO	80	36
15	PdI_2 (5)	I_2 (2)	1,4-dioxane	80	trace
16	PdI_2 (5)	I_2 (2)	DCE	80	60
17	PdI_2 (5)	I_2 (2)	toluene	80	60
18	PdI_2 (10)	I_2 (2)	MeCN	80	75
19	PdI_2 (1)	I_2 (2)	MeCN	80	28

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), [Pd], additive, and solvent (2 mL) for 22 h under N_2 atmosphere.
[b] Isolated yield.

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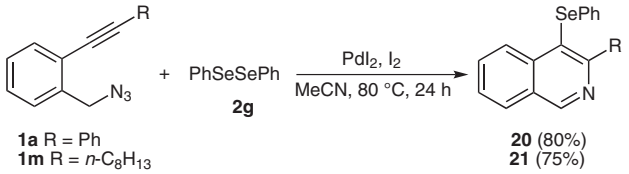
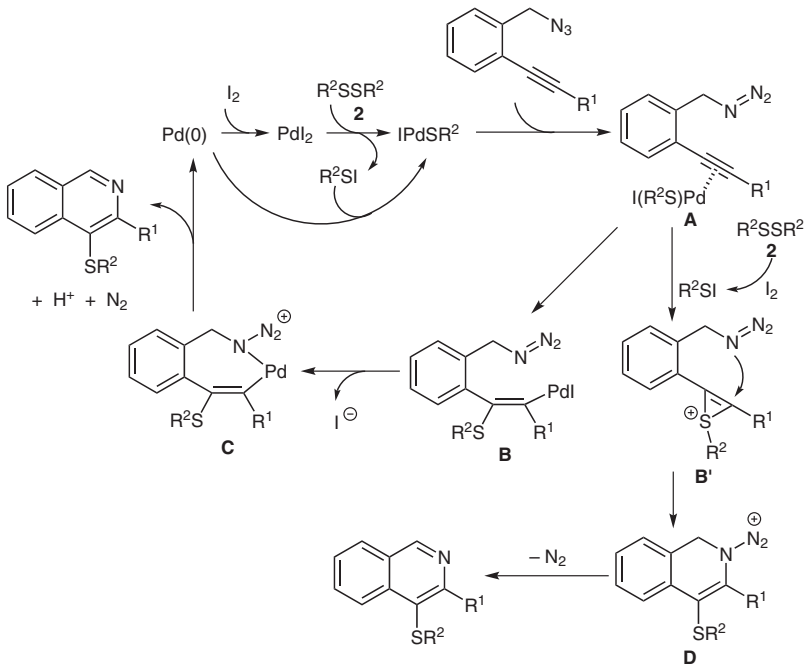
iodocyclization process.[4] Recently, we also developed an efficient synthesis of 3-chalcogen-benzo[*b*]furans via palladium-promoted annulation reaction of 2-alkynylphenol derivatives with disulfides or diselenides and iodide (Scheme 1, equation 1).[7d] In continuation of our interest in the synthesis of chalcogen-substituted compounds,[7] we decided to explore the feasibility of synthesizing sulfenylisoquinolines using 2-alkynylbenzyl azides as the starting substrates because the S-contained group has a significant effect on the biological activity and often manifests changes in chemical and physical properties.[6] Here, we report a new, selective protocol for the synthesis of 4-sulfenylisoquinolines by PdI_2/I_2-catalyzed thiolation-annulation of alkynes with azides and disulfides (Scheme 1, equation 2).

