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Synthesis of 3-substituted indazoles and benzoisoxazoles via Pd-catalyzed cyclization reactions: application to the synthesis of nigellicine

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Abstract—Syntheses of 3-substituted indazoles and benzoisoxazoles were efficiently accomplished with the aid of Pd-catalyzed intramolecular carbon–nitrogen and carbon–oxygen bond formations. The catalyst system described herein allows the cyclization to proceed under very mild conditions and thus could be applied to a wide range of substrates with acid- or base-sensitive functional groups. A total synthesis for the indazole ring-containing natural product nigellicine is also described.

1. Introduction

Bicyclic aromatic heterocycles containing nitrogen and oxygen atoms, such as quinolines, isoquinolines, indoles, and benzofurans, are ubiquitous in pharmaceuticals and natural products, many of which exhibit unique biological activities. Indazole derivatives, which are bioisosteres of indoles, are also an important class of compounds in the medicinal arena.[1] In fact, compounds containing the indazole skeleton are known to show a variety of biological activities, such as high binding affinity for estrogen receptor,[2] inhibition of protein kinase C-β,[3] 5-HT_2 and 5-HT_3 receptor antagonisms,[4] HIV protease inhibition,[5] and anti-tumor activity.[6] Thus, the search for an efficient synthesis of the indazole ring system has been a longstanding goal. However, to date, methods reported for the synthesis of indazoles have met with only limited success.

Many methods classically used for indazole synthesis[7–9] require harsh reaction conditions, thus limiting their usefulness in obtaining variously functionalized indazoles. Recently, several indazole syntheses utilizing a Pd-catalyzed amination reaction[10] have been reported. For example, Song and Yee have shown that *N*-arylindazoles can be obtained from *N*-aryl-*N*-(2-bromobenzyl)hydrazines.[11a] A one-pot synthesis from 2-bromobenzaldehydes and arylhydrazines, developed by Cho et al., provides another access.[11b] More recently, Voskoboynikov et al. indicated that indazoles can also be obtained from the cyclization of arylhydrazones.[11c] Although these newer methods certainly provide improved results over the classical indazole syntheses, the reaction conditions required are still relatively harsh, so that their applicability towards functionalized substrates remains limited. Moreover, 3-substituted indazoles, which are an especially important class of pharmacophore, cannot be obtained by these methods. Indeed, a general and efficient method for the synthesis of a wide variety of 3-substituted indazoles has, until now, not been reported.[12,13]

Herein, we report an efficient and highly applicable method for the synthesis of 3-substituted indazoles using an intramolecular Pd-catalyzed amination reaction[10f–h] of hydrazones (Fig. 1, Y=NTs).[14] The catalyst systems developed by our group permitted the cyclization to proceed smoothly under

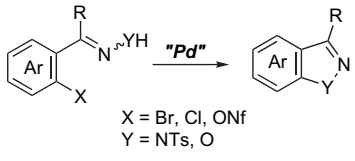

Figure 1. Synthesis of 3-substituted indazoles and benzoisoxazoles via Pd-catalyzed cyclization reactions.

Keywords: Palladium; Amination; Hydrazone; Indazole; Benzoisoxazole; Nigellicine.
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very mild conditions, from room temperature to 50 °C, with functional groups such as alkoxycarbonyl and carbamoyl surviving intact. Thus, our results represent the first general method for the preparation of a range of 3-substituted indazoles, which could not be achieved by previously reported systems. Moreover, the same catalyst systems were applied to the cyclization of oximes, producing 3-substituted benzoisoxazoles (Fig. 1, Y=O). In addition, using this Pd-catalyzed cyclization as a key step, we were able to accomplish the total synthesis of nigellicine,[15a] a rare example of the class of naturally occurring compounds possessing the indazole backbone.[15]

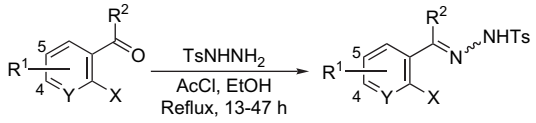
2. Results and discussion

2.1. Preparation of hydrazone and oxime derivatives and their structural determinations

Various hydrazones **2a**–**2l** were prepared from the corresponding carbonyl compounds **1a**–**1l**, with the results summarized in Table 1. From the reaction of variously substituted 2-bromophenylketones **1a**–**1i** with *p*-toluenesulfonylhydrazide in the presence of hydrogen chloride in ethanol (generated in situ from acetyl chloride and ethanol), the desired hydrazones **2a**–**2i** were generally obtained in good yields (entries 1–9). In addition to these aryl bromides, aryl nonaflate [ArONf=ArOSO$_2$(CF$_2$)$_3$CF$_3$] **2j**, aryl chloride **2k**, and heteroaryl bromide **2l** were also synthesized. Some of the hydrazones (**2a**, **2d**, **2f**, and **2k**) were obtained as a mixture of *E*- and *Z*-isomer, which could then be separated by silica gel column chromatography or by recrystallization from the appropriate solvent (see Section 4).

The configurations for some of the hydrazones were determined as follows: in the case of **2a**, a signal attributable to the methyl group (boldface in Fig. 2) was observed in the ^{13}C NMR spectrum at upper field in one isomer than in the other (17.7 vs 24.0 ppm), probably due to a sterically induced upfield shift (Fig. 2).[16] Thus, the configuration of this isomer was suspected to be *E*. This speculation was confirmed by the NOE experiment shown in Figure 2. The structure of **2k** was determined in a similar manner.

Table 1. Preparation of hydrazones **2a**–**2l**[a]



1a-l **2a-l**

Entry	1	X	Y	R^1	R^2	Yield (%) (*E*:*Z*)
1	**1a**	Br	CH	H	Me	>99 (4.6:1)
2	**1b**	Br	CH	H	^{i}Pr	53 (Single isomer)
3[b]	**1c**	Br	CH	H	CO$_2$^{t}Bu	87 (*E*, Single isomer)
4	**1d**	Br	CH	H	CONEt$_2$	96 (1.3:1)
5	**1e**	Br	CH	H	Ph	74 (Single isomer)
6	**1f**	Br	CH	4-NO$_2$	Ph	47[d]
7	**1g**	Br	CH	5-OMe	Ph	67 (Single isomer)
8	**1h**	Br	CH	4-Me	Ph	80 (Single isomer)
9	**1i**	Br	CH	H	4-(MeO)C$_6$H$_4$	99 (Single isomer)
10	**1j**	ONf[c]	CH	H	Ph	73 (Single isomer)
11	**1k**	Cl	CH	H	Et	70 (1:2.4)
12	**1l**	Br	N	H	Ph	41 (Single isomer)

[a] Reaction conditions: **1** (1.0 equiv), TsNHNH$_2$ (1.5–4.0 equiv), and AcCl (2.0–5.0 equiv) in ethanol.
[b] The reaction was carried out without AcCl at 50 °C.
[c] ONf=OSO$_2$(CF$_2$)$_3$CF$_3$.
[d] The ratio between the major and the minor isomers is 2.9:1.

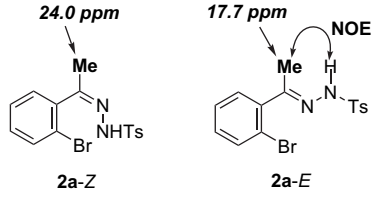


Figure 2. Structural determination of hydrazones **2a**-*Z* and **2a**-*E*.

Structural determinations of hydrazones **2c** and **2d** were accomplished as follows: in the course of the nigellicine synthesis (discussed below), we obtained hydrazone **15** as a separable mixture of *E*- and *Z*-isomer. The signal in the ^{1}H NMR spectrum of the proton on the nitrogen atom was observed at 7.84 ppm in one isomer (**15**-*E*) and at 12.28 ppm in the second isomer (**15**-*Z*). In addition, the absorption by the stretching of the carbonyl groups in the IR spectrum was observed at 1717 and 1693 cm^{-1}, respectively. In the *Z*-isomer, intramolecular hydrogen bonding between the amide proton and the oxygen atom of the ester carbonyl group can be achieved, as shown in Figure 3. The downfield shift in the ^{1}H NMR spectrum, as well as the low wavenumber shift in the IR spectrum, might be caused by this hydrogen bond formation; thus, the configuration of the latter isomer was assigned as *Z*. As similar peak shifts in the ^{1}H NMR spectra were observed for the hydrazones **2c** and **2d**, we concluded that **2c** was obtained as a single *E*-isomer, and **2d** as a 1.3:1 mixture of *E*- and *Z*-isomer.

On the other hand, the oximes **3e**, **3f**, **3g**, **3j**, and **3m** were prepared under standard conditions (NH$_2$OH·HCl, ethanol, reflux). The yields and isomer ratios of the oximes are summarized in Table 2.

2.2. Differences in reactivity and stability between the two isomers of 2a

To examine the reactivity of the hydrazones, we first carried out the Pd-catalyzed cyclization of **2a** (Table 3). Specifically, the two isomers (**2a**-*E* and **2a**-*Z*) were allowed to react independently in the presence of a catalytic amount of Pd$_2$(dba)$_3$ and P(2-Tol)$_3$ along with LiHMDS in toluene.[10b] As a result, the desired indazole **4a** could be obtained from **2a**-*Z* isomer; in contrast **2a**-*E* was completely decomposed during the reaction time (entries 1 and 2). Although **2a**-*E* isomer completely decomposed during the reaction condition, the

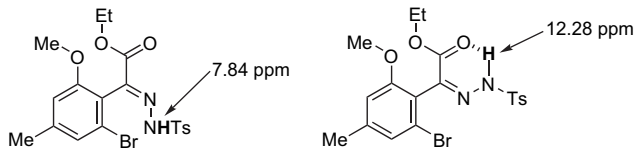
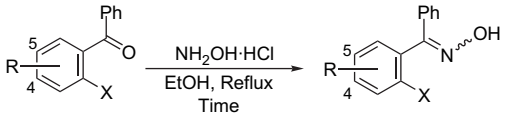


Figure 3. Structural determination of hydrazones **15**-*E* and **15**-*Z*.

Table 2. Preparation of oximes **3e**, **3f**, **3g**, **3j**, and **3m**

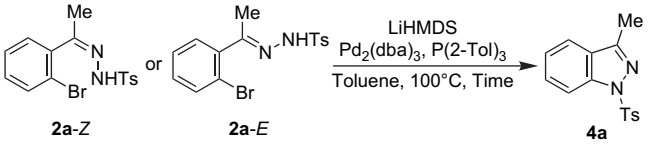


1e, f, g, j, m **3e, f, g, j, m**

Entry	**1**	X	R	Time (h)	Yield[a] (%)
1	**1e**	Br	H	71	92 (6.3:1)
2	**1f**	Br	4-NO_2	43	96 (3.1:1)
3	**1g**	Br	5-OMe	43	92 (5.3:1)
4	**1j**	ONf[b]	H	45	96 (5.1:1)
5	**1m**	Cl	H	41	99 (4.0:1)

[a] Numbers in parentheses are ratios between the major and minor isomers.
[b] ONf=$OSO_2(CF_2)_3CF_3$.

Table 3. Differences in reactivity and stability between **2a**-*E* and **2a**-*Z*



2a-*Z* **2a**-*E* **4a**

Entry	Starting material	$Pd_2(dba)_3$, $P(2\text{-Tol})_3$	Time (h)	Yield[c] (%)
1[a]	**2a**-*E*	+	1.5	0
2[a]	**2a**-*Z*	+	1.5	91 (0)
3[b]	**2a**-*E*	–	4	— (0)
4[b]	**2a**-*Z*	–	4	— (89)
5[b]	**4a**	–	4	— (94)

[a] Reaction conditions: **2a**-*E* or **2a**-*Z* (1.0 equiv), LiHMDS (1.4 equiv), $Pd_2(dba)_3$ (5 mol %), and $P(2\text{-Tol})_3$ (15 mol %) in toluene.
[b] Reaction conditions: **2a**-*E* or **2a**-*Z* or **4a** (1.0 equiv) and LiHMDS (1.4 equiv) in toluene.
[c] The numbers in parentheses are recovered yield of the starting materials.

possibility for the equilibrium between the **2a**-*E* and **2a**-*Z* isomers during the reaction, which could possibly be driven by a base and/or palladium,[17] cannot be ruled out. Moreover, a comparison of the stabilities between **2a**-*E* and **2a**-*Z* under these basic conditions provided another insight into the reaction mechanism. When the reactions of both isomers were conducted independently in the absence of the catalyst system, all of the starting material was completely decomposed after 4 h in the case of **2a**-*E* (entry 3). On the other hand, 89% of the starting material remained when **2a**-*Z* was subjected to the same reaction conditions (entry 4). The product, indazole **4a**, was quite stable even under these strongly basic conditions and no decomposition was observed (entry 5). These results suggest that decomposition of the starting material must be competing with the cyclization reaction at high temperatures and under highly basic conditions, so that the longer reaction time, especially in the case of the *E*-isomer, causes a drastic decrease in the yield, although the reason for the difference in stabilities is not yet clear.[18]

2.3. Indazoles' syntheses

Based on the results summarized above, our focus shifted to search for the mildest reaction conditions possible. Among the various reaction conditions examined, we were delighted to find that the use of a base, such as ^{t}BuONa or Cs_2CO_3 and a bidentate phosphine, such as dppp or dppf, was effective in accomplishing the cyclization under mild conditions. $Pd(OAc)_2$ generally gave better results than $Pd_2(dba)_3$ and dioxane as a solvent proved to be crucial. Thus, all reactions proceeded smoothly at room temperature or 50 °C and the desired 3-substituted indazoles were generally obtained in high yields. For example, the reaction of hydrazone **2b** occurred at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$ and dppf, with Cs_2CO_3 as a base, to give indazole **4b** in 82% yield (entry 1). Alkoxycarbonyl (**2c**, entry 2) and carbamoyl (**2d**, entry 3) moieties remained unchanged under these reaction conditions. Variously substituted 3-arylindazoles **4e**–**4i** could also be synthesized under these conditions, using the appropriate combination of base and bidentate ligand (entries 4–8). In these cases, the cyclization reactions also proceeded efficiently between room temperature and 50 °C, and the desired products were obtained in good-to-high yield. Aryl nonaflate [**2j**, Ar-ONf=$ArOSO_2(CF_2)_3CF_3$][19] was a highly reactive substrate in this system and cyclization proceeded at room temperature to give the desired indazole in quantitative yield (entry 9). Aryl chloride **2k** also reacted to produce 3-ethylindazole **4k**, albeit in moderate yield (entry 10). This system has also been successfully applied to the cyclization of heteroaryl bromide **2l** (entry 11). Unfortunately, relatively large amount of the catalyst (15 mol %) is only a drawback of this cyclization reaction, namely, a reduced amount of the catalyst less than 15 mol % led to decrease in the yield of the product.

