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CONCISE SYNTHESIS OF AZAFLUORENONE AND ITS APPLICATION TO INDENO[1,2-*c*]ISOQUINOLONE

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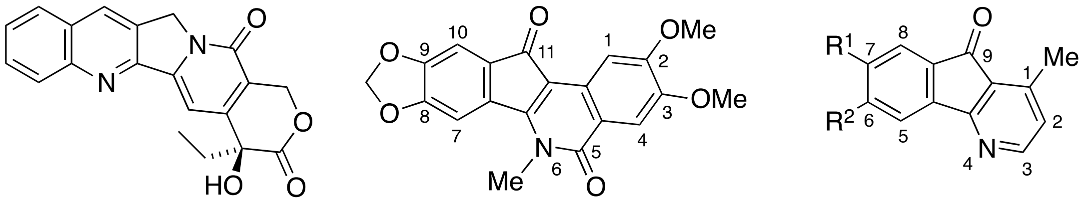
We dedicate this paper to Professor Dr. Kiyoshi Tomioka on the celebration of his 70th birthday.

Abstract – The total synthesis of azafluorenone alkaloid, an onychine isolated from *Onychopetalum amazonicum*, was newly achieved by constructing an azafluorene framework using thermal electrocyclization of the aza 6π-electron system. This methodology was applied for the synthesis of indeno[1,2-*c*]isoquinolones as an attractive scaffold for developing anticancer agents.

INTRODUCTION



1: camptothecin **2**: NSC 314622 **3**: onychine (R^1=R^2=H)
4: polyfothine (R^1=R^2=OMe)
5: isoursuline (R^1=OMe, R^2=OH)

Figure 1

Camptothecin (**1**) is a cytotoxic quinoline alkaloid; its derivatives, irinotecan and topotecan, are used clinically as anticancer drugs. However, the lactone hydrolysis of **1** at physiological pH values results in the loss of its biological activity.[1] Much research has been performed to evaluate the synthesis and activity of its analogs, and the indeno[1,2-*c*]isoquinolone (tetracyclic azafluorenone) derivative NSC 314622 (**2**) is considered as a potential anticancer agent with cytotoxic and topoisomerase I (Topo1) inhibitory properties.[2]

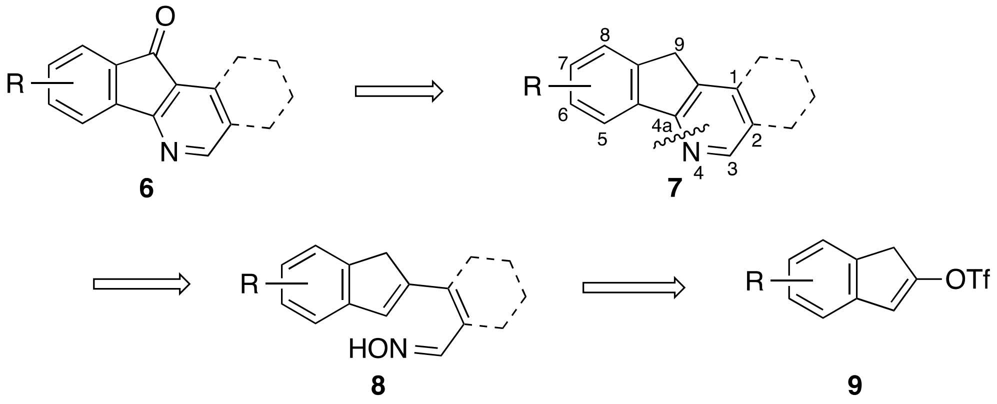
Conversely, onychine (**3**) is an azafluorenone alkaloid that was isolated from *Onychopetalum* in 1976,[3] and has also been reported to exhibit potent antimicrobial activity against multiple bacterial strains.[4] The first total synthesis of **3** was achieved by Prostakov and coworkers.[5a] In 2010, Kraus and coworkers reported the total synthesis of **3** using an intramolecular Heck cyclization reaction of 2-bromoaryl 3-pyridyl ketones.[5l] Moreover, the synthesis of **3** based on the Pd-catalyzed cross-coupling arylboronic acid with bromonicotinate has been reported by Snieckus and coworkers.[5d] Padwa and coworkers achieved its synthesis using the cyclization–deprotonation–cycloaddition cascade of imidosulfoxide.[5i] Recently, Marquise and coworkers described the total synthesis of **3** using Pd-catalyzed Suzuki coupling–intramolecular arylation auto-tandem reactions.[5q] Till date, the total synthesis of **3** (including formal synthesis) has been reported by 17 research groups.[5] Many synthetic studies are being performed to obtain a new bioactive lead compounds for anticancer agents. Based on the above considerations, azafluorenones and indenoisoquinolones are considered as attractive scaffolds for developing anticancer agents.