As shown in Table 1, the reaction between 1-azidomethyl-2-(phenylethynyl)benzene (**1a**) and 1,2-diphenyldisulfane (**2a**) was chosen as the model reaction to screen the optimal reaction conditions. Initially, treatment of azide **1a** with disulfide **2a** under the reported reaction conditions[7d] afforded a low yield: a trace of the desired product **3** was observed in the absence of I_2, and 35% yield in the presence of two equivalents of I_2 (Table 1, entries 1 and 2). It is noteworthy that 12% yield was still isolated using I_2 alone (entry 3). After a series of trials, it was found that PdI_2 combined with I_2 displayed the most efficiency, enhancing the yield of **3** to 73% (entries 1–6). The results demonstrated that the amount of I_2 affected the reaction to some extent (entries 7 and 8). While identical results were obtained at a loading of three equivalents of I_2 (entry 7), the yield was lowered to 53% using one equivalent of I_2 (entry 8). In light of these results, some other additives, such as NIS, ICl, and *n*-Bu_4NI were subsequently investigated (entries 9–11). However, the results showed that they were less active than I_2. Among the reaction temperature and solvents examined, it turned out that the reaction in MeCN at 80 °C gave the best yields (entries 12–17). Finally, the loading of PdI_2 was evaluated (entries 18 and 19). We found that a good yield was achieved at 10 mol% PdI_2, and 1 mol% PdI_2 resulted in an unsatisfactory yield.



Scheme 2 Selenation of 2-alkynylbenzyl azides **1** with 1,2-diphenyldiselane (**2g**)

As shown in Table 2, the scope of both azides **1** and disulfides **2** was investigated under the standard reaction conditions. The results demonstrated that disulfides **2b–d**, bearing a Me, MeO, or Cl group on the aryl moiety, were tolerated well in moderate to good yields (Table 2, entries 1–3). However, disulfides **2e** with an electron-deficient group displayed no activity (entry 4). It was pleasing to note that aliphatic disulfide **2f** successfully underwent the annulation with azide **1a**, PdI_2, and I_2 in 60% yield (entry 5). To our delight, a variety of azides **1b–l** were smoothly annulated with 1,2-diphenyldisulfane (**2a**), PdI_2, and I_2, providing moderate to good yields of the products (entries 6–16). It was found that several functional groups, including methoxy, methyl, nitro, acetyl, and chloro groups, on the terminal alkyne were perfectly consistent with the standard conditions, and electron-withdrawing groups favored the reaction (entries 6–12). While substrate **1b** with a methoxy group resulted in 49% yield (entry 6), nitro-substituted substrate **1f** gave the desired product **13** in 80% yield (entry 10). Aliphatic alkynes **1i** and **1j** were



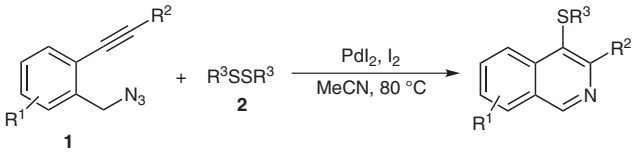
Scheme 3 Possible mechanisms of thiolation-annulation reaction

also suitable substrates for the thiolation-annulation reaction with disulfide **2a**, PdI_2, and I_2 affording the products **16** and **17** in 68% and 72% yield, respectively (entries 13 and 14). Gratifyingly, the standard conditions were compatible with substrates **1k**,**l** with a MeO or OCH_2O group on the aryl ring of the benzyl azide moiety (entries 15 and 16). For example, 5-(azidomethyl)-6-(phenylethynyl)benzo[*d*][1,3]dioxole (**1l**) underwent the annulation with 1,2-diphenyldisulfane (**2a**), PdI_2, and I_2 to give **19** in 68% yield (entry 16).

Selenylation of 2-alkynylbenzyl azides **1** with 1,2-diphenyldiselane (**2g**) was subsequently investigated in the presence of PdI_2 and I_2 (Scheme 2). Treatment of 2-alkynylbenzyl azides **1** with 1,2-diphenyldiselane (**2g**), PdI_2 and I_2 afforded the corresponding 4-selenylisoquinoline products **20** and **21** in 80% and 75% yield, respectively.

Screening revealed that the reaction could take place in the presence of PdI_2 or I_2 alone, suggesting an electrophilic addition process (Table 1, entries 3 and 5). Thus, possible mechanisms as outlined in Scheme 3 were proposed. The reaction between PdI_2 and R^2SSR^2 yields the $Pd(SR^2)I$ complex together with R^2SI, followed by coordination of $Pd(SR^2)I$ with an alkyne affording the intermediate **A**. Thiopalladation of the alkyne takes place leading to intermediate **B**. Subsequently, intramolecular addition of Pd into the N=N bond of intermediate **B** gives intermediate **C**. Intermediate **C** undergoes reductive elimination/deprotonation to afford the desired product, N_2, HI, and the Pd(0) species. The Pd(0) species may react with I_2 or R^2SI to regenerate the corresponding active PdI_2 or $Pd(SR^2)I$ species.