2.4. Benzoisoxazoles' syntheses

The catalyst system described above, developed initially for indazole syntheses, was subsequently also applied successfully to intramolecular carbon–oxygen bond formation in the syntheses of 3-substituted benzoisoxazoles (Table 5).[20] Specifically, when we carried out the reaction of the major isomer of oxime **3e** with $Pd(OAc)_2$/dppf catalyst system in dioxane, 3-phenylbenzoisoxazole (**5e**) was obtained in 72% yield (entry 1). In the case of 4-nitro-substituted aryl bromide **3f**, the combination of ^{t}BuONa and dppp gave a better yield than that obtained with ^{t}BuONa and dppf (entries 2 and 3). Disappointingly, much lower yields were observed for substrates with electron donating substituents on the aromatic ring (entries 4 and 5). Although aryl nonaflate **3j** was also not very reactive under these conditions (entries 6 and 7), aryl chloride **3m** was successfully reacted, albeit at a higher temperature (entries 8 and 9).

2.5. Total synthesis of nigellicine

The indazole nucleus is rarely encountered in nature. To date, only three natural products, nigellicine (**6**), nigellidine (**7**), and nigeglanine (**8**) have appeared in the literature, and two of them are 3-substituted indazoles (Fig. 4).[15] Moreover, when we began this study, no report existed in the literature on the total synthesis of these three compounds.[21] Having developed a mild and practical method for the construction of 3-substituted indazoles, we next turned our focus to the synthesis of nigellicine (**6**), using the established Pd-catalyzed chemistry as a key step.

Our retrosynthetic analysis of nigellicine (**6**) relied on the construction of the appropriately substituted indazole **9** from hydrazone **10** via a Pd-catalyzed intramolecular amination reaction, and the subsequent double N-alkylation with

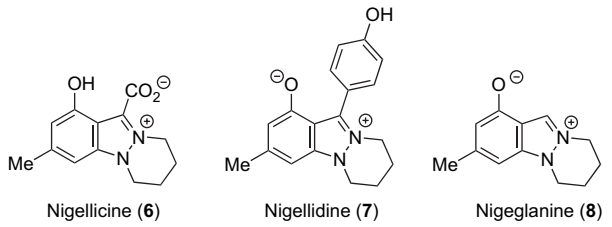
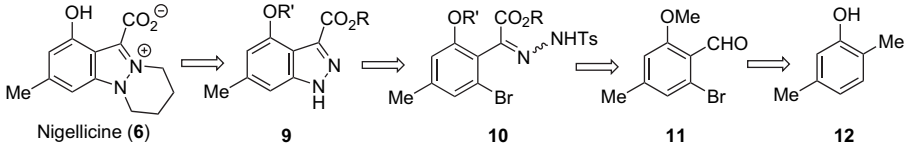


Figure 4. Three natural products containing the indazole skeleton.

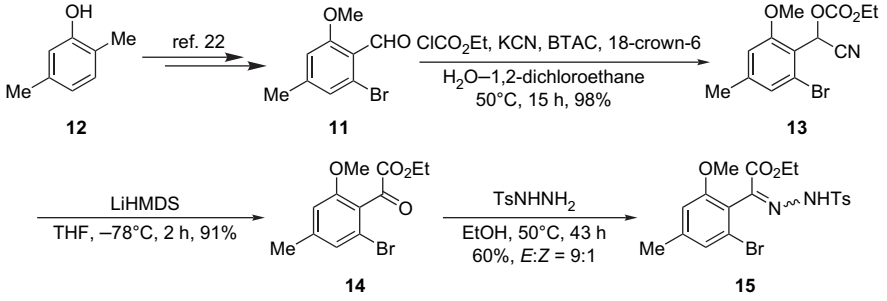
1,4-dibromobutane of **9** (Scheme 1). Thus, we first examined the synthesis of hydrazone **10** from 2-bromo-6-methoxy-4-methylbenzaldehyde (**11**), which could be prepared from commercially available 2,5-dimethylphenol (**12**) according to Clive's method.[22]

Treatment of aldehyde **11** with KCN and ethyl chloroformate in the presence of benzyltrimethylammonium chloride (BTAC) and 18-crown-6 in a mixture of water and 1,2-dichloroethane gave cyanohydrin carbonate ester **13**, which was subsequently converted to α-ketoester **14** by LiHMDS-induced rearrangement.[23] The reaction of **14** with *p*-toluenesulfonylhydrazide gave the key intermediate hydrazone **15** as a mixture of *E*- and *Z*-isomer, which was separable by column chromatography (*E*:*Z*=9:1) (Scheme 2). The determination of regiochemistry in these two compounds was accomplished as described in Section 2.1.

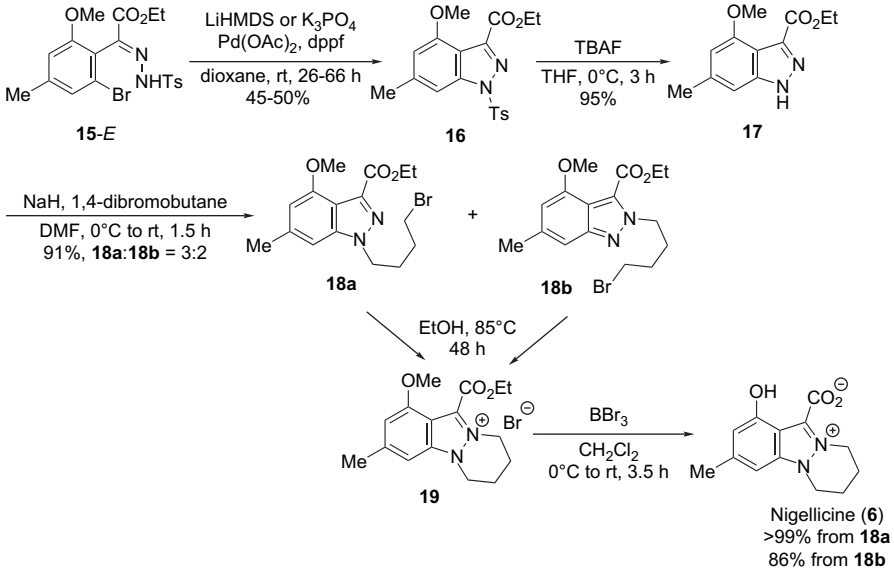
With hydrazone **15** in hand, we attempted the Pd-catalyzed cyclization for the construction of the indazole ring (Scheme 3). The cyclization reaction of **15**-*E*, however, employing the established catalyst systems consisting of inorganic base/bidentate phosphine in dioxane (Table 4) gave the desired **16** in poor yield (up to 16%). In all cases, competition between decomposition of the starting material **15**-*E* and the desired cyclization reaction was observed, even at room temperature,



Scheme 1. Retrosynthetic analysis of nigellicine (**6**).

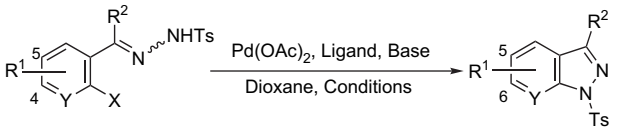


Scheme 2. Synthesis of the key intermediate **15**.



Scheme 3. Total synthesis of nigellicine (**6**).

Table 4. Intramolecular Pd-catalyzed amination reactions of hydrazones[a]



2b-l **4b-l**

Entry	**2**	X	Y	R^1	R^2	Base/ligand	Conditions	Yield (%)
1	**2b**	Br	CH	H	^{i}Pr	Cs_2CO_3/dppf	rt, 7 h	82 (**4b**)
2	**2c**-*E*	Br	CH	H	$CO_2{}^t$Bu	Cs_2CO_3/P(2-Tol)$_3$[b]	rt, 3 h	81 (**4c**)
3	**2d**-*E*	Br	CH	H	$CONEt_2$	^{t}BuONa/dppf	50 °C, 17 h	72 (**4d**)
4	**2e**	Br	CH	H	Ph	^{t}BuONa/dppp	50 °C, 17 h	83 (**4e**)
5	**2f**	Br	CH	4-NO_2	Ph	Cs_2CO_3/dppf	50 °C, 12 h	74 (**4f**: R^1=6-NO_2)
6	**2g**	Br	CH	5-OMe	Ph	^{t}BuONa/dppp	50 °C, 2 h	56 (**4g**: R^1=5-OMe)
7	**2h**	Br	CH	4-Me	Ph	^{t}BuONa/dppf	50 °C, 15 h	66 (**4h**: R^1=6-Me)
8	**2i**	Br	CH	H	4-(MeO)C_6H_4	^{t}BuONa/dppf	rt, 8 h	94 (**4i**)
9	**2j**	ONf	CH	H	Ph	Cs_2CO_3/dppf	rt, 2 h	96 (**4e**)
10	**2k**-*Z*	Cl	CH	H	Et	^{t}BuONa/dppp	50 °C, 15 h	43 (**4k**)
11	**2l**	Br	N	H	Ph	^{t}BuONa/dppf	50 °C, 13 h	82 (**4l**)

[a] Reaction conditions: **2** (1.0 equiv), base (1.5 equiv), $Pd(OAc)_2$ (15 mol %), and ligand (22.5 mol %) in dioxane.
[b] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$.

prompting us to screen other reaction conditions. After testing various bases, we were pleased to discover that using LiHMDS or K_3PO_4 as a base at room temperature allows only the cyclization to proceed, giving the desired indazole **16**, albeit in moderate yields (45–50%). The product **16** thus obtained was then subjected to detosylation to give indazole **17**.

Our nigellicine synthesis then entered its last stage, which concerned the construction of the third ring (Scheme 3). Deprotonation of indazole **17** followed by N-alkylation using 1,4-dibromobutane afforded a mixture of 1-alkylated indazole **18a** and 2-alkylated indazole **18b** in the ratio of 3:2, respectively. Interestingly, this result is somewhat different from Kelly's report, in which the 1-alkylated indazole was formed predominantly, along with a trace amount of the 2-alkylated product.[21] A second N-alkylation of **18a** and **18b** proceeded smoothly in both cases to form the same tricyclic compound, **19**. Finally, the ethyl ester and methyl ether of **19** were cleaved at the same time with BBr_3 to complete the total synthesis of nigellicine (**6**). The spectral properties of **6** were found to be in full agreement with previously reported data.[15a,21]

3. Conclusion

In summary, we have developed an efficient catalyst system for intramolecular Pd-catalyzed carbon–nitrogen and carbon–oxygen bond formations, allowing cyclization under mild reaction conditions to provide 3-substituted indazoles and benzoisoxazoles. This methodology accommodates a variety of functional groups and generally affords the cyclized product in good yield. It has also been successfully applied to the total synthesis of nigellicine.

4. Experimental

4.1. General

All reactions were carried out under Ar atmosphere unless otherwise noted. 1,4-Dioxane was distilled from benzophenone ketyl under Ar atmosphere. Ethanol was distilled from sodium under Ar atmosphere. Melting points were measured with a Yazawa micro melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 (400 MHz) or JNM-ECA600 (600 MHz) using tetramethylsilane (TMS) and from residual non-deuterated solvent peak in other solvents (CD_3OD: 3.30 ppm and C_6D_6: 7.15 ppm) as internal standard. Chemical shifts (δ) are given from TMS (0 ppm) and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sep=septet, dd=double doublet, dt=double triplet, td=triple doublet, ddd=double double doublet, m=multiplet, br s=broad singlet, and br=broad signal. ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 (100 MHz) or JNM-ECA600 (150 MHz) and chemical shifts (δ) are given from $^{13}CDCl_3$ (77.0 ppm), $^{13}CD_3OD$ (49.0 ppm), and $^{13}C_6D_6$ (128.0 ppm). Mass spectra and high-resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. Fast atom bombardment mass spectra were measured on JEOL JMS-700 spectrometer. Elemental analyses were performed by Yanako CHN CORDER MT-6.

4.2. General procedure for the preparation of hydrazones 2a–2l

Acetyl chloride was slowly added to ethanol (1 mL) at 0 °C and stirred for 30 min at the same temperature. The reaction mixture was warmed to room temperature and stirred for another 30 min. The resulting mixture and a solution of ketone **1** in ethanol were added to a solution of *p*-toluenesulfonylhydrazide in ethanol and heated under reflux. The mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography.