We have performed the synthesis of bioactive-fused nitrogen-containing heteroaromatic compounds including natural products and search studies on anticancer agents using them.[7,8] The total synthesis of bioactive-fused heteroaromatic compounds via the construction of fused pyridine ring systems using a conventional and/or microwave (MW)-assisted thermal electrocyclization of an aza 6π-electron system been reported.[9]

In this study, an alternative synthesis of **3** by constructing azafluorene based on thermal electrocyclization of a 1-aza 6π electron system is described. Furthermore, this methodology is applied to the synthesis of indeno[1,2-*c*]isoquinolones.

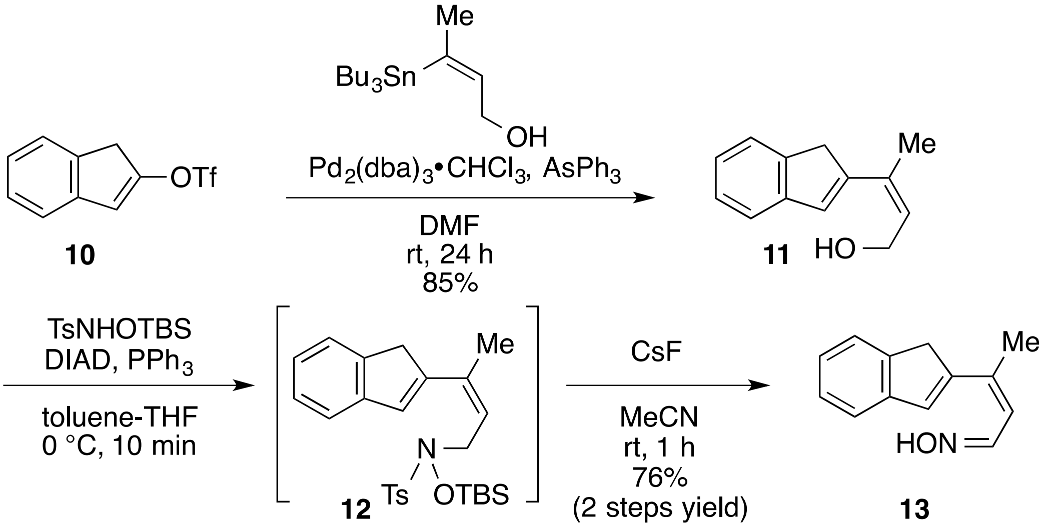
RESULTS AND DISCUSSION

Scheme 1 illustrates our retrosynthetic strategy for synthesizing azafluorenone and its derivatives. We envisaged that azafluorenone **6** could be derived from azafluorene **7** via oxidation. The azafluorene **7** might be obtained via thermal electrocyclization of the oxime **8** (as a 1-azahexatriene system), which was derived via cleavage of the 4,4a-bond of the azafluorene framework. The oxime **8** can be easily obtained from the known indene **9**.



Scheme 1

As shown in Scheme 2, 2-(trifluoromethylsulfonyloxy)indene (**10**) (the starting material) was prepared according to Manabe's procedure.[10] 2-Alkenylindene **11** was obtained from triflate **10** and 3-(tributylstannyl)but-2-en-1-ol[11] via the Stille reaction[12] with 85% yield. Next, conversion from alcohol to oxime was performed using Fukuyama's procedure.[13] The treatment of **11** with *O*-TBS-*N*-tosylhydroxylamine via the Mitsunobu reaction, followed by the desilylative elimination of *p*-toluenesulfinate via treatment with CsF, resulted in 76% yield of oxime **13** (two-step yield).

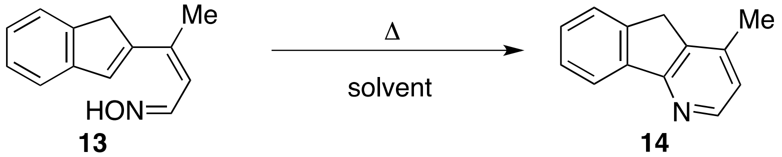


Scheme 2

Subsequently, the synthesis of azafluorene **14** from oxime **13** via electrocyclization was investigated. In addition, the reaction conditions were optimized (solvent type, temperature, and microwave parameters) (Table 1).