Table 2 Thiolation Annulation Reactions of 2-Alkynylbenzyl Azides **1** with Disulfides **2**[a]



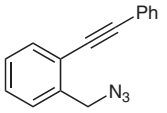
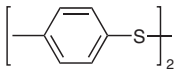
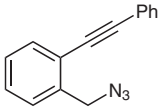
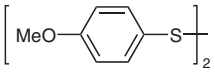
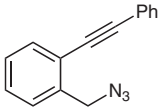
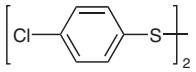
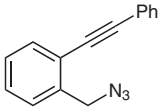
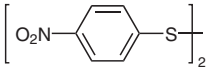
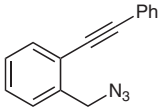
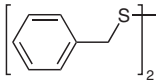
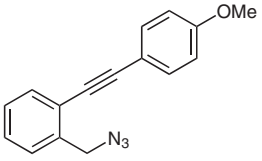
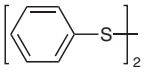
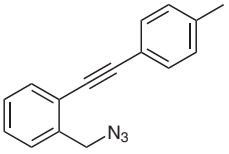
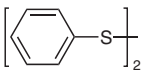
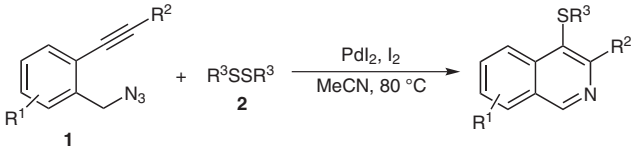
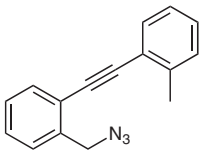
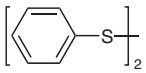
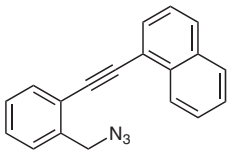
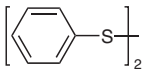
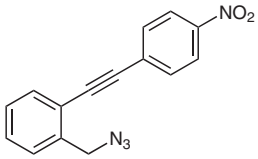
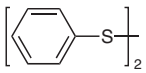
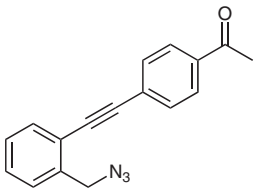
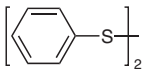
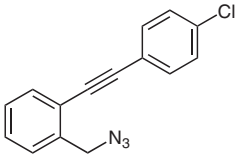
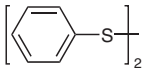
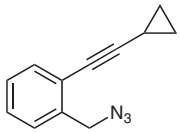
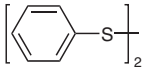
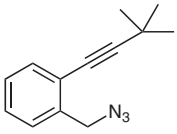
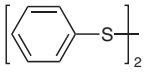
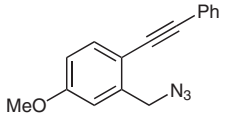
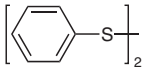
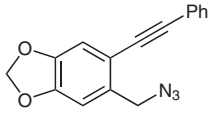
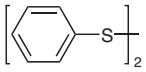
Entry	Azide **1**		Disulfide **2**		Product (yield)[b]
1	**1a**		**2b**		**4** (72%)
2	**1a**		**2c**		**5** (86%)
3	**1a**		**2d**		**6** (36%)
4	**1a**		**2e**		**7** (trace)
5	**1a**		**2f**		**8** (60%)
6	**1b**		**2a**		**9** (49%)
7	**1c**		**2a**		**10** (57%)

Table 2 Thiolation Annulation Reactions of 2-Alkynylbenzyl Azides **1** with Disulfides **2**[a] (continued)