4.2.1. 2-Bromoacetophenone 4-methylphenylsulfonylhydrazone (2a) (Table 1, entry 1). According to the general procedure, a mixture of **1a** (0.22 g, 1.1 mmol), acetyl

chloride (0.44 g, 5.6 mmol), and *p*-toluenesulfonylhydrazide (0.41 g, 2.2 mmol) in ethanol (10 mL) was refluxed for 24 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **2a** as a mixture of two isomers, which was re-chromatographed on silica gel (chloroform) to give **2a**-*E* (0.33 g, 82%) and **2a**-*Z* (0.071 g, 18%) as colorless solids, respectively. Isomers **2a**-*E*: mp 153–154 °C (colorless needles from hexane–acetone); IR ν (Nujol, cm^{-1}) 3198, 1377, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 2.43 (3H, s), 7.14–7.19 (2H, m), 7.26 (1H, td, J=7.5, 1.2 Hz), 7.32 (2H, d, J=8.5 Hz), 7.50 (1H, d, J=7.5 Hz), 7.89 (2H, d, J=8.5 Hz), 8.13 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.6, 121.2, 127.3, 128.1, 129.6, 130.1, 130.2, 133.0, 135.5, 140.2, 144.1, 154.7; MS *m*/*z* 368 (M^++2, 1.2), 366 (M^+, 1.1), 132 (100); HRMS calcd for $C_{15}H_{15}{}^{79}BrN_2O_2S$ 366.0038, found 366.0590. Anal. Calcd for $C_{15}H_{15}BrN_2O_2S$: C, 49.06; H, 4.12; N, 7.63. Found: C, 48.92; H, 3.93; N, 7.59. Isomers **2a**-*Z*: mp 153–154 °C (colorless needles from hexane–acetone); IR ν (Nujol, cm^{-1}) 3203, 1340, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.44 (3H, s), 6.99 (1H, dd, J=7.7, 1.7 Hz), 7.14 (1H, s), 7.26–7.32 (3H, m), 7.39 (1H, t, J=7.7 Hz), 7.59 (1H, d, J=7.7 Hz), 7.80 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.0, 119.5, 128.0, 128.2, 128.7, 129.4, 131.2, 133.5, 135.1, 135.4, 143.9, 153.3; MS *m*/*z* 368 (M^++2, 8.7), 366 (M^+, 8.4), 132 (100); HRMS calcd for $C_{15}H_{15}{}^{79}BrN_2O_2S$: 366.0038, found: 366.0000. Anal. Calcd for $C_{15}H_{15}BrN_2O_2S$: C, 49.06; H, 4.12; N, 7.63. Found: C, 49.04; H, 4.11; N, 7.60.

4.2.2. 1-(2-Bromophenyl)-2-methylpropan-1-one 4-methylphenylsulfonylhydrazone (2b) (Table 1, entry 2). Isopropylmagnesium bromide (0.65 M solution in THF, 12.5 mL, 8.1 mmol) was added to a solution of 2-bromobenzaldehyde (1.5 g, 8.1 mmol) in THF (5 mL) at −78 °C and stirred for 3 h at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h at the same temperature. Saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (25 mL×3). The combined organic solution was washed with water (5 mL) and brine (5 mL), and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to give 2-bromo-α-isopropylbenzylalcohol (0.33 g, 18%) as a colorless oil.

A mixture of the alcohol (0.33 g, 1.5 mmol) and PCC (1.56 g, 7.2 mmol) in anhydrous dichloromethane (15 mL) was stirred for 3 h at room temperature. The reaction mixture was diluted with diethyl ether (5 mL) and Florisil® was added. The mixture was filtered through a pad of Celite® and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (19:1)] to afford 2-bromophenyl isopropyl ketone (**1b**) (0.29 g, 89%) as a colorless oil; IR ν (neat, cm^{-1}) 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (6H, d, J=6.5 Hz), 3.31 (1H, sep, J=6.5 Hz), 7.25–7.30 (2H, m), 7.35 (1H, t, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 40.0, 118.4, 127.0, 127.9, 130.8, 133.1, 141.7, 208.2; MS *m*/*z* 228 (M^++2, 12.0), 226 (M^+, 12.4), 183 (100); HRMS calcd for $C_{10}H_{11}{}^{79}BrO$: 225.9993, found: 225.9997.

According to the general procedure, a mixture of **1b** (0.11 g, 0.49 mmol), acetyl chloride (0.19 g, 2.4 mmol), and *p*-toluenesulfonylhydrazide (0.18 g, 0.97 mmol) in ethanol (5 mL) was refluxed for 19 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **2b** (0.10 g, 53%, single isomer) as a colorless solid; mp 117–118 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3200, 1340, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.8 Hz), 2.43 (3H, s), 2.66 (1H, sep, J=6.8 Hz), 6.94 (1H, dd, J=7.4, 1.6 Hz), 7.01 (1H, s), 7.27 (1H, ddd, J=8.0, 7.6, 1.6 Hz), 7.30 (2H, d, J=8.0 Hz), 7.38 (1H, ddd, J=7.6, 7.4, 1.2 Hz), 7.58 (1H, dd, J=8.0, 1.2 Hz), 7.81 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.8, 21.7, 35.9, 120.3, 128.0, 128.1, 129.1, 130.9, 133.4, 133.9, 135.0, 143.8, 160.2; MS *m*/*z* 396 (M^++2, 4.5), 394 (M^+, 4.4), 315 (73.0), 168 (100); HRMS calcd for $C_{17}H_{19}{}^{79}BrN_2O_2S$: 394.0351, found: 394.0379. Anal. Calcd for $C_{17}H_{19}BrN_2O_2S$: C, 51.65; H, 4.84; N, 7.09. Found: C, 51.73; H, 4.81; N, 6.88.

4.2.3. *tert*-Butyl 2-(2-bromophenyl)-2-oxoacetate 4-methylphenylsulfonylhydrazone (2c) (Table 1, entry 3). A mixture of 2-bromoacetophenone (1.0 g, 5.0 mmol) and selenium dioxide (0.84 g, 7.6 mmol) in anhydrous pyridine (15 mL) was heated at 100 °C for 3 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated to give α-ketocarboxylic acid as an orange liquid. To a solution of the α-ketocarboxylic acid in dichloromethane (15 mL) were added DMAP (0.12 g, 1.0 mmol) and DIPC (1.3 g, 10.0 mmol) at 0 °C. After stirring for 30 min at 0 °C, ^{t}BuOH (0.74 g, 10.0 mmol) was added at 0 °C and stirred for 12 h at room temperature. The reaction mixture was extracted with chloroform (20 mL×3). The combined organic solution was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (30:1)] to afford *tert*-butyl 2-(2-bromophenyl)-2-oxoacetate (**1c**) (0.51 g, 35%) as a colorless solid; mp 53 °C (colorless prisms from hexane); IR ν (film, cm^{-1}) 1746, 1724, 1211, 1155; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (9H, s), 7.37–7.45 (2H, m), 7.60–7.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 84.7, 121.0, 127.5, 131.6, 133.4, 133.5, 135.9, 161.4, 187.8; MS *m*/*z* 185 (M^++2−$CO_2{}^t$Bu, 98.4), 183 (M^+−$CO_2{}^t$Bu, 98.7), 57 (100).

A mixture of **1c** (0.51 g, 1.8 mmol) and *p*-toluenesulfonylhydrazide (1.0 g, 5.4 mmol) in ethanol (6 mL) was heated at 50 °C for 3 h. The solvent was evaporated and the residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (3:1)] to give **2c** (0.70 g, 87%, *E*-isomer) as a colorless solid; mp 155 °C (colorless prisms from hexane–ethyl acetate–methanol); IR ν (film, cm^{-1}) 1705, 1354, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 2.43 (3H, s), 7.09 (1H, d, J=7.7 Hz), 7.30–7.32 (3H, m), 7.39 (1H, t, J=7.7 Hz), 7.59 (1H, d, J=7.7 Hz), 7.82–7.84 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.9, 82.7, 121.5, 128.1, 128.3, 129.5, 129.9, 130.4, 131.7, 133.3, 134.7, 144.48, 144.52, 160.6; MS *m*/*z* 455 (M^++3, 0.4), 453 (M^++1, 0.4); HRMS calcd for $C_{19}H_{22}{}^{79}BrN_2O_4S$: 453.0483, found:

453.0496. Anal. Calcd for $C_{19}H_{21}BrN_2O_4S$: C, 50.34; H, 4.67; N, 6.18. Found: C, 50.18; H, 4.50; N, 6.47.

4.2.4. *N*,*N*-Diethyl-2-(2-bromophenyl)-2-oxoacetamide 4-methylphenylsulfonylhydrazone (2d) (Table 1, entry 4). A mixture of 2-bromoacetophenone (1.0 g, 5.0 mmol) and selenium dioxide (0.83 g, 7.5 mmol) in anhydrous pyridine (15 mL) was heated at 100 °C for 3 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated to give an orange liquid, which was dissolved in HMPA (10 mL) and thionyl chloride (1.2 g, 10.0 mmol) was added at 0 °C. After stirring at room temperature for 3 h, diethylamine (1.3 g, 17.5 mmol) was added at 0 °C and stirred at room temperature overnight. After the reaction was completed, the reaction mixture was extracted with diethyl ether (20 mL×3). The combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to give *N*,*N*-diethyl-2-(2-bromophenyl)-2-oxoacetamide (**1d**) (0.67 g, 47%) as a pale brown oil; IR ν (film, cm^{-1}) 1645; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.29 (6H, m), 3.37 (2H, q, J=7.1 Hz), 3.52 (2H, q, J=7.1 Hz), 7.39–7.45 (2H, m), 7.64 (1H, d, J=7.5 Hz), 7.81 (1H, dd, J=7.5, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 13.8, 39.3, 42.4, 121.5, 127.6, 132.7, 133.9, 134.1, 135.2, 165.8, 190.7; MS *m*/*z* 286 (M^++3, 5.2), 284 (M^++1, 5.4), 100 (100); HRMS calcd for $C_{12}H_{15}{}^{79}BrNO_2$: 284.0286, found: 284.0250.

According to the general procedure, a mixture of **1d** (1.1 g, 4.0 mmol), acetyl chloride (1.6 g, 19.8 mmol), and *p*-toluenesulfonylhydrazide (1.5 g, 7.9 mmol) in ethanol (20 mL) was refluxed for 20 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (2:1)] to afford **2d** as a mixture of two isomers, which was re-chromatographed on silica gel [chloroform to chloroform–ethyl acetate (9:1)] to give the *E*-isomer (0.97 g, 54%) and the *Z*-isomer (0.75 g, 42%) as colorless solids, respectively. *E*-Isomer: mp 178–179 °C (colorless prisms from hexane–acetone); IR ν (film, cm^{-1}) 3050, 1616, 1342, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.1 Hz), 2.45 (3H, s), 3.39 (4H, br), 7.26–7.35 (4H, m), 7.42 (1H, t, J=7.7 Hz), 7.61 (1H, d, J=7.7 Hz), 7.65 (1H, s), 7.80 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.4, 21.7, 40.6, 43.5, 120.6, 127.9, 128.2, 129.6, 130.8, 131.2, 131.8, 133.2, 135.1, 144.5, 146.2, 163.2; MS *m*/*z* 454 (M^++3, 1.2), 452 (M^++1, 1.2), 72 (100); HRMS calcd for $C_{19}H_{23}{}^{79}BrN_3O_3S$: 452.0643, found: 452.0605. Anal. Calcd for $C_{19}H_{22}BrN_3O_3S$: C, 50.45; H, 4.90; N, 9.29. Found: C, 50.36; H, 4.87; N, 9.25. *Z*-Isomer: mp 179–180 °C (colorless scales from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3064, 1624, 1346, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, J=7.2 Hz), 1.20 (3H, t, J=7.2 Hz), 2.36 (3H, s), 3.05 (2H, q, J=7.2 Hz), 3.45 (2H, q, J=7.2 Hz), 7.19–7.35 (4H, m), 7.53–7.55 (2H, m), 7.82 (2H, d, J=8.3 Hz), 9.57 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 13.1, 21.5, 39.8, 42.5, 121.2, 127.6, 127.8, 129.4, 130.4, 130.7, 133.8, 134.6, 135.1, 143.9, 147.3, 161.8; MS *m*/*z* 454 (M^++3, 3.8), 452 (M^++1, 3.7), 72 (100); HRMS calcd for $C_{19}H_{23}{}^{79}BrN_3O_3S$: 452.0643, found: 452.0646. Anal. Calcd for $C_{19}H_{22}BrN_3O_3S$: C, 50.45; H, 4.90; N, 9.29. Found: C, 50.58; H, 4.89; N, 9.02.

4.2.5. 2-Bromobenzophenone 4-methylphenylsulfonylhydrazone (2e) (Table 1, entry 5). A mixture of 2-bromobenzoic acid (1.0 g, 5.0 mmol) and thionyl chloride (1.2 g, 10.0 mmol) in chloroform (10 mL) was heated under reflux for 3 h. After the excess thionyl chloride and chloroform had been evaporated, the crude benzoyl chloride was dissolved in benzene (4 mL) and added to a suspension of aluminum chloride (0.75 g, 5.5 mmol) in benzene (8 mL). After being refluxed for 6 h, the reaction mixture was quenched with diluted HCl (2 mL). The mixture was extracted with ethyl acetate (20 mL×3) and the combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to give 2-bromobenzophenone (**1e**) (1.0 g, 77%) as a colorless oil; IR ν (neat, cm^{-1}) 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.44 (3H, m), 7.48 (2H, t, J=7.5 Hz), 7.59 (1H, d, J=8.2 Hz), 7.63–7.65 (1H, m), 7.83 (2H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.3, 127.0, 128.5, 128.8, 130.0, 131.0, 133.0, 133.5, 135.9, 140.4, 195.5; MS *m*/*z* 262 (M^++2, 32.0), 260 (M^+, 31.4), 105 (100); HRMS calcd for $C_{13}H_9{}^{79}BrO$: 259.9837, found: 259.9811.

According to the general procedure, a mixture of **1e** (1.5 g, 5.7 mmol), acetyl chloride (2.3 g, 28.7 mmol), and *p*-toluenesulfonylhydrazide (2.1 g, 11.5 mmol) in ethanol (25 mL) was refluxed for 43 h. The crude stuff was chromatographed on silica gel [hexane–ethyl acetate (4:1)] to afford **2e** (1.8 g, 74%, single isomer) as a colorless solid; mp 125–126 °C (colorless prisms from hexane–chloroform, lit.[24] mp 126 °C); IR ν (Nujol, cm^{-1}) 3196, 1389, 1167; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 7.10 (1H, d, J=7.8 Hz), 7.20–7.49 (10H, m), 7.70 (1H, d, J=7.8 Hz), 7.89 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 121.4, 126.9, 128.0, 128.3, 128.6, 129.4, 129.5, 129.8, 130.1, 131.5, 132.5, 133.6, 135.3, 144.0, 152.0; MS *m*/*z* 430 (M^++2, 9.8), 428 (M^+, 9.1), 193 (100); HRMS calcd for $C_{20}H_{17}{}^{79}BrN_2O_2S$: 428.0194, found: 428.0182. Anal. Calcd for $C_{20}H_{17}BrN_2O_2S$: C, 55.95; H, 3.99; N, 6.52. Found: C, 55.83; H, 3.87; N, 6.59.