First, the heating of **13** in 1,2-dichlorobenzene at 180 °C for 10 min (monitoring the disappearance of oxime **13** via TLC) led to **14** being obtained with 41% yield (run 1). Subsequently, this reaction was performed in the same solvent at 150 °C, 120 °C, and 80 °C until oxime **13** disappeared, and the heating of **13** in the same solvent at 120 °C resulted in **14** with 60% yield (runs 2–4). Second, the use of bromobenzene and toluene as solvents (instead of 1,2-dichlorobenzene) was investigated in relation to cyclization conditions (runs 5 and 6). Heating of **13** at 120 °C in toluene afforded **14** with 64% yield (run 6).

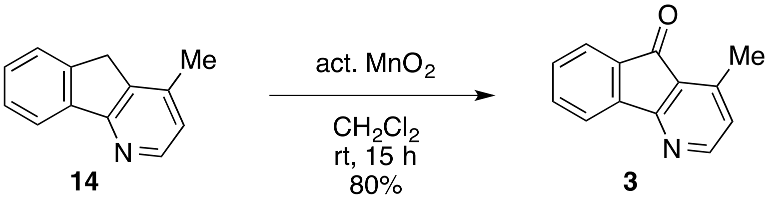
Table 1. Synthesis of **14** via thermal electrocyclization



Run	Solvent	Temp. (°C)	MW*	Time (h)	Yield (%) of **14**
1	1,2-dichlorobenzene	180	–	10 min	41
2	1,2-dichlorobenzene	150	–	1	49
3	1,2-dichlorobenzene	120	–	3	60
4	1,2-dichlorobenzene	80	–	12	34
5	bromobenzene	120	–	1.5	43
6	toluene	120	–	12	64
7	1,2-dichlorobenzene	120	+	3	70
8	bromobenzene	120	+	1.5	36
9	toluene	120	+	5	42

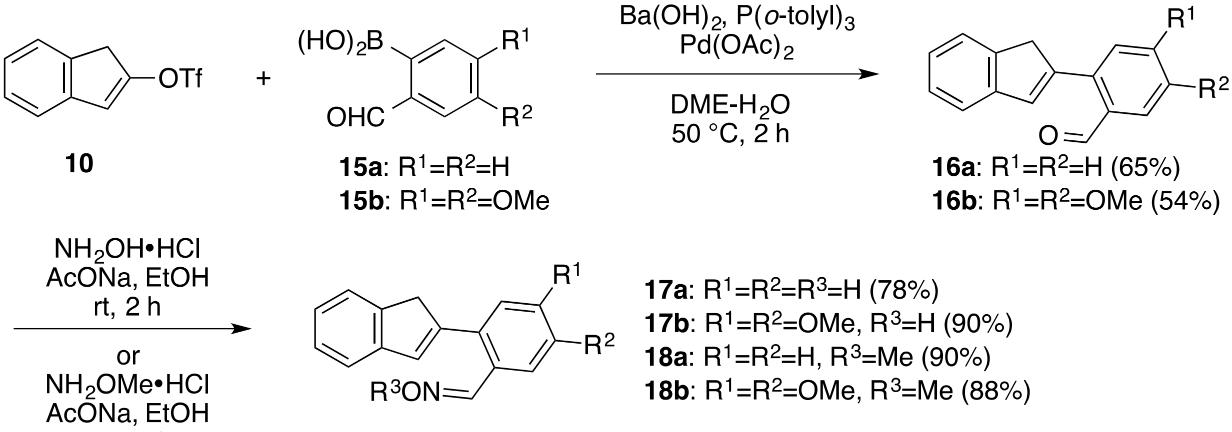
*MW: microwave.

Next, cyclization under MW irradiation was examined and compared with conventional conditions (runs 7–9). When the reaction was performed in 1,2-dichlorobenzene at 120 °C for 3 h under MW irradiation, **14** was obtained with 70% yield (run 7). From the above results, it can be seen that heating at 120 °C in 1,2-dichlorobenzene under MW irradiation was the best condition for the completion of reaction (run 7).