Entry	Azide **1**		Disulfide **2**		Product (yield)[b]
8	**1d**		**2a**		**11** (55%)
9	**1e**		**2a**		**12** (58%)
10	**1f**		**2a**		**13** (80%)
11	**1g**		**2a**		**14** (84%)
12	**1h**		**2a**		**15** (76%)
13	**1i**		**2a**		**16** (68%)
14	**1j**		**2a**		**17** (72%)
15	**1k**		**2a**		**18** (70%)
16	**1l**		**2a**		**19** (68%)

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), PdI_2 (5 mol%), I_2 (2 equiv) and MeCN (2 mL) at 80 °C for 20–26 h under N_2 atmosphere.
[b] Isolated yield.

We can not rule out that the desired product is obtained via another electrophilic mechanism: the thionium intermediate **B′** can be generated from intermediate **A** with the aid of Pd catalyst, followed by addition with a nitrogen atom and elimination yields the desired product.

In summary, we have developed a novel PdI_2/I_2-catalyzed thiolation-annulation protocol for the synthesis of 4-sulfenylisoquinolines using 2-alkynylbenzyl azides and disulfides as the reaction partners. In the presence of PdI_2 and I_2, a variety of 2-alkynylbenzyl azides were reacted with numerous disulfides smoothly to afford the corresponding 4-sulfenylisoquinolines in moderate to good yields. Moreover, this method allows 2-alkynylbenzyl azides to react with 1,2-diphenyldiselane giving the products in good yields under the same conditions. Notably, several features of the present reaction are obvious: (1) selectivity was shifted toward to 4-sulfenylisoquinolines or 4-selenylisoquinolines, and not to 4-iodoisoquinolines using the PdI_2/I_2 system, (2) the reaction can take place in the presence of PdI_2 or I_2 alone, but PdI_2 combined with I_2 was the most efficient, and (3) the electron-deficient aryl groups at the terminal alkynes favor the reaction, however, disulfides with electron-deficient aryl groups are inert.

NMR spectroscopy was performed on a Bruker 500 spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). TMS was used an internal standard and CD_3Cl was used as the solvent. Mass spectrometric analysis was performed on a GC-MS instrument (Shimadzu GCMS-QP2010 plus). All melting points are uncorrected.

Palladium-Catalyzed Annulation of 2-Alkynylbenzyl Azides 1 with Disulfides 2; General Procedure

2-(Alk-1-ynyl)benzyl azide **1** (0.2 mmol), disulfide **2** (0.1 mmol), PdI_2 (5 mol%), I_2 (2 equiv), and MeCN (2 mL) were added in turn to a Schlenk tube. Then, the mixture was stirred at 80 °C under N_2 atmosphere for the indicated time until complete consumption of starting material as monitored by TLC and GC-MS analysis (ca. 20–26 h). After completion of the reaction, the mixture was poured into H_2O (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 × 3 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc) to afford the desired product.

3-Phenyl-4-(phenylthio)isoquinoline (3)

Brown solid; mp 129.5–130.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.41 (d, *J* = 8.5 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.64–7.61 (m, 3 H), 7.41–7.37 (m, 3 H), 7.11 (t, *J* = 7.5 Hz, 2 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 153.4, 140.7, 138.3, 138.0, 131.8, 129.7, 128.9, 128.2 (2 C), 128.1, 127.7, 127.5, 126.7, 126.2, 125.3, 121.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 315 (M^+ + 2, 11), 313 (M^+, 58), 312 (17), 280 (10), 237 (18), 236 (100), 235 (15).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}NS$ (M^+): 313.0925; found: 313.0922.

3-Phenyl-4-(*p*-tolythio)isoquinoline (4)

Brown solid; mp 126.5–127.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.41 (d, *J* = 8.5 Hz, 1 H), 8.21 (d, *J* = 8.5 Hz, 1 H), 8.02–7.92 (m, 4 H), 7.49–7.38 (m, 3 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 2.21 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 153.2, 140.8, 138.3, 135.1, 134.4, 131.6, 129.8, 129.7, 128.2, 128.1 (2C), 127.6, 127.4, 126.9, 126.2, 122.2, 20.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 329 (M^+ + 2, 20), 327 (M^+, 80), 326 (20), 294 (13), 251(19), 250 (23), 235 (100).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NS$ (M^+): 327.1082; found: 327.1081.