4.2.6. 2-Bromo-4-nitrobenzophenone 4-methylphenylsulfonylhydrazone (2f) (Table 1, entry 6). A mixture of 2-bromo-4-nitrobenzoic acid (1.0 g, 4.0 mmol) and thionyl chloride (0.95 g, 8.0 mmol) in chloroform (8 mL) was heated under reflux for 3 h. After the excess thionyl chloride and chloroform had been evaporated, the crude benzoyl chloride was dissolved in benzene (3 mL) and added to a suspension of aluminum chloride (0.61 g, 4.4 mmol) in benzene (6 mL). After being refluxed for 5 h, the reaction mixture was quenched with diluted HCl (2 mL). The mixture was extracted with ethyl acetate (20 mL×3), the combined organic layer was washed with brine (5 mL), and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (6:1)] to give 2-bromo-4-nitrobenzophenone (**1f**) (1.1 g, 91%) as a colorless solid; mp 116–118 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1674, 1510, 1300; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, t, J=7.6 Hz), 7.66 (1H, t, J=7.6 Hz), 7.79 (2H, d, J=7.6 Hz), 7.85 (1H, d, J=8.5 Hz), 8.19 (1H, s), 8.19–8.21 (1H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 124.6, 126.7, 127.2, 130.0, 131.1, 135.5, 135.7, 136.5, 143.2, 148.5, 194.9; MS

m/z 307 (M^++2, 18.0), 305 (M^+, 18.4), 105 (100); HRMS calcd for $C_{13}H_8{}^{79}BrNO_3$: 304.9688, found: 304.9687.

According to the general procedure, a mixture of **1f** (34.2 mg, 0.11 mmol), acetyl chloride (44.2 mg, 0.6 mmol), *p*-toluenesulfonylhydrazide (0.17 g, 0.9 mmol), and $MgSO_4$ (50 mg) in ethanol (3 mL) was refluxed for 44 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **2f** as a mixture of two isomers, which was separated by re-chromatography on silica gel (chloroform) to provide the major isomer (18.6 mg, 35%) and the minor isomer (6.3 mg, 12%) as colorless solids, respectively. Major isomer: mp 194–195 °C (colorless scales from hexane–diisopropyl ether); IR ν (Nujol, cm^{-1}) 3175, 1526, 1340, 1167; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (3H, s), 7.22–7.40 (7H, m), 7.88 (2H, d, J=8.4 Hz), 7.92–7.94 (3H, m), 8.24 (1H, dd, J=8.4, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 125.0, 125.9, 126.7, 127.7, 128.0, 128.4, 128.5, 129.4, 129.5, 134.1, 134.5, 134.9, 144.4, 147.6, 149.9; MS *m/z* 475 (M^++2, 11.0), 473 (M^+, 10.7), 393 (100); HRMS calcd for $C_{20}H_{16}{}^{79}BrN_3O_4S$: 473.0045, found: 473.0041. Anal. Calcd for $C_{20}H_{16}BrN_3O_4S$: C, 50.64; H, 3.40; N, 8.86. Found: C, 50.55; H, 3.33; N, 8.66. Minor isomer: mp 221–222 °C (colorless plates from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1533, 1348, 1167; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (3H, s), 7.26–7.29 (2H, m), 7.40 (2H, d, J=8.2 Hz), 7.48–7.50 (3H, m), 7.68 (1H, d, J=8.8 Hz), 7.84 (2H, d, J=8.2 Hz), 7.89 (1H, d, J=2.6 Hz), 8.05 (1H, dd, J=8.8, 2.6 Hz), 8.19 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 124.7, 126.7, 128.1, 128.5, 129.6, 129.8, 130.06, 130.11, 130.9, 134.6, 139.9, 144.9, 146.8, 151.5; MS *m/z* 475 (M^++2, 6.7), 473 (M^+, 6.4), 393 (100). Anal. Calcd for $C_{20}H_{16}BrN_3O_4S$: C, 50.64; H, 3.40; N, 8.86. Found: C, 50.69; H, 3.36; N, 8.75.

4.2.7. 2-Bromo-5-methoxybenzophenone 4-methylphenylsulfonylhydrazone (2g) (Table 1, entry 7). A mixture of 2-bromo-5-methoxybenzoic acid (2.3 g, 10.0 mmol) and thionyl chloride (2.4 g, 20.0 mmol) in chloroform (15 mL) was heated under reflux for 3 h. After the excess thionyl chloride and chloroform had been evaporated, the crude benzoyl chloride was dissolved in benzene (6 mL) and added to a suspension of aluminum chloride (1.7 g, 12.5 mmol) in benzene (12 mL). After being refluxed for 6 h, the reaction mixture was quenched with diluted HCl (2 mL). The mixture was extracted with ethyl acetate (30 mL×3) and the combined organic layer was washed with brine (7 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to afford 2-bromo-5-methoxybenzophenone (**1g**) (2.3 g, 80%) as a colorless oil; IR ν (neat, cm^{-1}) 1674; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 6.86–6.91 (2H, m), 7.46 (2H, t, J=7.7 Hz), 7.50 (1H, d, J=8.1 Hz), 7.59 (1H, t, J=7.7 Hz), 7.82 (2H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 109.5, 114.0, 117.2, 128.4, 130.0, 133.5, 133.7, 135.7, 141.2, 158.5, 195.3; MS *m/z* 292 (M^++2, 38.0), 290 (M^+, 38.6), 105 (100); HRMS calcd for $C_{14}H_{11}{}^{79}BrO_2$: 289.9942, found: 289.9925.

According to the general procedure, a mixture of **1g** (0.11 g, 0.4 mmol), acetyl chloride (66.2 mg, 0.8 mmol), and *p*-toluenesulfonylhydrazide (0.15 g, 0.8 mmol) in ethanol (7 mL) was refluxed for 21 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (4:1)] to afford **2g** (0.12 g, 67%, single isomer) as a colorless solid; mp 164–165 °C (colorless needles from hexane–diisopropyl ether); IR ν (film, cm^{-1}) 3189, 1392, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s), 3.75 (3H, s), 6.58 (1H, d, J=2.9 Hz), 6.90 (1H, dd, J=9.0, 2.9 Hz), 7.27–7.34 (5H, m), 7.43 (1H, s), 7.45 (2H, d, J=8.1 Hz), 7.53 (1H, d, J=9.0 Hz), 7.86 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.6, 126.9, 127.8, 128.1, 128.5, 129.2, 129.4, 129.7, 131.3, 133.7, 134.0, 135.1, 135.2, 142.2, 143.9, 152.2; MS *m/z* 460 (M^++2, 1.0), 458 (M^+, 1.0), 195 (100); HRMS calcd for $C_{21}H_{19}{}^{79}BrN_2O_3S$: 458.0300, found: 458.0277. Anal. Calcd for $C_{21}H_{19}BrN_2O_3S$: C, 54.91; H, 4.17; N, 6.10. Found: C, 54.81; H, 4.12; N, 6.15.

4.2.8. 2-Bromo-4-methylbenzophenone 4-methylphenylsulfonylhydrazone (2h) (Table 1, entry 8). A mixture of 2-bromo-4-methylbenzoic acid (0.50 g, 2.3 mmol) and thionyl chloride (0.55 g, 4.6 mmol) in chloroform (4.0 mL) was heated under reflux for 3 h. After the excess thionyl chloride and chloroform had been evaporated, the crude benzoyl chloride was dissolved in benzene (2 mL) and added to a suspension of aluminum chloride (0.35 g, 2.5 mmol) in benzene (3.7 mL). After being refluxed for 6 h, the reaction mixture was quenched with diluted HCl (1 mL). The mixture was extracted with ethyl acetate (20 mL×3) and the combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to give 2-bromo-4-methylbenzophenone (**1h**) (0.58 g, 91%) as a colorless oil; IR ν (neat, cm^{-1}) 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (3H, s), 7.34–7.36 (1H, m), 7.38 (1H, s), 7.58–7.60 (1H, m), 7.61 (2H, t, J=7.2 Hz), 7.73 (1H, t, J=7.2 Hz), 7.94 (2H, d, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 119.4, 127.7, 128.4, 129.0, 130.0, 133.3, 133.5, 136.3, 137.4, 141.7, 195.6; MS *m/z* 276 (M^++2, 98.2), 274 (M^+, 98.0), 197 (100); HRMS calcd for $C_{14}H_{11}{}^{79}BrO$: 273.9993, found: 273.9982.

According to the general procedure, a mixture of **1h** (0.42 g, 1.5 mmol), acetyl chloride (0.61 g, 7.7 mmol), and *p*-toluenesulfonylhydrazide (0.58 g, 3.1 mmol) in ethanol (15 mL) was refluxed for 13 h. The residue was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **2h** (0.55 g, 80%, single isomer) as a colorless solid; mp 138–139 °C (colorless prisms from diisopropyl ether–chloroform); IR ν (film, cm^{-1}) 3196, 1386, 1167; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 2.43 (3H, s), 6.96 (1H, d, J=7.8 Hz), 7.25–7.34 (6H, m), 7.42–7.44 (3H, m), 7.51 (1H, s), 7.87 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.6, 126.9, 127.8, 128.1, 128.5, 129.2, 129.4, 129.7, 131.3, 133.7, 134.0, 135.1, 135.2, 142.2, 143.9, 152.2; MS *m/z* 444 (M^++2, 53.2), 442 (M^+, 51.0), 208 (100); HRMS calcd for $C_{21}H_{19}{}^{79}BrN_2O_2S$: 442.0351, found: 442.0391. Anal. Calcd for $C_{21}H_{19}BrN_2O_2S$: C, 56.89; H, 4.32; N, 6.32. Found: C, 56.84; H, 4.23; N, 6.26.

4.2.9. 2-Bromo-4′-methoxybenzophenone 4-methylphenylsulfonylhydrazone (2i) (Table 1, entry 9). BuLi (1.45 M solution in hexane, 2.76 mL, 4.0 mmol) was added to a solution of 4-bromoanisole (0.75 g, 4.0 mmol) in THF at −78 °C and stirred for 30 min at the same temperature. A solution of 2-bromobenzaldehyde (0.74 g, 4.0 mmol) in

THF was dropped into the reaction mixture at −78 °C. After being stirred for 2 h at the same temperature, saturated aqueous NH_4Cl solution was added to the mixture and the aqueous phase was extracted with ethyl acetate (20 mL×3). The combined organic solution was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to give 2-bromo-α-(4-methoxyphenyl)benzyl alcohol (0.68 g, 58%) as a colorless oil.

A mixture of the alcohol (0.66 g, 2.3 mmol) and PCC (1.2 g, 5.7 mmol) in anhydrous dichloromethane (20 mL) was stirred for 2 h at room temperature. The reaction mixture was diluted with diethyl ether (10 mL) and Florisil® was added. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [hexane–ethyl acetate (5:1)] to give 2-bromo-4′-methoxybenzophenone (**1i**) (0.59 g, 90%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 6.93 (2H, d, J=8.8 Hz), 7.31–7.35 (2H, m), 7.40 (1H, t, J=7.6 Hz), 7.63 (1H, d, J=7.6 Hz), 7.78 (2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 113.9, 119.3, 127.1, 128.7, 129.0, 130.7, 132.6, 133.0, 141.0, 164.0, 194.3.

According to the general procedure, a mixture of **1i** (0.58 g, 2.0 mmol), acetyl chloride (0.77 g, 9.9 mmol), and *p*-toluenesulfonylhydrazide (0.55 g, 3.0 mmol) in ethanol (20 mL) was refluxed for 16 h. The crude stuff was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **2i** (0.90 g, 99%, single isomer) as a colorless solid; mp 178–180 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3200, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 3.79 (3H, s), 6.81 (2H, d, J=9.0 Hz), 7.07 (1H, d, J=6.7 Hz), 7.19 (1H, s), 7.30 (2H, d, J=8.1 Hz), 7.35–7.39 (3H, m), 7.47 (1H, t, J=7.2 Hz), 7.68 (1H, d, J=7.2 Hz), 7.87 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 55.3, 113.7, 121.4, 127.7, 128.0, 128.5, 128.6, 129.4, 130.1, 131.5, 132.8, 133.6, 135.3, 144.0, 152.0, 161.0; MS *m*/*z* 460 (M^++2, 42.5), 458 (M^+, 40.1), 305 (98.9), 303 (100); HRMS calcd for $C_{21}H_{19}{}^{79}BrN_2O_3S$: 458.0300, found: 458.0316. Anal. Calcd for $C_{21}H_{19}BrN_2O_3S$: C, 54.91; H, 4.17; N, 6.10. Found: C, 54.81; H, 4.08; N, 6.25.

4.2.10. 2-(Nonafluorobutanesulfonyloxy)benzophenone 4-methylphenylsulfonylhydrazone (2j) (Table 1, entry 10). To a suspension of NaH (0.18 g, 7.6 mmol) in anhydrous THF (10 mL) was added a solution of 2-hydroxybenzophenone (1.0 g, 5.0 mmol) in THF (10 mL) at 0 °C and the mixture was stirred for 30 min at the same temperature. $CF_3(CF_2)_3SO_2F$ (2.6 g, 8.6 mmol) was dropped at 0 °C and the whole reaction mixture was stirred for 23 h at room temperature. The reaction mixture was extracted with ethyl acetate (20 mL×3) and the combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (19:1)] to give 2-(nonafluorobutanesulfonyloxy)benzophenone (**1j**) (2.2 g, 92%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.65 (7H, m), 7.80–7.82 (2H, m); MS *m*/*z* 480 (M^+, 97.0), 105 (100); HRMS calcd for $C_{17}H_9F_9O_4S$: 480.0078, found: 480.0048.