Scheme 3

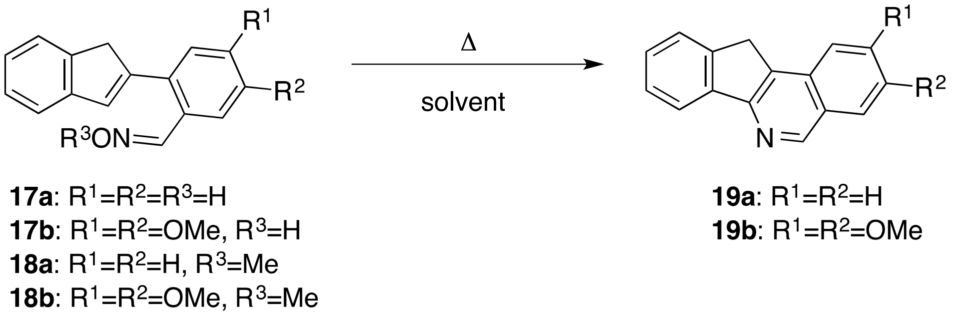
Finally, the oxidation of **14** with active MnO_2 in CH_2Cl_2 afforded **3** with 80% yield (Scheme 3). As described above, we were able to establish the construction methodology of the azafluorenone framework.



Scheme 4

In addition, we applied the above procedure to the synthesis of indeno[1,2-*c*]isoquinolines (tetracyclic azafluorenone). As shown in Scheme 4, the Suzuki–Miyaura reaction of indene **10** with phenylboronic acids **15a** and **15b** afforded 2-arylindenes **16a** and **16b** with 65% and 54% yields, respectively. Subsequently, the treatment of **16a** and **16b** with hydroxylamine afforded oximes **17a** and **17b** with 78% and 90% yields, respectively.

Table 2. Synthesis of indeno[1,2-*c*]isoquinoline via thermal electrocyclization

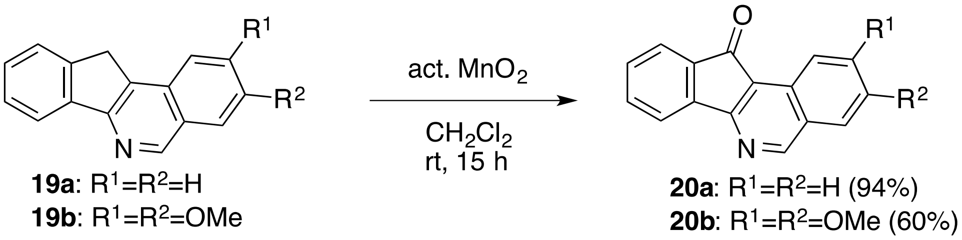


Run	Comd. No.	Solvent	Temp. (°C)	MW*	Time (h)	Yield (%)	
1	**17a**	1,2-dichlorobenzene	180	–	15	**19a**	trace
2	**17a**	1,2-dichlorobenzene	180	+	5	**19a**	32
3	**17a**	diphenyl ether	260	–	1.5	**19a**	62
4	**17b**	diphenyl ether	260	–	5	**19b**	50
5	**18a**	diphenyl ether	260	–	45 min	**19a**	75
6	**18b**	diphenyl ether	260	–	2	**19b**	77

*MW: microwave.

Next, to synthesize the indenoisoquinoline, oxime **17a** was heated at 120 °C in 1,2-dichlorobenzene under MW irradiation (Table 1, run 7); however, the cyclization reaction did not proceed. Therefore, the optimum conditions for this reaction were further investigated (Table 2). First, **17a** was reacted at 180 °C in 1,2-dichlorobenzene to afford only traces of indenoisoquinoline **19a** (run 1). The same reaction was performed under MW irradiation (run 2), giving a slightly improved yield (32%) compared with run 1. Next, diphenyl ether was used as the solvent. The reaction was carried out without MW irradiation because the MW generator could not be heated to 260 °C. When **17a** was heated in diphenyl ether at 260 °C (run 3), the yield of **19a** was improved (62%) and the reaction time was decreased. Similarly, heating of **17b** gave 2,3-dimethoxyindenoisoquinoline **19b** in 50% yield (run 4). Furthermore, to improve the yield, the cyclization reaction using oxime ether instead of oxime was examined with reference to our previous work.[14] As shown in Scheme 4, **16a** and **16b** were treated with *O*-methylhydroxylamine to give oxime ethers **18a** and **18b** in 90% and 88% yields, respectively.

When oxime ethers **18a** and **18b** were heated at the same temperature, indenoisoquinolines **19a** and **19b** were obtained in 75% and 77% yields, respectively; moreover, the reaction times were decreased (run 3 vs. run 5 and run 4 vs. run 6). In this case, a high temperature was required for synthesis of the indenoisoquinolines, and oxime ether was a more suitable precursor than oxime. Finally, the oxidation of indenoisoquinolines **19a** and **19b** with active MnO_2 in CH_2Cl_2 afforded indenoisoquinolones **20a** and **20b** with 94% and 60% yields, respectively (Scheme 5).