4-(4-Methoxyphenylthio)-3-phenylisoquinoline (5)

Brown solid; mp 128.6–130.1 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 8.48 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.64–7.59 (m, 3 H), 7.43–7.38 (m, 3 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 6.64 (d, *J* = 8.5 Hz, 2 H), 3.68 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 157.9, 152.9, 140.8, 138.2, 131.5, 129.9, 129.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.4, 126.2, 123.5, 114.6, 55.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 343 (M^+, 96), 342 (16), 267 (22), 236 (100), 251 (25), 223 (23), 222 (10).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NOS$ (M^+): 343.1030; found: 343.1026.

4-(4-Chlorophenylthio)-3-phenylisoquinoline (6)

Brown solid; mp 125.8–127.3 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.66 (d, *J* = 7.5 Hz, 1 H), 7.61–7.59 (m, 2 H), 7.41–7.39 (m, 3 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 153.6, 140.6, 138.1, 136.4, 131.9, 131.2, 129.7, 129.1, 128.3 (2C), 128.2, 128.1, 127.8, 127.7, 125.9, 121.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 349 (M^+ + 2, 40), 347 (M^+, 98), 348 (33), 346 (21), 314 (12), 272 (41), 271 (21), 270 (40), 236 (100).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}ClNS$ (M^+): 347.0536; found: 347.0532.

4-(Benzylthio)-3-phenylisoquinoline (8)

Brown solid; mp 126.9–128.4 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 8.62 (d, *J* = 8.5 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.78 (t, *J* = 7.5 Hz, 1 H), 7.64 (t, *J* = 7.0 Hz, 1 H), 7.56–7.54 (m, 2 H), 7.43–7.42 (m, 3 H), 7.09–7.03 (m, 3 H), 6.75 (d, *J* = 7.0 Hz, 2 H), 3.69 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 152.1, 141.0, 138.6, 137.1, 131.3, 130.1, 128.7, 128.1 (2 C), 127.8 (2C), 127.6, 127.2, 126.9, 125.9, 124.1, 40.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 329 (M^+ + 2, 20), 327 (M^+, 80), 326 (20), 294 (13), 251 (19), 250 (100), 204 (30).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NS$ (M^+): 327.1082; found: 327.1080.

3-(4-Methoxyphenyl)-4-(phenylthio)isoquinoline (9)

Brown solid; mp 128.5–129.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.38 (d, *J* = 8.5 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.64–7.60 (m, 3 H), 7.13 (t, *J* = 7.5 Hz, 2 H), 7.05 (t, *J* = 7.0 Hz, 1 H), 6.95–6.93 (m, 4 H), 3.84 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 157.9, 152.9, 140.8, 138.2, 131.5, 129.9, 129.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.4, 126.2, 123.5, 114.6, 55.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 343 (M^+, 96), 342 (16), 267 (22), 266 (100), 251 (25), 223 (23), 222 (10).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NOS$ (M^+): 343.1030; found: 343.1028.

4-(Phenylthio)-3-(*p*-tolyl)isoquinoline (10)
Brown solid; mp 131.8–133.3 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 7.62 (t, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.12 (t, *J* = 7.0 Hz, 2 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 2.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 153.4, 138.3, 138.2, 138.0, 137.9, 131.7, 129.7, 128.9, 128.4, 128.2 (2C), 127.4, 126.6, 126.2, 125.2, 121.3, 21.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 329 (M^+ + 2, 20), 327 (M^+, 80), 326 (20), 294 (13), 251 (19), 250 (100), 235 (23).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NS$ (M^+): 327.1082; found: 327.1085.