According to the general procedure, a mixture of **1j** (2.2 g, 4.6 mmol), acetyl chloride (1.80 g, 22.9 mmol), and *p*-toluenesulfonylhydrazide (1.3 g, 6.9 mmol) in ethanol (20 mL) was refluxed for 47 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (3:1)] to afford **2j** (2.2 g, 73%, single isomer) as a colorless solid; mp 100–102 °C (colorless needles from acetone–hexane); IR ν (film, cm^{-1}) 3206; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s), 7.26–7.47 (9H, m), 7.51 (1H, s), 7.58–7.66 (2H, m), 7.87 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 122.8, 126.0, 126.8, 128.18, 128.25, 129.3, 129.7, 130.2, 131.4, 132.4, 134.6, 135.0, 144.2, 146.0, 148.1 (the ^{13}C signals corresponding to $CF_2CF_2CF_2CF_3$ group were not detected); MS *m*/*z* 648 (M^+, 31.2), 210 (100); HRMS calcd for $C_{24}H_{17}F_9N_2O_5S_2$: 648.0435, found: 648.0412. Anal. Calcd for $C_{24}H_{17}F_9N_2O_5S_2$: C, 44.45; H, 2.64; N, 4.32. Found: C, 44.37; H, 2.82; N, 4.37.

4.2.11. 2-Chloropropiophenone 4-methylphenylsulfonylhydrazone (2k) (Table 1, entry 11). To a solution of 2-chlorobenzaldehyde (1.0 g, 7.1 mmol) in THF (4.4 mL) was dropped ethylmagnesium bromide (1.0 M solution in THF, 7.1 mL, 7.1 mmol) at −78 °C and stirred for 20 min at the same temperature, and then warmed to room temperature. After being stirred for 4 h at the same temperature, saturated aqueous NH_4Cl solution (10 mL) was added to the mixture and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water (5 mL) and brine (5 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography eluting with hexane–ethyl acetate (4:1) to give 2-chloro-α-ethylbenzyl alcohol (0.79 g, 65%) as a colorless oil.

A mixture of the alcohol (0.50 g, 2.9 mmol) and PCC (0.69 g, 3.2 mmol) in anhydrous dichloromethane (15 mL) was stirred for 2 h at room temperature. The reaction mixture was diluted with diethyl ether (10 mL) and Florisil® was added. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [hexane–ethyl acetate (5:1)] to give 2-chloropropiophenone (**1k**) (0.48 g, 99%) as a colorless oil; IR ν (neat, cm^{-1}) 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, J=7.3 Hz), 2.96 (2H, q, J=7.3 Hz), 7.30 (1H, td, J=7.3, 1.5 Hz), 7.36 (1H, td, J=7.3, 1.5 Hz), 7.39–7.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 36.2, 126.7, 128.5, 130.3, 130.6, 131.3, 139.5, 204.0; MS *m*/*z* 170 (M^++2, 4.1), 168 (M^+, 8.4), 139 (M^+−29, 100); HRMS calcd for $C_9H_9{}^{35}ClO$: 168.0342, found: 168.0340.

According to the general procedure, a mixture of **1k** (0.28 g, 1.7 mmol), acetyl chloride (0.66 g, 8.4 mmol), and *p*-toluenesulfonylhydrazide (0.94 g, 5.0 mmol) in ethanol (10 mL) was heated under reflux for 25 h. The crude stuff was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **2k** as a mixture of two isomers, which were re-chromatographed on silica gel flash column chromatography eluting with chloroform–ethyl acetate (50:1) to afford the *E*-isomer (0.12 g, 21%) and the *Z*-isomer (0.28 g, 49%) as colorless solids, respectively. *E*-Isomer: mp 140–142 °C (colorless scales from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3211, 1167; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 0.95 (3H, t, J=7.6 Hz), 2.43 (3H, s), 2.57 (2H, q, J=7.6 Hz), 7.11 (1H, dd, J=7.4, 1.4 Hz), 7.20–7.32 (5H, m), 7.87 (2H, d, J=8.0 Hz), 8.27 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 21.7, 23.4, 126.6, 127.9, 129.47, 129.49, 129.7, 130.3, 132.2, 135.3, 136.9, 144.0, 158.7; MS m/z 338 (M^++2, 3.2), 336 (M^+, 7.5), 181 (100); HRMS calcd for $C_{16}H_{17}{}^{35}ClN_2O_2S$: 336.0699, found: 366.0670. Anal. Calcd for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32. Found: C, 56.87; H, 5.11; N, 8.34. *Z*-Isomer: mp 116–117 °C (colorless scales from hexane–acetone); IR ν (film, cm^{-1}) 3203, 1338, 1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, t, J=7.6 Hz), 2.43 (3H, s), 2.46 (2H, q, J=7.6 Hz), 6.96 (1H, dd, J=6.8, 1.9 Hz), 7.11 (1H, s), 7.29 (2H, d, J=7.9 Hz), 7.32–7.40 (3H, m), 7.78 (2H, d, J=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 21.6, 30.9, 127.7, 127.8, 128.4, 129.2, 130.1, 130.7, 130.9, 132.1, 135.1, 143.8, 156.2; MS m/z 338 (M^++2, 3.3), 336 (M^+, 7.9), 181 (100); HRMS calcd for $C_{16}H_{17}{}^{35}ClN_2O_2S$: 336.0699, found: 366.0701. Anal. Calcd for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32. Found: C, 57.05; H, 5.15; N, 8.23.

4.2.12. 3-(2-Bromopyridinyl) phenyl ketone 4-methylphenylsulfonylhydrazone (2l) (Table 1, entry 12). A solution of LDA (12.0 mmol), prepared from BuLi (1.26 M solution in hexane, 9.5 mL, 12.0 mmol) and diisopropylamine (1.2 g, 12.0 mmol) in anhydrous THF (10 mL) at 0 °C, was slowly added to a solution of 2-bromopyridine (1.6 g, 10.0 mmol) in anhydrous THF (5 mL) at −78 °C, and the reaction mixture was stirred for 3 h at the same temperature. Benzaldehyde (1.3 g, 12.0 mmol) was added at −78 °C and the whole reaction mixture was gradually warmed up to room temperature, and then stirred for 14 h at the same temperature. Saturated aqueous NH_4Cl solution (5 mL) was added to the mixture and the inorganic precipitate was filtered through a pad of Celite®. The filtrate was extracted with ethyl acetate (15 mL×3) and the combined organic layer was washed with brine (3 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with hexane–ethyl acetate (4:1) to give 2-bromo-3-(α-hydroxybenzyl)pyridine (1.2 g, 46%) as a colorless oil.

To a solution of the alcohol (1.2 g, 4.6 mmol) in anhydrous dichloromethane (50 mL) was added PCC (3.9 g, 18.3 mmol) at room temperature and the reaction mixture was stirred for 4 h at the same temperature. Florisil® was added and the mixture was filtered through a pad of Celite®. The filtrate was extracted with chloroform (15 mL×3) and the combined organic layer was washed with brine (3 mL) and dried over $MgSO_4$. The organic solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography eluting with hexane–ethyl acetate (4:1) to give 3-(2-bromopyridinyl) phenyl ketone (**1l**) (1.1 g, 93%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, dd, J=7.7, 4.9 Hz), 7.49 (2H, t, J=7.7 Hz), 7.62–7.68 (2H, m), 7.80–7.82 (2H, m), 8.52 (1H, dd, J=4.9, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.3, 95.6, 96.9, 101.0, 102.3, 104.0, 104.5, 105.3, 117.8, 160.5; MS m/z 263 (M^++2, 38.2), 261 (M^+, 38.3), 105 (100); HRMS calcd for $C_{12}H_8{}^{79}BrNO$: 260.9789, found: 260.9774.

According to the general procedure, a mixture of **1l** (1.1 g, 4.2 mmol), acetyl chloride (1.7 g, 21.1 mmol), and *p*-toluenesulfonylhydrazide (1.6 g, 8.4 mmol) in ethanol (20 mL) was refluxed for 24 h. The residue was chromatographed on silica gel [hexane–ethyl acetate (2:1)] to afford **2l** (0.74 g, 41%, single isomer) as a colorless solid; mp 188–190 °C (colorless plates from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3194, 1396, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (3H, s), 7.26–7.44 (6H, m), 7.32 (2H, d, J=7.9 Hz), 7.54 (1H, dd, J=7.6, 2.0 Hz), 7.60 (1H, s), 7.86 (2H, d, J=7.9 Hz), 8.54 (1H, dd, J=5.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 123.3, 126.7, 127.1, 127.9, 128.5, 129.6, 130.2, 134.6, 134.9, 139.5, 144.3, 148.8, 149.2, 151.4; MS m/z 431 (M^++2, 0.7), 429 (M^+, 0.7), 194 (64.4), 166 (100); HRMS calcd for $C_{19}H_{16}{}^{79}BrN_3O_2S$: 429.0147, found: 429.0157.

4.3. General procedure for the synthesis of the oximes 3e, 3f, 3g, 3j, and 3m

A mixture of ketone **1** and hydroxylamine hydrochloride in ethanol was refluxed under Ar atmosphere. H_2O was added to the mixture and extracted with ethyl acetate. The combined organic solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography.

4.3.1. 2-Bromobenzophenone oxime (3e) (Table 2, entry 1). According to the general procedure, a mixture of **1e** (20.9 mg, 0.080 mmol) and hydroxylamine hydrochloride (0.17 g, 2.4 mmol) in ethanol (5 mL) was refluxed for 71 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **3e** [the major isomer (17.5 mg, 79%) and the minor isomer (2.8 mg, 13%)] as colorless solids. Major isomer: mp 122–125 °C (colorless scales from diethyl ether–hexane, lit.[25] mp 125 °C); IR ν (film, cm^{-1}) 3300; ^{1}H NMR (400 MHz, C_6D_6) δ 6.70 (1H, ddd, J=7.9, 7.7, 1.6 Hz), 6.87 (1H, dd, J=7.7, 7.6 Hz), 6.91 (1H, dd, J=7.6, 1.6 Hz), 7.02–7.04 (3H, m), 7.36 (1H, d, J=7.9 Hz), 7.63 (1H, s), 7.62–7.64 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 122.4, 127.2, 127.3, 128.7, 129.6, 130.0, 130.3, 132.9, 135.1, 135.8, 156.8; MS m/z 277 (M^++2, 72.7), 275 (M^+, 73.3), 260 (36.7), 258 (37.5), 196 (100). Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.69; H, 3.74; N, 5.06. Minor isomer: mp 124–126 °C (colorless scales from diethyl ether–hexane, lit.[25] mp 125 °C); IR ν (film, cm^{-1}) 3200; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, td, J=8.0, 1.6 Hz), 7.33–7.37 (4H, m), 7.43 (1H, dd, J=7.6, 1.6 Hz), 7.56–7.59 (3H, m), 9.50 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3, 127.3, 127.9, 129.5, 130.0, 130.3, 131.6, 131.9, 133.3, 137.8, 156.7; MS m/z 277 (M^++2, 59.4), 275 (M^+, 60.0), 260 (33.7), 258 (34.2), 196 (100). Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.62; H, 3.75; N, 5.04.

4.3.2. 2-Bromo-4-nitrobenzophenone oxime (3f) (Table 2, entry 2). According to the general procedure, a mixture of **1f** (0.14 g, 0.46 mmol) and hydroxylamine hydrochloride (0.64 g, 9.2 mol) in ethanol (6 mL) was refluxed for 43 h. The crude product was chromatographed on silica gel eluting with chloroform to afford **3f** [the major isomer (0.11 g, 73%) and the minor isomer (0.034 g, 23%)] as

colorless solids. Major isomer: IR ν (film, cm^{-1}) 3287; ^1H NMR (400 MHz, CD_3OD) δ 7.32–7.44 (6H, m), 7.97 (1H, d, J=8.9 Hz), 8.04 (1H, d, J=2.7 Hz), 8.18 (1H, dd, J=8.9, 2.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 125.5, 126.1, 127.4, 129.5, 130.4, 130.5, 135.1, 135.5, 138.9, 148.6, 154.8; MS m/z 322 (M^++2, 98.8), 320 (M^+, 100), 305 (23.5), 303 (23.8), 259 (23.5), 257 (23.7); HRMS calcd for $C_{13}H_9{}^{79}BrN_2O_3$: 319.9797, found: 319.9821. Anal. Calcd for $C_{13}H_9BrNO_3$: C, 48.62; H, 2.82; N, 8.72. Found: C, 48.44; H, 2.96; N, 8.61. Minor isomer: IR ν (film, cm^{-1}) 3182; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.43 (3H, m), 7.54–7.57 (2H, m), 7.79 (1H, d, J=8.8 Hz), 7.98 (1H, br s), 8.12 (1H, dd, J=8.8, 2.8 Hz), 8.30 (1H, d, J=2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.7, 126.5, 128.2, 129.8, 130.1, 130.7, 130.9, 134.4, 139.3, 146.9, 155.4; MS m/z 322 (M^++2, 98.2), 320 (M^+, 100), 305 (25.2), 303 (25.4), 259 (24.6), 257 (23.9); HRMS calcd for $C_{13}H_9{}^{79}BrN_2O_3$: 319.9797, found: 319.9803.