Scheme 5

Again, we applied the process to the synthesis of the indenoisoquinolone (tetracyclic azafluorenone) framework. The structures of the azafluorenones and indenoisoquinolones were supported by ^{1}H-NMR, ^{13}C-NMR, and mass spectra.

CONCLUSIONS

In conclusion, the total synthesis of the azafluorenone alkaloid, onychine (**3**), was newly achieved by constructing an azafluorene framework using electrocyclization of the 1-aza 6π-electron system as the key reaction. The target compound **3** was obtained in five steps in 36.2% overall yield from 2-(trifluoromethylsulfonyloxy)indene (**10**). In addition, this methodology could be applied to the synthesis of indeno[1,2-*c*]isoquinolones (tetracyclic azafluorenone) as an attractive scaffold for developing anticancer agents. The biologic activity of azafluorenones, indenoisoquinolones, and their derivatives is under investigation.

EXPERIMENTAL

General Methods: All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin layer chromatography was performed with Silica gel 60PF$_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Chemical Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL AL-300. Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and high-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system. The reaction of microwave (MW) irradiation was carried out by Discover of CEM Co. Ltd. with 2450 MHz.

3-(Inden-2-yl)but-2-en-1-ol (11): A solution of 3-(tributylstannyl)but-2-en-1-ol (273 mg, 0.76 mmol) in DMF (5 mL) was added to the mixture of triflate **10** (100 mg, 0.38 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (39 mg, 0.038 mmol), and $AsPh_3$ (23 mg, 0.076 mmol) in DMF (5 mL). After being stirred at rt for 24 h, the mixture was quenched with an aqueous KF solution (30%), and then the mixture was stirred at rt for 30 min. The mixture was filtered through a Celite pad, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give 2-alkenylindene **11** (60 mg, 85%) as yellow solid. mp 85–86 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 7.44 (1H, d, J = 7.6 Hz), 7.38 (1H, d, J = 7.6 Hz), 7.27 (1H, t, J = 7.6 Hz), 7.17 (1H, t, J = 7.6 Hz), 6.75 (1H, s), 5.68 (1H, t, J = 6.6 Hz), 4.41 (2H, d, J = 6.6 Hz), 3.56 (2H, s), 2.06 (3H, s), 1.43 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 145.8, 144.5, 143.2, 134.0, 130.5, 128.1, 126.6, 124.8, 123.5, 121.1, 60.4, 40.8, 24.0. MS *m/z*: 186 (M^+). HRMS (EI) calcd for $C_{13}H_{14}O$ 186.1045; found 186.1036.

3-(Inden-2-yl)but-2-enal oxime (13): DEAD (40% in toluene, 0.15 mL, 0.32 mmol) was added slowly to a mixture of 2-alkenylindole **11** (150 mg, 0.81 mmol), *O*-TBS-*N*-tosylhydroxylamine (218 mg, 0.72 mmol), and PPh_3 (424 mg, 1.62 mmol) in toluene (6 mL) and THF (2 mL) at 0 °C. After stirring at the temperature for 10 min, the solvent was evaporated to half an amount. The mixture was dissolved in MeCN (10 mL), and CsF (245 mg, 1.62 mmol) was added. After stirring at rt for 1 h, saturated NH_4Cl aq. was added and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give the oxime **13** (123 mg, 76%) as yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 8.23 (2/3H, d, J =

10.4 Hz), 7.61 (1/3H, d, *J* = 10.4 Hz), 7.46 (1/3H, d, *J* = 7.2 Hz), 7.42 (2/3H, d, *J* = 7.2 Hz), 7.41 (1H/3, d, *J* = 7.2 Hz), 7.36 (2/3H, d, *J* = 7.2 Hz), 7.30 (1/3H, t, *J* = 7.2 Hz), 7.27 (1/3H, t, *J* = 7.2 Hz), 7.23 (2/3H, d, *J* = 7.2 Hz), 7.19 (2/3H, d, *J* = 7.2 Hz), 7.00 (2/3H, s), 6.98 (1/3H, s), 6.72 (1/3H, d, *J* = 10.4 Hz), 6.43 (2/3H, d, *J* = 10.4 Hz), 3.64 (4/3H, s), 3.63 (2/3H, s), 2.20 (3/3H, s), 2.18 (6/3H, s), one proton (OH) was not observed. MS *m/z*: 199 (M^+). HRMS (EI) calcd for $C_{13}H_{13}NO$ 199.0997; found 199.0988.