4-(Phenylthio)-3-*o*-tolylisoquinoline (11)
Brown solid; mp 130.2–131.7 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.42 (d, *J* = 8.5 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 7.5 Hz, 1 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.29–7.23 (m, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 7.09–7.02 (m, 3 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 2.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 153.1, 140.6, 138.0, 137.3, 135.9, 131.7, 129.9, 129.0, 128.7, 128.3, 128.2, 128.1, 127.6 (2 C), 126.0, 125.5, 125.2, 123.6, 19.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 329 (M^+ + 2, 20), 327 (M^+, 80), 326 (20), 294 (13), 251 (19), 250 (100), 235 (23).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NS$ (M^+): 327.1082; found: 327.1081.

3-(Naphthalen-1-yl)-4-(phenylthio)isoquinoline (12)
Pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.43 (s, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 2 H), 7.77 (t, *J* = 7.5 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.47–7.40 (m, 4 H), 7.33 (t, *J* = 7.0 Hz, 1 H), 7.03–6.97 (m, 3 H), 6.85–6.83 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 153.2, 138.5, 138.0, 137.5, 133.6, 131.9, 131.8, 128.7, 128.5, 128.3, 128.2, 127.8, 127.5, 126.9, 126.1, 125.7, 125.6, 125.4, 124.9, 124.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 365 (M^+ + 2, 27), 363 (M^+, 81.5), 362 (76), 287 (24), 286 (100), 285 (19), 284 (12), 254 (37), 253 (29).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{17}NS$ (M^+): 363.1082; found: 363.1079.

3-(4-Nitrophenyl)-4-(phenylthio)isoquinoline (13)
Brown solid; mp 140.1–140.5 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 8.47 (d, *J* = 8.5 Hz, 1 H), 8.23 (d, *J* = 9.0 Hz, 2 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.80 (t, *J* = 8.5 Hz, 3 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.14–7.06 (m, 3 H), 6.88 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8, 153.7, 147.5, 147.1, 138.3, 137.2, 132.3, 130.8, 129.2, 128.6, 128.4, 128.3, 126.9, 126.2, 125.8, 123.1, 123.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 360 (M^+ + 2, 27), 358 (M^+, 100), 357 (14), 311 (11), 282 (10), 281 (52), 236 (15), 235 (63).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}N_2O_2S$ (M^+): 358.0776; found: 358.0773.

1-{4-[4-(Phenylthio)isoquinolin-3-yl]phenyl}ethanone (14)
White solid; mp 126.3.1–127.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 8.43 (d, *J* = 8.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.5, 2 H), 7.78–7.66 (m, 4 H), 7.12 (t, *J* = 7.0 Hz, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 7.5 Hz, 2 H), 2.63 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 157.2, 153.6, 145.4, 138.3, 137.6, 136.4, 132.0, 130.1, 129.1, 128.4, 128.0, 127.8, 127.7, 126.7, 126.2, 125.5, 122.4, 26.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 357 (M^+ + 2, 27), 355 (M^+, 92), 354 (21), 340 (19), 280 (11), 279 (19), 278 (100), 235 (44), 236 (21).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{17}NOS$ (M^+): 355.1031; found: 355.1029.

3-(4-Chlorophenyl)-4-(phenylthio)isoquinoline (15)
Brown solid; mp 125.4–126.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.42 (d, *J* = 8.0 Hz, 1 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.5 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 6.5 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.90 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 153.5, 139.1, 138.4, 137.7, 134.3, 131.9, 131.2, 129.0, 128.3, 128.2, 127.9, 127.8, 126.7, 126.1, 125.5, 122.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 349 (M^+ + 2, 40), 347 (M^+, 98), 346 (21), 314 (12), 272 (41), 271 (21), 270 (100).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}ClNS$ (M^+): 347.0536; found: 347.0532.

3-Cyclopropyl-4-(phenylthio)isoquinoline (16)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.15 (t, *J* = 7.5 Hz, 2 H), 7.07–7.03 (m, 3 H), 3.08–3.04 (m, 1 H), 1.20–1.18 (m, 2 H), 0.99–0.97 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 153.7, 138.4, 137.5, 131.4, 128.9, 127.9, 127.4, 126.4, 126.2, 125.1 (2C), 120.1, 15.2, 10.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 279 (M^+ + 2, 27), 277 (M^+, 100), 236 (20), 200 (19), 127 (10).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}NS$ (M^+): 277.0925; found: 277.0923.