4.3.3. 2-Bromo-5-methoxybenzophenone oxime (3g) (Table 2, entry 3). According to the general procedure, a mixture of **1g** (0.16 g, 0.54 mmol) and hydroxylamine hydrochloride (1.0 g, 15 mmol) in ethanol (18 mL) was refluxed for 43 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **3g** [the major isomer (0.13 g, 77%) and the minor isomer (0.024 g, 15%)] as colorless solids. Major isomer: IR ν (film, cm^{-1}) 3286; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.76 (1H, d, J=2.9 Hz), 6.87 (1H, dd, J=8.7, 2.9 Hz), 7.32–7.38 (3H, m), 7.49 (2H, dd, J=6.9, 1.9 Hz), 7.57 (1H, d, J=8.7 Hz), 7.76 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 113.6, 116.4, 117.0, 127.9, 129.6, 130.0, 131.7, 133.9, 138.4, 156.5, 158.6; MS m/z 307 (M^++2, 52.5), 305 (M^+, 53.0), 226 (100); HRMS calcd for $C_{14}H_{12}{}^{79}BrNO_2$: 305.0051, found: 305.0052. Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58. Found: C, 54.85; H, 3.99; N, 4.32. Minor isomer: IR ν (film, cm^{-1}) 3232; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.83 (1H, dd, J=8.8, 3.0 Hz), 6.99 (1H, d, J=3.0 Hz), 7.36–7.38 (3H, m), 7.45 (1H, d, J=8.8 Hz), 7.59–7.61 (2H, ddd, J=5.8, 2.6, 1.6 Hz), 8.93 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 113.6, 116.4, 117.0, 127.9, 129.6, 130.0, 131.7, 133.9, 138.4, 156.7, 158.7; MS m/z 307 (M^++2, 50.9), 305 (M^+, 51.3), 226 (100); HRMS calcd for $C_{14}H_{12}{}^{79}BrNO_2$: 305.0051, found: 305.0045.

4.3.4. 2-(Nonafluorobutanesulfonyloxy)benzophenone oxime (3j) (Table 2, entry 4). According to the general procedure, a mixture of **1j** (2.1 g, 4.5 mmol) and hydroxylamine hydrochloride (6.4 g, 92 mmol) in ethanol (24 mL) was refluxed for 45 h. The crude stuff was purified by silica gel column chromatography [hexane–ethyl acetate (19:1)] to afford **3j** [the major isomer (1.8 g, 80%) and the minor isomer (0.34 g, 16%)] as colorless solids. Major isomer: IR ν (film, cm^{-1}) 3276; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.41 (4H, m), 7.45–7.51 (4H, m), 7.56 (1H, td, J=7.8, 2.0 Hz), 8.00 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 126.7, 127.1, 128.1, 128.4, 129.9, 130.9, 131.0, 134.3, 146.8, 153.0 (the ^{13}C signals corresponding to $CF_2CF_2CF_2CF_3$ group were not detected); MS m/z 495 (M^+, 93.8), 196 (100); HRMS calcd for $C_{17}H_{19}F_9NO_4S$: 495.0187, found: 495.0190. Anal. Calcd for $C_{17}H_{10}F_9NO_4S$: C, 41.22; H, 2.03; N, 2.83. Found: C, 41.28; H, 2.20; N, 2.94. Minor isomer: IR ν (film, cm^{-1}) 3280; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.41 (6H, m), 7.44–7.49 (1H, m), 7.51–7.54 (2H, m), 9.20 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.2, 128.1, 128.2, 129.6, 129.7, 130.6, 131.0, 131.6, 132.4, 147.5 (the ^{13}C signals corresponding to $CF_2CF_2CF_2CF_3$ group were not detected); MS m/z 495 (M^+, 99.6), 196 (100); HRMS calcd for $C_{17}H_{19}F_9NO_4S$: 495.0187, found: 495.0175.

4.3.5. 2-Chlorobenzophenone oxime (3m) (Table 2, entry 5). 2-Chlorobenzoyl chloride (0.35 g, 2.0 mmol) in benzene (8 mL) was dropped to a suspension of aluminum chloride (0.28 g, 2.1 mmol) in benzene (2 mL) at room temperature. After being refluxed for 19.5 h, the reaction mixture was quenched with diluted HCl (1 mL). The mixture was extracted with ethyl acetate (20 mL×3) and the combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (19:1)] to give 2-chlorobenzophenone (**1m**) (0.43 g, 100%) as a colorless solid.

According to the general procedure, a mixture of **1m** (0.13 g, 0.60 mmol) and hydroxylamine hydrochloride (0.83 g, 12 mmol) in ethanol (3 mL) was refluxed for 41 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to give **3m** [the major isomer (0.11 g, 79%) and the minor isomer (0.027 g, 20%)] as colorless solids. Major isomer: IR ν (film, cm^{-1}) 3248; ^1H NMR (400 MHz, C_6D_6) δ 6.75–6.80 (1H, m), 6.94 (1H, ddd, J=9.3, 7.5, 1.9 Hz), 7.02 (1H, m), 7.14–7.19 (6H, m), 7.63–7.66 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 126.7, 127.1, 128.7, 129.6, 129.7, 129.9, 130.3, 133.0, 133.5, 153.3, 155.7; MS m/z 233 (M^++2, 39.1), 231 (M^+, 100), 216 (23.2), 214 (62.2), 196 (48.9); HRMS calcd for $C_{13}H_{10}{}^{35}ClNO$: 231.0451, found: 231.0441. Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.44; H, 4.48; N, 5.88. Minor isomer: IR ν (film, cm^{-1}) 3190; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (6H, m), 7.45 (1H, dd, J=6.8, 2.4 Hz), 7.56 (2H, dd, J=6.8, 2.8 Hz), 9.32 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.7, 127.9, 129.5, 129.7, 130.1, 130.2, 131.5, 132.0, 133.7, 135.7, 155.3; MS m/z 233 (M^++2, 39.3), 231 (M^+, 100), 216 (23.2), 214 (61.2), 196 (46.8); HRMS calcd for $C_{13}H_{10}{}^{35}ClNO$: 231.0451, found: 231.0450.

4.4. Typical procedure for intramolecular Pd-catalyzed amination reaction of hydrazone 2a (Table 3, entry 2)

A mixture of **2a**-*Z* (50.0 mg, 0.14 mmol), $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol), P(2-Tol)$_3$ (6.4 mg, 0.020 mmol), and LiHMDS (1.0 M solution in THF, 0.20 mL, 0.20 mmol) in toluene (0.7 mL) was stirred at 100 °C for 1.5 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated. The residue was purified by silica gel column chromatography eluting with hexane–ethyl acetate (4:1) to give **4a** (35.5 mg, 91%) as a colorless solid.

4.4.1. 3-Methyl-1-(4-methylphenylsulfonyl)indazole (4a) (Table 3, entry 2). Mp 131–132 °C (colorless needles from hexane–acetone); IR ν (film, cm^{-1}) 1379, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.53 (3H, s), 7.23 (2H, d, J=8.3 Hz), 7.32 (1H, t, J=8.1 Hz), 7.54 (1H, t,

J=8.1 Hz), 7.59 (1H, d, J=8.1 Hz), 7.84 (2H, d, J=8.3 Hz), 8.17 (1H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 21.8, 113.3, 120.4, 123.7, 126.0, 127.3, 129.0, 129.6, 134.6, 140.9, 144.8, 150.5; MS m/z 286 (M^+, 53.7), 222 (100); HRMS calcd for $C_{15}H_{14}N_2O_2S$: 286.0776, found: 286.0774. Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.96; H, 4.99; N, 9.88.

4.5. General procedure for intramolecular Pd-catalyzed amination reaction for indazole synthesis (Table 4)

A mixture of a hydrazone **2**, $Pd(OAc)_2$, a ligand, and a base (1.5 equiv) in dioxane was stirred under the conditions listed in Table 4. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated. The residue was purified by silica gel column chromatography.

4.5.1. 3-Isopropyl-1-(4-methylphenylsulfonyl)indazole (4b) (Table 4, entry 1). According to the general procedure, a mixture of **2b** (94.8 mg, 0.24 mmol), $Pd(OAc)_2$ (8.1 mg, 0.036 mmol), dppf (29.9 mg, 0.054 mmol), and Cs_2CO_3 (0.12 g, 0.36 mmol) in dioxane (8 mL) was stirred at room temperature for 7 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to afford **4b** (61.5 mg, 82%) as a colorless solid; mp 95–96 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1377, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (6H, d, J=6.8 Hz), 2.32 (3H, s), 3.32 (1H, sep, J=6.8 Hz), 7.18 (2H, d, J=8.4 Hz), 7.28 (1H, t, J=8.0 Hz), 7.50 (1H, t, J=8.0 Hz), 7.65 (1H, d, J=8.0 Hz), 7.80 (2H, d, J=8.4 Hz), 8.15 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.6, 27.9, 113.6, 120.8, 123.6, 124.7, 127.3, 128.7, 129.4, 134.4, 141.6, 144.7, 159.3; MS m/z 314 (M^+, 71.6), 91 (100); HRMS calcd for $C_{17}H_{18}N_2O_2S$: 314.1089, found: 314.1068. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.78; H, 5.68; N, 8.89.

4.5.2. *tert*-Butyl 1-(4-methylphenylsulfonyl)indazole-3-carboxylate (4c) (Table 4, entry 2). According to the general procedure, a mixture of **2c**-*E* (20.9 mg, 0.046 mmol), $Pd_2(dba)_3$ (2.1 mg, 2.3 μmol), P(2-Tol)$_3$ (2.1 mg, 6.9 μmol), and Cs_2CO_3 (21.0 mg, 0.067 mmol) in dioxane (0.5 mL) was stirred at room temperature for 3 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (3:1)] to afford **4c** (13.9 mg, 81%) as a colorless solid; mp 115–116 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1736, 1369, 1269, 1178, 1107; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (9H, s), 2.37 (3H, s), 7.26 (2H, d, J=8.2 Hz), 7.39 (1H, t, J=7.8 Hz), 7.56 (1H, t, J=7.8 Hz), 7.94 (2H, d, J=8.2 Hz), 8.11 (1H, d, J=7.8 Hz), 8.22 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 28.2, 83.1, 113.0, 122.5, 124.0, 124.9, 127.8, 129.2, 129.9, 134.1, 141.1, 143.0, 145.7, 160.1; MS m/z 372 (M^+, 80.2), 91 (100); HRMS calcd for $C_{19}H_{20}N_2O_4S$: 372.1144, found: 372.1136. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.07; H, 5.47; N, 7.47.

4.5.3. *N*,*N*-Diethyl-1-(4-methylphenylsulfonyl)indazole-3-carboxamide (4d) (Table 4, entry 3). According to the general procedure, a mixture of **2d**-*E* (50.0 mg, 0.11 mmol), $Pd(OAc)_2$ (3.7 mg, 0.017 mmol), dppf (13.8 mg, 0.025 mmol), and ^{t}BuONa (15.9 mg, 0.17 mmol) in dioxane (4 mL) was stirred at 50 °C for 17 h. The crude stuff was chromatographed on silica gel [hexane–ethyl acetate (4:1)] to afford **4d** (29.6 mg, 72%) as a colorless oil; IR ν (film, cm^{-1}) 3439, 1630; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, J=7.1 Hz), 1.27 (3H, t, J=7.1 Hz), 2.36 (3H, s), 3.58 (2H, q, J=7.1 Hz), 3.59 (2H, q, J=7.1 Hz), 7.23 (2H, d, J=8.3 Hz), 7.36 (1H, t, J=7.8 Hz), 7.56 (1H, t, J=7.8 Hz), 7.85 (2H, d, J=8.3 Hz), 8.02 (1H, d, J=7.8 Hz), 8.20 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.8, 21.1, 41.0, 43.3, 113.0, 123.6, 124.7, 126.1, 127.5, 129.3, 129.7, 135.0, 141.1, 145.1, 146.2, 161.2; MS m/z 372 (M^++1, 0.54), 72 (100); HRMS calcd for $C_{19}H_{22}N_3O_3S$: 372.1381, found: 372.1365.

4.5.4. 1-(4-Methylphenylsulfonyl)-3-phenylindazole (4e) (Table 4, entry 4). According to the general procedure, a mixture of **2e** (50.0 mg, 0.12 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol), dppp (10.8 mg, 0.026 mmol), and ^{t}BuONa (16.8 mg, 0.17 mmol) in dioxane (4 mL) was stirred at 50 °C for 17 h. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **4e** (33.6 mg, 83%) as a colorless solid; mp 115–116 °C (colorless scales from hexane–ethyl acetate); IR ν (Nujol, cm^{-1}) 1366, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 7.15–7.53 (8H, m), 7.90–7.94 (4H, m), 8.26 (1H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 113.5, 121.6, 124.2, 124.3, 127.5, 128.2, 128.7, 129.0, 129.5, 129.7, 131.3, 134.6, 141.8, 145.1, 151.6; MS m/z 348 (M^+, 49.3), 193 (100); HRMS calcd for $C_{20}H_{16}N_2O_2S$: 348.0932, found: 348.0887. Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04. Found: C, 68.81; H, 4.64; N, 8.01.

4.5.5. 1-(4-Methylphenylsulfonyl)-6-nitro-3-phenylindazole (4f) (Table 4, entry 5). According to the general procedure, a mixture of **2f** (50.0 mg, 0.11 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), dppf (8.7 mg, 0.016 mmol), and Cs_2CO_3 (51.4 mg, 0.16 mmol) in dioxane (4 mL) was stirred at 50 °C for 12 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to afford **4f** (30.5 mg, 74%) as a colorless solid; mp 179–180 °C (colorless scales from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1550, 1378, 1300, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s), 7.05–7.14 (2H, m), 7.27–7.28 (1H, m), 7.40 (2H, d, J=8.4 Hz), 7.45 (1H, t, J=7.7 Hz), 7.52 (2H, t, J=7.7 Hz), 7.91 (2H, d, J=8.4 Hz), 8.21 (1H, d, J=9.3 Hz), 8.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 113.9, 118.6, 123.7, 123.8, 127.8, 128.1, 129.0, 129.9, 130.0, 130.2, 133.9, 143.6, 144.6, 146.0, 152.1; MS m/z 393 (M^+, 55.4), 238 (100); HRMS calcd for $C_{20}H_{15}N_3O_4S$: 393.0783, found: 393.0791. Anal. Calcd for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 61.11; H, 3.86; N, 10.67.