1-Methyl-4-azafluorene (14): The solution of the oxime **13** (40 mg, 0.21 mmol) in 1,2-dichlorobenzene (3 mL) was heated under microwave irradiation at 120 °C for 3 h. After removal of solvent, the residue was purified by column chromatography using EtOAc/hexane (2:8, v/v) as an eluent to give the azafluorene **14** (27 mg, 70%) as orange solid. mp 82–83 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.47 (1H, d, *J* = 4.8 Hz), 8.09 (1H, d, *J* = 7.5 Hz), 7.58 (1H, d, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 4.8 Hz), 3.77 (2H, s), 2.42 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 159.8, 148.3, 143.3, 143.1, 141.1, 136.0, 128.4, 127.2, 125.1, 122.4, 120.9, 33.2, 18.5. MS *m/z*: 181 (M^+). HRMS (EI) calcd for $C_{13}H_{11}N$ 181.0891; found 181.0902.

Onychine (3): A suspension of the azafluorene **14** (45 mg, 0.25 mmol) and active MnO_2 (392 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 15 h. The reaction mixture was filtrated through a Celite pad. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give onychine (**3**) (39 mg, 80%) as yellow solid. mp 124–125 °C (EtOAc) (Lit.[6g] mp 125–127 °C). IR (ATR) ν: 1701, 1566 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.43 (1H, d, *J* = 5.3 Hz), 7.84 (1H, d, *J* = 7.5 Hz), 7.70 (1H, d, *J* = 7.5 Hz), 7.59 (1H, t, *J* = 7.5 Hz), 7.43 (1H, t, *J* = 7.5 Hz), 6.97 (1H, d, *J* = 5.3 Hz), 2.64 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 193.2, 165.2, 152.8, 147.5, 143.0, 135.0, 134.9, 130.8, 125.9, 125.8, 123.7, 120.7, 17.3. MS *m/z*: 195 (M^+). HRMS (EI) calcd for $C_{13}H_9NO$ 195.0684; found 195.0699.

2-(Inden-2-yl)benzaldehyde (16a): A mixture of triflate **10** (140 mg, 0.52 mmol), phenylboronic acid **15a** (117 mg, 0.78 mmol), $Ba(OH)_2$ (265 mg, 0.78 mmol), P(*o*-tolyl)$_3$ (30 mg, 0.1 mmol), and $Pd(OAc)_2$ (12 mg, 0.052 mmol) in DME/H_2O (4.3/0.7 mL) was stirred at 50 °C for 2 h. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the arylindene **16a** (74 mg, 65%) as orange oil. IR (ATR) ν: 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.26 (1H, s), 7.98 (1H, d, *J* = 8.0 Hz), 7.63 (1H, t, *J* = 8.0 Hz), 7.50–7.54 (2H, m), 7.42–7.47 (2H, m), 7.34 (1H, t, *J* = 7.8 Hz), 7.24–7.29 (1H, m), 6.85 (1H, s), 3.87 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 192.2, 144.5, 143.4, 142.8, 140.8, 135.3, 134.6, 133.4, 129.4, 128.3, 127.5, 126.9, 125.6, 123.8, 121.5, 41.9. MS *m/z*: 220 (M^+). HRMS (EI) calcd for $C_{16}H_{12}O$ 220.0888; found 220.0856.

2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde (16b): The same procedure as above was carried out using phenylboronic acid **15b** (100 mg, 0.76 mmol) to give arylindene **16b** (114 mg, 54%) as white solid. mp 187–188 °C (EtOAc). IR (ATR) ν: 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.13 (1H, s), 7.53 (1H, d, *J* = 7.2 Hz), 7.52 (1H, s), 7.46 (1H, d, *J* = 7.2 Hz), 7.34 (1H, t, *J* = 7.2 Hz), 7.26 (1H, t, *J* = 7.2 Hz), 6.90 (1H, s), 6.85 (1H, s), 3.99 (3H, s), 3.98 (3H, s), 3.85 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 190.6, 153.3, 148.6, 144.4, 143.2, 142.2, 136.4, 134.7, 127.9, 126.8, 125.4, 123.7, 121.3, 110.9, 109.1, 56.1, 56.0, 42.3. MS *m/z*: 280 (M^+). HRMS (EI) calcd for $C_{18}H_{16}O_3$ 280.1099; found 280.1078.