3-*tert*-Butyl-4-(phenylthio)isoquinoline (17)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.26 (s, 1 H), 8.31 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 7.5 Hz, 1 H), 7.58–7.52 (m, 2 H), 7.12 (t, *J* = 7.5 Hz, 2 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 6.85 (d, *J* = 7.5 Hz, 2 H), 1.66 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 151.8, 139.2, 138.9, 131.1, 128.9, 127.9, 127.8, 126.8, 125.8, 125.7, 124.7, 121.0, 40.3, 30.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 295 (M^+ + 2, 20), 293 (M^+, 13), 217 (18), 216 (100), 200 (12), 175 (8).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NS$ (M^+): 293.1238; found: 293.1237.

7-Methoxy-3-phenyl-4-(phenylthio)isoquinoline (18)
White solid; mp 114.2–115.7 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 8.30 (d, *J* = 9.5 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.40–7.33 (m, 4 H), 7.29 (s, 1 H), 7.11 (t, *J* = 7.5 Hz, 2 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 7.5 Hz, 2 H), 3.95 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 156.6, 152.0, 140.8, 138.2, 133.9, 129.8, 129.6, 129.0, 128.0 (2C), 127.7, 126.7, 125.3, 124.7, 121.7, 105.3, 55.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 345 (M^+ + 2, 25), 343 (M^+, 100), 342 (16), 310 (13), 267 (21), 266 (88), 223 (36).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}NOS$ (M^+): 343.1031; found: 343.1028.

7-Phenyl-8-(phenylthio)[1,3]dioxolo[4,5-*g*]isoquinoline (19)
White solid; mp 120.4–121.7 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.10 (s, 1 H), 7.72 (s, 1 H), 7.59–7.57 (m, 2 H), 7.38–7.35 (m, 3 H), 7.25 (s, 1 H), 7.11 (t, *J* = 7.0 Hz, 2 H), 7.05 (t, *J* = 7.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 6.08 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 152.5, 151.0, 148.6, 140.8, 137.8, 137.7, 129.6, 129.0, 128.0, 127.6, 126.5, 125.6, 125.2, 120.9, 103.5, 102.8, 101.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 359 (M^+ + 2, 12), 357 (M^+, 100), 280 (36), 248 (13), 159 (34).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{15}NO_2S$ (M^+): 357.0824; found: 357.0822.

3-Phenyl-4-(phenylselanyl)isoquinoline (20)
Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.44 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.72–7.69 (m, 1 H), 7.62 (t, *J* = 7.5 Hz, 1 H), 7.57 (t, *J* = 7.5 Hz, 2 H), 7.41–7.39 (m, 3 H), 7.07–7.02 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 153.1, 141.9, 138.6, 133.0, 131.7, 129.8, 129.6, 129.1, 128.6, 128.1, 128.1, 127.9, 127.6, 127.4, 126.1, 121.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 361 (M^+, 1), 284 (1), 204 (1), 176 (1), 44 (16), 40 (100).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}NSe$ (M^+): 361.0370; found: 361.0368.

3-Octyl-4-(phenylselanyl)isoquinoline (21)
Black oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 8.40 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 15.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.10 (s, 5 H), 3.33 (t, *J* = 7.5 Hz, 2 H), 1.76–1.70 (m, 2 H), 1.39–1.34 (m, 2 H), 1.28–1.23 (m, 8 H), 0.86 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0, 153.5, 138.8, 132.7, 131.4, 129.2, 129.1, 128.0, 128.0, 127.7, 126.8, 126.0, 120.9, 39.2, 31.8, 30.7, 29.7, 29.4, 29.2, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 397 (M^+, 3), 320 (11), 299 (39), 240 (59), 218 (52), 40 (100).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{27}NSe$ (M^+): 397.1309; found: 397.1306.

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

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