4.5.6. 5-Methoxy-1-(4-methylphenylsulfonyl)-3-phenylindazole (4g) (Table 4, entry 6). According to the general procedure, a mixture of **2g** (50.0 mg, 0.11 mmol), $Pd(OAc)_2$ (3.7 mg, 0.016 mmol), dppp (10.1 mg, 0.024 mmol), and ^{t}BuONa (15.7 mg, 0.16 mmol) in dioxane (4 mL) was stirred at 50 °C for 2 h. The residue was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **4g** (23.1 mg, 56%) as a colorless solid; mp 154–155 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1379, 1176, 1095; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.85 (3H, s),

7.20–7.22 (3H, m), 7.46–7.50 (4H, m), 7.85–7.87 (4H, m), 8.14 (1H, d, J=9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 55.9, 101.9, 114.5, 119.6, 125.1, 127.4, 128.0, 128.7, 129.3, 129.6, 131.4, 134.4, 137.0, 144.9, 151.3, 157.0; MS m/z 378 (M^+, 100); HRMS calcd for $C_{21}H_{18}N_2O_3S$: 378.1038, found: 378.1016. Anal. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 7.40. Found: C, 66.66; H, 4.93; N, 7.37.

4.5.7. 6-Methyl-1-(4-methylphenylsulfonyl)-3-phenylindazole (4h) (Table 4, entry 7). According to the general procedure, a mixture of **2h** (50.0 mg, 0.11 mmol), $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), dppf (14.1 mg, 0.025 mmol), and ^{t}BuONa (16.3 mg, 0.17 mmol) in dioxane (4 mL) was stirred at 50 °C for 15 h. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **4h** (26.9 mg, 66%) as a colorless solid; mp 121–122 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1379, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.57 (3H, s), 7.18–7.25 (4H, m), 7.45–7.47 (4H, m), 7.78 (1H, d, J=8.3 Hz), 7.89 (2H, d, J=8.1 Hz), 8.01 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 55.9, 101.9, 114.5, 119.6, 125.1, 127.4, 128.0, 128.7, 129.3, 129.6, 131.4, 134.4, 137.0, 144.9, 151.3, 157.0; MS m/z 362 (M^+, 54.7), 207 (100); HRMS calcd for $C_{21}H_{18}N_2O_2S$: 362.1089, found: 362.1075. Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.51; H, 5.10; N, 7.77.

4.5.8. 3-(4-Methoxyphenyl)-1-(4-methylphenylsulfonyl)-indazole (4i) (Table 4, entry 8). According to the general procedure, a mixture of **2i** (50.0 mg, 0.11 mmol), $Pd(OAc)_2$ (3.7 mg, 0.016 mmol), dppf (13.6 mg, 0.024 mmol), and ^{t}BuONa (15.7 mg, 0.16 mmol) in dioxane (4 mL) was stirred at room temperature for 8 h. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **4i** (38.9 mg, 94%) as a colorless solid; mp 143–145 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1371, 1256, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.85 (3H, s), 7.01 (2H, d, J=8.8 Hz), 7.20 (2H, d, J=8.0 Hz), 7.34 (1H, t, J=8.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.84–7.89 (5H, m), 8.24 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 55.4, 113.5, 114.1, 121.6, 123.8, 124.2, 124.3, 127.4, 128.9, 129.5, 129.6, 134.5, 141.7, 145.0, 151.4, 160.5; MS m/z 378 (M^+, 75.2), 223 (100); HRMS calcd for $C_{21}H_{18}N_2O_3S$: 378.1038, found: 378.1043. Anal. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 7.40. Found: C, 66.46; H, 4.73; N, 7.51.

4.5.9. 1-(4-Methylphenylsulfonyl)-3-phenylindazole (4e) (Table 4, entry 9). According to the general procedure, a mixture of **2j** (50.0 mg, 0.077 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), dppf (9.6 mg, 0.017 mmol), and Cs_2CO_3 (37.7 mg, 0.12 mmol) in dioxane (4 mL) was stirred at room temperature for 2 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (4:1)] to afford **4e** (25.6 mg, 96%) as a colorless solid.

4.5.10. 3-Ethyl-1-(4-methylphenylsulfonyl)indazole (4k) (Table 4, entry 10). According to the general procedure, a mixture of **2k**-*Z* (50.0 mg, 0.15 mmol), $Pd(OAc)_2$ (13.5 mg, 0.060 mmol), dppp (9.2 mg, 0.022 mmol), and ^{t}BuONa (21.3 mg, 0.22 mmol) in dioxane (4 mL) was stirred at 50 °C for 15 h. The residue was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **4k** (18.9 mg, 43%) as a colorless solid; mp 130–131 °C (colorless needles from hexane–acetone); IR ν (film, cm^{-1}) 1369, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, J=7.6 Hz), 2.32 (3H, s), 2.93 (2H, q, J=7.6 Hz), 7.19 (2H, d, J=8.3 Hz), 7.28 (1H, td, J=7.7, 1.2 Hz), 7.51 (1H, td, J=7.7, 1.2 Hz), 7.61 (1H, d, J=7.7 Hz), 7.82 (2H, d, J=8.3 Hz), 8.54 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 20.7, 21.6, 113.5, 120.5, 123.7, 125.4, 127.4, 128.9, 129.5, 134.6, 141.3, 144.8, 155.7; MS m/z 300 (M^+, 100); HRMS calcd for $C_{16}H_{16}N_2O_2S$: 300.0932, found: 300.0900. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.11; H, 5.47; N, 9.28.

4.5.11. 1*H*-1-(4-Methylphenylsulfonyl)-3-phenylpyrazolo[5,4-*b*]pyridine (4l) (Table 4, entry 11). According to the general procedure, a mixture of **2l** (50.0 mg, 0.12 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol), dppf (14.5 mg, 0.026 mmol), and ^{t}BuONa (16.8 mg, 0.17 mmol) in dioxane (4 mL) was stirred at 50 °C for 13 h. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (3:1)] to afford **4l** (35.5 mg, 82%) as a colorless solid; mp 168–169 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1383, 1192; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 7.26 (2H, d, J=8.4 Hz), 7.34 (1H, dd, J=8.0, 4.8 Hz), 7.47–7.53 (3H, m), 7.93 (2H, dd, J=7.8, 1.4 Hz), 8.10 (2H, d, J=8.4 Hz), 8.29 (1H, dd, J=8.0, 1.6 Hz), 8.75 (1H, dd, J=4.8, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 116.2, 119.7, 127.7, 128.1, 128.9, 129.7, 129.8, 130.9, 131.0, 134.9, 145.3, 148.6, 150.3, 152.6; MS m/z 349 (M^+, 90.8), 285 (100); HRMS calcd for $C_{19}H_{15}N_3O_2S$: 349.0885, found: 349.0887. Anal. Calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.33; H, 4.49; N, 11.96.

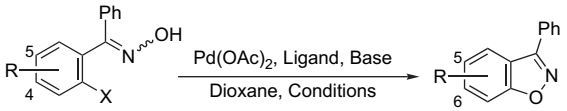
4.6. General procedure for intramolecular Pd-catalyzed cyclization reaction for benzoisoxazole synthesis (Table 5)

A mixture of an oxime **3**, $Pd(OAc)_2$, a ligand, and a base in dioxane was stirred under the conditions listed in Table 5. The reaction mixture was filtered through a pad of Celite® and filtrate was evaporated. The residue was purified by silica gel column chromatography.

4.6.1. 3-Phenylbenzo[*d*]isoxazole (5e) (Table 5, entries 1 and 6–9). *Entry 1*: according to the general procedure, a mixture of **3e** (50.0 mg, 0.18 mmol), $Pd(OAc)_2$ (6.1 mg, 0.027 mmol), ^{t}BuONa (26.1 mg, 0.27 mmol), and dppf (22.6 mg, 0.041 mmol) in dioxane (4 mL) was stirred at 50 °C for 62 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (9:1)] to afford **5e**[26] (25.6 mg, 72%) as a colorless solid; IR ν (film, cm^{-1}) 3065, 1612, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, ddd, J=8.3, 6.8, 1.2 Hz), 7.53–7.60 (4H, m), 7.64 (1H, d, J=8.4 Hz), 7.92 (1H, d, J=8.0 Hz), 7.95–7.97 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.1, 120.4, 122.1, 123.8, 128.0, 128.9, 129.0, 129.7, 130.1, 157.1, 163.7; MS m/z 195 (M^+, 100); HRMS calcd for $C_{13}H_9NO$: 195.0684, found: 195.0668.

Entry 6: according to the general procedure, a mixture of **3j** (0.050 g, 0.10 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol),

Table 5. Benzoisoxazole synthesis via intramolecular Pd-catalyzed cyclization reactions of oximes[a]



3e, f, g, j, m **5e, f, g**

Entry	**3**	X	R	Base/ligand	Conditions	Product	Yield[b] (%)
1	**3e**	Br	H	^{t}BuONa/dppf	50 °C, 62 h	**5e** (R=H)	72
2	**3f**	Br	4-NO_2	^{t}BuONa/dppf	rt, 15 h	**5f** (R=6-NO_2)	67
3				^{t}BuONa/dppp	rt, 6 h		88
4	**3g**	Br	5-OMe	^{t}BuONa/dppf	80 °C, 34.5 h	**5g** (R=5-OMe)	23 (29)
5				^{t}BuONa/dppp	80 °C, 15 h		36 (10)
6	**3j**	ONf	H	^{t}BuONa/dppf	80 °C, 17.5 h	**5e** (R=H)	14
7				Cs_2CO_3/dppf	80 °C, 4.5 h		20
8	**3m**	Cl	H	^{t}BuONa/dppf	80 °C, 11 h	**5e** (R=H)	67 (20)
9				^{t}BuONa/dppp	80 °C, 8 h		55 (23)

[a] Reaction conditions: **3** (1.0 equiv), base (1.5 equiv), $Pd(OAc)_2$ (15 mol %), and ligand (22.5 mol %) in dioxane.
[b] The numbers in parentheses are recovered yield of the starting materials.

^{t}BuONa (0.015 g, 0.15 mmol), and dppf (0.013 g, 0.023 mmol) in dioxane (4 mL) was stirred at 80 °C for 17.5 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (29:1)] to afford **5e** (2.7 mg, 14%).

Entry 7: according to the general procedure, a mixture of **3j** (0.050 g, 0.10 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), Cs_2CO_3 (0.050 g, 0.15 mmol), and dppf (0.013 g, 0.023 mmol) in dioxane (4 mL) was stirred at 80 °C for 4.5 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (29:1)] to afford **5e** (4.0 mg, 20%).

Entry 8: according to the general procedure, a mixture of **3m** (0.050 g, 0.22 mmol), $Pd(OAc)_2$ (7.3 mg, 0.032 mmol), ^{t}BuONa (0.031 g, 0.33 mmol), and dppf (0.027 g, 0.049 mmol) in dioxane (4 mL) was stirred at 80 °C for 11 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (29:1)] to afford **5e** (0.028 g, 67%), and **3m** (0.010 g, 20%) was recovered from the later fractions.

Entry 9: according to the general procedure, a mixture of **3m** (0.050 g, 0.22 mmol), $Pd(OAc)_2$ (7.3 mg, 0.032 mmol), ^{t}BuONa (0.031 g, 0.33 mmol), and dppp (0.020 g, 0.049 mmol) in dioxane (4 mL) was stirred at 80 °C for 8 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (29:1)] to afford **5e** (0.023 g, 55%), and **3m** (0.049 g, 23%) was recovered from the later fractions.

4.6.2. 6-Nitro-3-phenylbenzo[*d*]isoxazole (5f) (Table 5, entries 2 and 3). *Entry 2*: according to the general procedure, a mixture of **3f** (0.050 g, 0.16 mmol), $Pd(OAc)_2$ (5.3 mg, 0.023 mmol), ^{t}BuONa (0.023 g, 0.23 mmol), and dppf (0.020 g, 0.035 mmol) in dioxane (4 mL) was stirred at room temperature for 15 h. Compound **5f** (0.025 g, 67%) was obtained as a colorless solid after silica gel column chromatography [hexane–ethyl acetate (19:1)]; mp 140–141 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1522, 1352; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.63 (3H, m), 7.77 (1H, d, J=9.2 Hz), 7.96 (2H, dt, J=5.7, 1.6 Hz), 8.53 (1H, dd, J=9.2, 2.2 Hz), 8.87 (1H, d, J=2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.8, 119.5, 121.2, 125.3, 127.1, 128.0, 129.4, 131.1, 144.8, 158.2, 165.8; MS *m/z* 240 (M^+, 100); HRMS calcd for $C_{13}H_8N_2O_3$: 240.0535, found: 240.0526. Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 64.86; H, 3.41; N, 11.60.

Entry 3: according to the general procedure, a mixture of **3f** (0.050 g, 0.16 mmol), $Pd(OAc)_2$ (5.3 mg, 0.023 mmol), ^{t}BuONa (0.023 g, 0.23 mmol), and dppp (0.015 g, 0.035 mmol) in dioxane (4 mL) was stirred at room temperature for 6 h. Compound **5f** (0.033 g, 88%) was obtained after silica gel column chromatography [hexane–ethyl acetate (19:1)].

4.6.3. 5-Methoxy-3-phenylbenzo[*d*]isoxazole (5g) (Table 5, entries 4 and 5). *Entry 4*: according to the general procedure, a mixture of **3g** (0.050 g, 0.16 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), ^{t}BuONa (0.024 g, 0.25 mmol), and dppf (0.020 g, 0.037 mmol) in dioxane (4 mL) was stirred at 80 °C for 34.5 h. The crude product was chromatographed on silica gel [hexane–ethyl acetate (19:1)] to afford **5g** (8.4 mg, 23%), and **3g** (0.0142 g, 29%) was recovered from the later fractions. Compound **5g**: IR ν (film, cm^{-1}) 2923, 1497; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 7.21–7.24 (2H, m), 7.53–7.59 (4H, m), 7.93 (2H, dd, J=7.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 56.0, 102.2, 110.8, 120.2, 120.7, 127.9, 129.0, 130.0, 156.6, 157.2, 159.4; MS *m/z* 225 (M^+, 100); HRMS calcd for $C_{14}H_{11}NO_2$: 225.0790, found: 225.0770.