2-(Inden-2-yl)benzaldehyde oxime (17a): A mixture of arylindene **16a** (100 mg, 0.43 mmol), $NH_2OH \cdot HCl$ (59 mg, 0.86 mmol), and AcONa (71 mg, 0.86 mmol) in EtOH (5 mL) was stirred at rt for 2 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc/hexane (3:7, v/v) as an eluent to give the oxime **17a** (79 mg, 78%) as white solid. mp 187–188 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.42 (1H, s), 7.84 (1H, d, *J* = 7.2 Hz), 7.59 (1H, br s), 7.50 (1H, d, *J* = 7.2 Hz), 7.42–7.46 (3H, m), 7.29–7.36 (2H, m), 7.24 (1H, t, *J* = 7.2 Hz), 6.84 (1H, s), 3.79 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 150.3, 144.9, 144.5, 143.2, 137.3, 133.0, 129.9, 129.7, 128.9, 127.5, 127.2, 126.7, 125.2, 123.7, 121.4, 42.1. MS *m/z*: 235 (M^+). HRMS (EI) calcd for $C_{16}H_{13}NO$ 235.0997; found 235.0976.

2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde oxime (17b): The same procedure as above was carried out using arylindene **16b** (40 mg, 0.14 mmol) to give the oxime **17b** (37 mg, 90%) as white solid. mp 165–167 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.39 (1H, s), 8.10 (1H, br s), 7.48 (1H, d, *J* = 7.4 Hz), 7.43 (1H, d, *J* = 7.4 Hz), 7.37 (1H, s), 7.31 (1H, t, *J* = 7.4 Hz), 7.22 (1H, t, *J* = 7.4 Hz), 6.87 (1H, s), 6.78 (1H, s), 3.94 (3H, s), 3.93 (3H, s), 3.76 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 150.3, 149.9, 148.5, 144.9, 144.2, 143.0, 132.5, 131.1, 126.8, 125.0, 123.6, 122.5, 121.3, 111.2, 108.7, 56.0, 56.0, 42.4. MS *m/z*: 295 (M^+). HRMS (EI) calcd for $C_{18}H_{17}NO_3$ 295.1208; found 295.1222.

2-(Inden-2-yl)benzaldehyde *O*-methyloxime (18a): A mixture of arylindene **16a** (146 mg, 0.43 mmol), $NH_2OMe \cdot HCl$ (60 mg, 0.86 mmol), and AcONa (71 mg, 0.86 mmol) in EtOH (5 mL) was stirred at rt for 2 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc/hexane (3:7, v/v) as an eluent to give the oxime ether **18a** (96 mg, 90%) as white solid. mp 68–69 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.35 (1H, s), 7.89 (1H, d, *J* = 7.7 Hz), 7.49 (1H, d, *J* = 7.7 Hz), 7.40–7.45 (3H, m), 7.28–7.35 (2H, m), 7.20–7.25 (1H, m), 6.82 (1H, s), 3.99 (3H, s), 3.77 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 148.4, 144.9, 144.5, 143.2, 137.1, 132.9, 129.9, 129.5, 128.8, 127.4, 127.1, 126.7, 125.1, 123.6, 121.3, 61.9, 42.3. MS *m/z*: 249 (M^+). HRMS (EI) calcd for $C_{17}H_{15}NO$ 249.1154; found 249.1143.

2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde *O*-methyloxime (18b): The same procedure as above was carried out using arylindene **16b** (180 mg, 0.58 mmol) to give the oxime ether **18b** (158 mg, 88%) as yellow solid. mp 138–140 °C (EtOAc). ^{1}H-NMR (CDCl$_3$) δ: 8.31 (1H, s), 7.48 (1H, d, *J* = 7.6 Hz), 7.43 (1H, d, *J* = 7.6 Hz), 7.41 (1H, s), 7.30 (1H, t, *J* = 7.6 Hz), 7.21 (1H, t, *J* = 7.6 Hz), 6.85 (1H, s), 6.76 (1H, s), 3.98 (3H×2, s), 3.93 (3H, s), 3.75 (2H, s). ^{13}C-NMR (CDCl$_3$) δ: 150.1, 148.4, 148.0, 144.8, 144.2, 143.0, 132.3, 130.9, 126.6, 124.9, 123.5, 122.6, 121.1, 111.1, 108.6, 61.8, 55.9, 55.8, 42.3. MS *m/z*: 309 (M$^+$). HRMS (EI) calcd for $C_{19}H_{19}NO_3$ 309.1365; found 309.1334.

Indeno[1,2-*c*]isoquinoline (19a): The solution of the oxime ether **18a** (40 mg, 0.17 mmol) in diphenyl ether (3 mL) was heated at 260 °C for 45 min. After removal of solvent, the residue was purified by column chromatography using EtOAc/hexane (2:8, v/v) as an eluent to give the indenoisoquinoline **19a** (28 mg, 75%) as yellow solid. mp 157–158 °C (EtOAc). ^{1}H-NMR (CDCl$_3$) δ: 9.23 (1H, s), 8.12 (1H, d, *J* = 7.4 Hz), 8.01 (1H, d, *J* = 8.3 Hz), 7.91 (1H, d, *J* = 8.3 Hz), 7.70 (1H, t, *J* = 7.4 Hz), 7.60 (1H, d, *J* = 7.4 Hz), 7.53 (1H, t, *J* = 7.4 Hz), 7.47 (1H, t, *J* = 7.4 Hz), 7.37 (1H, t, *J* = 7.4 Hz), 4.06 (2H, s). ^{13}C-NMR (CDCl$_3$) δ: 154.0, 152.5, 142.8, 142.0, 133.5, 131.2, 130.7, 128.8, 127.5, 127.2, 126.2, 125.0, 124.9, 123.1, 120.2, 33.1. MS *m/z*: 217 (M$^+$). HRMS (EI) calcd for $C_{16}H_{11}N$ 217.0891; found 217.0883.

2,3-Dimethoxyindeno[1,2-*c*]isoquinoline (19b): The same procedure as above was carried out using the oxime ether **18b** (55 mg, 0.18 mmol) to give the indenoisoquinoline **19b** (38 mg, 77%) as yellow solid. mp 218–220 °C (EtOAc). ^{1}H-NMR (CDCl$_3$) δ: 9.05 (1H, s), 8.09 (1H, d, *J* = 7.6 Hz), 7.61 (1H, d, *J* = 7.6 Hz), 7.47 (1H, t, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.28 (1H, s), 7.12 (1H, s), 4.09 (3H, s), 4.05 (3H, s), 4.04 (2H, s); ^{13}C-NMR (CDCl$_3$) δ: 153.2, 152.9, 149.6, 142.4, 142.2, 130.2, 130.1, 127.1, 127.1, 124.8, 123.5, 123.4, 119.9, 106.3, 101.5, 56.0, 55.9, 33.1. MS *m/z*: 277 (M$^+$). HRMS (EI) calcd for $C_{18}H_{15}NO_2$ 277.1103; found 277.1111.

Indeno[1,2-*c*]isoquinolin-11-one (20a): A suspension of the indenoisoquinoline **19a** (18 mg, 0.053 mmol) and active MnO$_2$ (22 mg, 0.25 mmol) in CH$_2$Cl$_2$ (3 mL) was stirred at rt for 15 h. The reaction mixture was filtrated through a Celite pad. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc/hexane (1:1, v/v) as an eluent to give the indenoisoquinolone **20a** (12 mg, 94%) as white solid. mp 242–243 °C (EtOAc). ^{1}H-NMR (CDCl$_3$) δ: 9.27 (1H, s), 8.78 (1H, d, *J* = 8.3 Hz), 7.95 (1H, d, *J* = 8.3 Hz), 7.76–7.82 (2H, m), 7.67 (1H, d, *J* = 7.0 Hz), 7.51–7.58 (2H, m), 7.36 (1H, t, *J* = 7.0 Hz). ^{13}C-NMR (CDCl$_3$) δ: 194.1, 162.3, 158.2, 143.7, 134.8, 134.5, 133.5, 132.4, 130.3, 129.1, 128.6, 127.5, 123.7, 123.4, 120.5, 119.6. MS *m/z*: 231 (M$^+$). HRMS (EI) calcd for $C_{16}H_9NO_2$ 231.0684; found 231.0688.

2,3-Dimethoxyindeno[1,2-*c*]isoquinolin-11-one (20b): The same procedure as above was carried out using indenoisoquinoline **19b** (30 mg, 0.14 mmol) to give the indenoisoquinolone **20b** (24 mg, 60%) as yellow solid. mp 262–263 ºC (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.97 (1H, s), 8.03 (1H, s), 7.74 (1H, d, J = 7.2 Hz), 7.61 (1H, d, J = 7.2 Hz), 7.51 (1H, t, J = 7.2 Hz), 7.32 (1H, t, J = 7.2 Hz), 7.12 (1H, s), 4.10 (3H, s), 4.02 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 194.5, 160.9, 156.0, 154.5, 150.6, 143.9, 134.7, 134.6, 129.9, 129.8, 125.7, 123.4, 120.1, 118.8, 105.9, 101.3, 56.5, 56.0. MS m/z: 291 (M^+). HRMS (EI) calcd for $C_{18}H_{13}NO_3$ 291.0895; found 291.0867.

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