Entry 5: according to the general procedure, a mixture of **3g** (0.050 g, 0.16 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), ^{t}BuONa (0.024 g, 0.25 mmol), and dppp (0.015 g, 0.037 mmol) in dioxane (4 mL) was stirred at 80 °C for 15 h. The crude product was purified by silica gel column chromatography [hexane–ethyl acetate (19:1)] to afford **5g** (0.013 g, 36%), and **3g** (0.0048 g, 10%) was recovered from the later fractions.

4.7. Total synthesis of nigellicine

4.7.1. 2-(2-Bromo-6-methoxy-4-methylphenyl)-2-(ethoxycarbonyloxy)acetonitrile (13). To a solution of the aldehyde **11** (0.91 g, 4.0 mmol) in 1,2-dichloroethane (40 mL) were added BTAC (0.050 g, 0.40 mmol), ethyl chloroformate (3.5 g, 31.8 mmol), and 18-crown-6 (8.4 g, 31.8 mmol) at 0 °C. After stirring for 30 min at 0 °C, a solution of potassium cyanide (2.1 g, 31.8 mmol) in distilled water (40 mL) was slowly added to the reaction mixture at 0 °C and stirred vigorously at 50 °C for 15 h. The reaction mixture was extracted with ethyl acetate (30 mL×2) and the combined organic layer was washed with water (10 mL) and brine (10 mL), and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **13** (1.3 g, 98%) as a colorless solid; mp 95–96 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1757, 1252, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J=7.1 Hz), 2.35 (3H, s), 3.92 (3H, s), 4.28 (2H, q, J=7.1 Hz), 6.73 (1H, s), 6.91 (1H, s), 7.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.6, 56.4, 62.0, 65.4, 111.8, 115.3, 116.5, 124.7, 126.0, 143.9, 153.4, 159.0; MS m/z 329 (M^++2, 76.2), 327 (M^+, 76.9), 158 (100); HRMS calcd for $C_{13}H_{14}{}^{79}BrNO_4$: 327.0106, found: 327.0080. Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27. Found: C, 47.28; H, 4.18; N, 4.01.

4.7.2. Ethyl (2-bromo-6-methoxy-4-methylphenyl)-2-oxoacetate (14). LiHMDS (1.0 M solution in THF, 2.3 mL, 2.3 mmol) was slowly added to a solution of **13** (0.51 g, 1.6 mmol) in THF (5 mL) at −78 °C and stirred for 2 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with ethyl acetate (30 mL×3). The combined organic layer was washed with water (5 mL) and brine (5 mL), and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (9:1)] to give **14** (0.43 g, 91%) as a colorless oil; IR ν (film, cm^{-1}) 1751, 1732, 1211, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, J=7.1 Hz), 2.36 (3H, s), 3.79 (3H, s), 4.36 (2H, q, J=7.1 Hz), 6.70 (1H, s), 7.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.8, 56.1, 62.4, 111.1, 120.9, 123.6, 126.4, 144.4, 159.3, 161.4, 185.7; MS m/z 302 (M^++2, 1.5), 300 (M^+, 1.5), 229 (98.9), 227 (100); HRMS calcd for $C_{12}H_{13}{}^{79}BrO_4$: 229.9997, found: 299.9994.

4.7.3. Ethyl 2-(2-bromo-6-methoxy-4-methylphenyl)-2-(4-methylphenylsulfonyl)hydrazonacetate (15). A mixture of **14** (0.13 g, 0.43 mmol) and *p*-toluenesulfonylhydrazide (0.24 g, 1.3 mmol) in ethanol (5 mL) was heated at 50 °C for 43 h. The solvent was evaporated and the residue was chromatographed on silica gel [hexane–ethyl acetate (2:1)] to afford **15**-*E* (0.11 g, 54%) and **15**-*Z* (0.011 g, 6%) as colorless solids. Isomer **15**-*E*: mp 177–179 °C (colorless prisms from hexane–methanol); IR ν (film, cm^{-1}) 3184, 1717, 1352, 1215, 1171, 1057; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, J=7.2 Hz), 2.35 (3H, s), 2.43 (3H, s), 3.62 (3H, s), 4.26 (2H, q, J=7.2 Hz), 6.68 (1H, s), 7.01 (1H, s), 7.31 (2H, d, J=8.4 Hz), 7.84 (2H, d, J=8.4 Hz), 7.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.65, 21.69, 55.8, 61.8, 111.2, 115.6, 122.1, 125.6, 127.9, 129.4, 135.0, 141.3, 143.7, 144.3, 157.3, 162.0. MS m/z 287 (M^++2−NNTs, 100), 285 (M^+−NNTs, 99.3); HRMS calcd for $C_{12}H_{14}{}^{79}BrO_3$: 285.0126, found: 285.0112. Anal. Calcd for $C_{19}H_{21}BrN_2O_5S$: C, 48.62; H, 4.51; N, 5.97. Found: C, 48.56; H, 4.69; N, 5.95. Isomer **15**-*Z*: IR ν (film, cm^{-1}) 3200, 1693, 1371, 1231, 1171, 1049; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, t, J=7.1 Hz), 2.32 (3H, s), 2.41 (3H, s), 3.66 (3H, s), 4.19 (2H, q, J=7.1 Hz), 6.61 (1H, s), 6.96 (1H, s), 7.28 (2H, d, J=8.4 Hz), 7.84 (2H, d, J=8.4 Hz), 12.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.59, 21.67, 55.8, 61.8, 110.7, 121.9, 123.9, 124.9, 127.9, 129.5, 134.6, 135.9, 141.4, 143.9, 158.8, 161.7; MS m/z 470 (M^++2, 0.1), 468 (M^+, 0.1), 132 (100); HRMS calcd for $C_{19}H_{21}{}^{79}BrN_2O_5S$: 468.0355, found: 468.0368.

4.7.4. Ethyl 4-methoxy-6-methyl-1-(4-methylphenylsulfonyl)indazole-3-carboxylate (16). A mixture of **15**-*E* (20.0 mg, 0.043 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol), dppf (10.6 mg, 0.019 mmol), and base [LiHMDS (1.0 M solution in THF): 0.06 mL, 0.064 mmol or K_3PO_4: 13.6 mg, 0.064 mmol] in dioxane (2 mL) was stirred at room temperature for 26 h (for K_3PO_4) and 66 h (for LiHMDS). The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to give the indazole **16** (7.5 mg, 45% for K_3PO_4 and 8.3 mg, 50% for LiHMDS) as a colorless solid; mp 148 °C (colorless needles from hexane–ethyl acetate); IR ν (film, cm^{-1}) 1738, 1387, 1194, 1090, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J=7.0 Hz), 2.36 (3H, s), 2.52 (3H, s), 3.89 (3H, s), 4.44 (2H, q, J=7.0 Hz), 6.52 (1H, s), 7.25 (2H, d, J=8.4 Hz), 7.57 (1H, s), 7.88 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.7, 22.7, 55.7, 62.0, 105.1, 106.5, 112.7, 127.7, 129.9, 134.2, 142.4, 142.8, 142.9, 145.6, 153.0, 162.0; MS m/z 388 (M^+, 100); HRMS calcd for $C_{19}H_{20}N_2O_5S$: 388.1093, found: 388.1093. Anal. Calcd for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21. Found: C, 58.63; H, 5.20; N, 7.15.

4.7.5. Ethyl 4-methoxy-6-methylindazole-3-carboxylate (17). TBAF (1.0 M solution in THF, 0.04 mL, 0.041 mmol) was slowly added to a solution of indazole **16** (4.0 mg, 0.010 mmol) in THF (2 mL) at 0 °C and the mixture was stirred for 3 h at the same temperature. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (2:1)] to afford **17** (2.3 mg, 95%) as a colorless solid; mp 117–119 °C (colorless prisms from hexane–ethyl acetate); IR ν (film, cm^{-1}) 3283, 1705, 1267, 1229; ^1H NMR (600 MHz, $CDCl_3$) δ 1.40 (3H, t, J=7.2 Hz), 2.45 (3H, s), 3.96 (3H, s), 4.48 (2H, q, J=7.2 Hz), 6.43 (1H, s), 6.96 (1H, s), 11.68 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.2, 55.5, 61.2, 102.6, 104.5, 111.6, 136.7, 139.3, 143.9, 153.3, 162.7; MS m/z 234 (M^+, 100), 189 (50); HRMS calcd for $C_{12}H_{14}N_2O_3$: 234.1004, found: 234.0992. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.33; H, 6.12; N, 11.85.

4.7.6. Ethyl 1-(4-bromobutyl)-4-methoxy-6-methylindazole-3-carboxylate (18a) and ethyl 2-(4-bromobutyl)-4-methoxy-6-methylindazole-3-carboxylate (18b). To a suspension of NaH (washed with hexane, 5.3 mg, 0.22 mmol) in DMF (1 mL) was dropped a solution of the indazole **17**

(42.8 mg, 0.18 mmol) in DMF (5 mL) at 0 °C. After stirring for 10 min at the same temperature, 1,4-dibromobutane (0.98 g, 4.6 mmol) was added at 0 °C and stirred for 1.5 h at room temperature. The mixture was quenched with phosphate buffer solution (pH 6.86) and the mixture was extracted with ethyl acetate (5 mL×3). The combined organic solution was washed with brine (5 mL), and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (4:1)] to afford **18a** (36.7 mg, 54%) and **18b** (24.8 mg, 37%) as colorless solids. Compound **18a**: IR ν (film, cm^{-1}) 1728, 1269; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, t, J=7.2 Hz), 1.87 (2H, quint, J=7.0 Hz), 2.10 (2H, quint, J=7.0 Hz), 2.48 (3H, s), 3.40 (2H, t, J=7.0 Hz), 3.96 (3H, s), 4.41 (2H, t, J=7.0 Hz), 4.48 (2H, q, J=7.2 Hz), 6.43 (1H, s), 6.79 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.4, 28.2, 29.7, 32.8, 48.6, 55.6, 61.1, 101.4, 104.3, 112.5, 135.3, 138.9, 142.8, 153.5, 162.4; MS m/z 370 (M^++2, 43), 368 (M^+, 43), 243 (100); HRMS calcd for $C_{16}H_{21}{}^{79}BrN_2O_3$: 368.0736, found: 368.0747. Compound **18b**: IR ν (film, cm^{-1}) 1705, 1236; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, t, J=7.2 Hz), 1.87 (2H, quint, J=7.0 Hz), 2.11 (2H, quint, J=7.0 Hz), 2.42 (3H, s), 3.40 (2H, t, J=7.0 Hz), 3.90 (3H, s), 4.46 (2H, q, J=7.2 Hz), 4.70 (2H, t, J=7.0 Hz), 6.33 (1H, s), 7.08 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.4, 29.4, 29.6, 32.8, 52.0, 55.2, 61.5, 104.6, 108.9, 113.1, 125.1, 137.1, 149.6, 152.4, 161.0; MS m/z 370 (M^++2, 29), 368 (M^+, 29), 289 (100); HRMS calcd for $C_{16}H_{21}{}^{79}BrN_2O_3$: 368.0736, found: 368.0747.

4.7.7. Nigellicine (6 from 18a or 18b). *From **18a***: a solution of the indazole **18a** (4.2 mg, 0.011 mmol) in ethanol (4 mL) was then bubbled with CO_2 gas for 30 min and heated at 85 °C in a sealed tube for 48 h. The solvent was evaporated under ice-water bath cooling to afford **19** (5.6 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 1.47 (3H, t, J=7.2 Hz), 2.45–2.52 (4H, m), 2.56 (3H, s), 3.97 (3H, s), 4.57 (2H, q, J=7.2 Hz), 4.93 (2H, t, J=6.0 Hz), 4.98 (2H, t, J=6.0 Hz), 6.63 (1H, s), 7.22 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 18.9, 19.5, 23.1, 48.0, 50.4, 56.0, 63.9, 101.8, 107.4, 109.6, 131.7, 141.6, 147.9, 153.2, 157.4; FABMS m/z 289 (M^+−Br).

BBr_3 (1.0 M solution in hexane, 0.17 mL, 0.17 mmol) was dropped into a solution of **19** in dichloromethane (3 mL) at 0 °C and stirred at room temperature for 3.5 h. H_2O was slowly added to the mixture at 0 °C. The mixture was extracted with 10% methanol in dichloromethane (5 mL×4) and the organic solution was dried over $MgSO_4$. The solvent was evaporated and the residue was washed with hexane (2 mL×2), diethyl ether (2 mL×2), and ethyl acetate (2 mL×2) and dried in vacuo to give nigellicine (**6**) (2.8 mg, >99% from **18a**); IR ν (KBr, cm^{-1}) 3422, 2922, 2853, 1630, 1578, 1516, 1458, 1408, 1283, 1261; ^1H NMR (400 MHz, $CDCl_3$–CD_3OD=5:1) δ 2.26–2.37 (4H, m), 2.47 (3H, s), 4.44 (2H, t, J=6.0 Hz), 5.17 (2H, t, J=6.0 Hz), 6.54 (1H, s), 6.66 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD=5:1) δ 19.2, 19.9, 22.5, 46.6, 49.8, 97.5, 110.4, 110.5, 137.9, 141.6, 148.0, 153.3, 159.5; FABMS m/z 247 (M^++1).

*From **18b***: a solution of the indazole **18b** (26.3 mg, 0.071 mmol) in ethanol (4 mL) was bubbled with CO_2 gas for 30 min and heated at 85 °C in a sealed tube for 48 h. The solvent was evaporated under ice-water bath cooling to afford **19** (26.5 mg), which was treated with BBr_3 (1.0 M solution in hexane, 0.79 mL, 0.79 mmol) in dichloromethane (2 mL) and worked up as same way as described above to afford nigellicine (**6**) (15.1 mg, 86% from **18b**).

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