# Silver(I)-Catalyzed Direct Route to Isoquinoline-*N*-Oxides

Hyun-Suk Yeom,[a] Sunghwan Kim,[b] Seunghoon Shin*[a]

[a] Department of Chemistry, Hanyang University, Seoul 133-791, Korea
Fax +82(2)22990762; E-mail: sshin@hanyang.ac.kr

[b] Korea Basic Science Institute, 804-1 Yangcheong-Ri, Ochang-Myun, Cheongwon-Gun, Chungcheongbuk-Do 363-883, Korea

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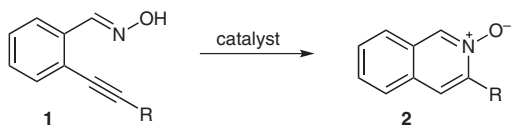
**Abstract:** Silver trifluoromethanesulfonate efficiently catalyzes the cyclization of 2-alkynylbenzaldoxime derivatives into the corresponding isoquinoline-*N*-oxides. The current protocol provides a direct route to the latter skeleton under a very mild reaction condition.

**Key words:** AgOTf, isoquinoline-*N*-oxide, heterocycles, cycloisomerization

Electrophilic metal-catalyzed addition of nucleophiles onto alkyne has witnessed a significant level of development recently, leading to diverse novel syntheses of heterocycles.[1] In this effort, a search for a new reaction partner has played a pivotal role in the development of synthetic route to biologically important heterocycles.[2] In particular, isoquinoline derivatives are widespread in natural products and the development of their efficient catalytic synthesis fits as a suitable goal.[3] Isoquinoline-*N*-oxides, on the other hand, are an important precursor for isoquinoline derivatives including pharmaceutically important 2-amino-functionalized nitrogen heterocycles,[4] and more recently they attracted renewed interests because of their use as a chiral scaffold in Lewis basic organocatalysis (Figure 1).[5] In addition, their utility extends to materials science because of their interesting optochemical/physical properties, such as charge-transfer and metal ($Li^+/Mg^{2+}$) sensor as well as applications as a radical initiator for atom-transfer radical polymerization (ATRP).[6] To our knowledge, however, there is no precedent for direct catalytic synthesis of isoquinoline-*N*-oxides and most of their preparation is still conducted by oxidation of parent nitrogen heterocycles, which suffers from poor atom-economy and/or generality and often are not environmentally friendly.[7]




**Scheme 1** Catalytic cycloisomerization into isoquinoline-*N*-oxides

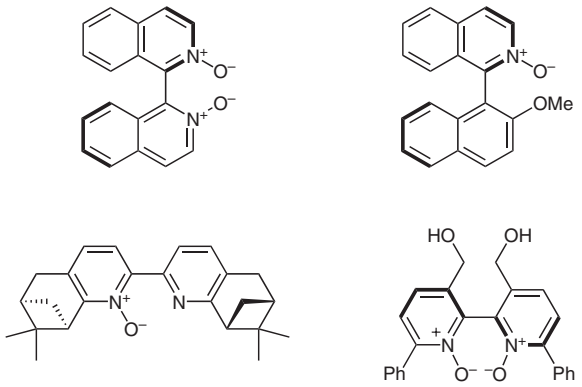



**Figure 1** Isoquinoline oxides and related chiral scaffold for asymmetric allylation of aldehyde

As a part of our ongoing projects on the reactions of substrates having N–O bond in electrophilic metal catalysis,[8]

**Table 1** Cyclization of **1a** (R = Ph)[a]

| Entry | Catalyst | Conditions[b] | Yield[c] (conv.[d]) |
|---|---|---|---|
| 1 | $AuPPh_3OTf$ | 70 °C, 12 h | (>95%) |
| 2 | Au[*t*-$Bu_2$P(*o*-biph)]OTf | 70 °C, 4 h | 83% (>95%) |
| 3 | Au(*t*-$Bu_3$P)OTf | 70 °C, 1 h | (>95%) |
| 4 | Au[$P(C_6F_5)_3$]OTf | r.t., 1.5 h | (>95%) |
| 5 | Au(IPr)Otf | r.t., 5 h | (>95%) |
| 6 | Au(IMes)OTf | r.t., 0.5 h | 96% (>99%) |
| 7 | $In(OTf)_3$ | 70 °C, 2.5 h | (85%) |
| 8 | $Zn(OTf)_2$ | 70 °C, 24 h | (>95%) |
| 9 | $Cu(OTf)_2$ | r.t., 12 h | NR[e] (52%) |
| 10 | CuI | r.t., 12 h | NR[e] (47%) |
| 9 | AgOTf | r.t., 0.5 h | 85% (>95%) |
| 10 | $AgSbF_6$ | r.t., 0.5 h | 80% (>95%) |
| 11 | $AgNTf_2$ | r.t., 0.5 h | 83% (>95%) |

[a] In $CH_2Cl_2$ (0.1 M) with 5 mol% of catalyst unless otherwise noted.
[b] Time required for full consumption of **1a** was indicated; reactions at 70 °C were conducted in a sealed tube.
[c] Isolated yield after chromatography.
[d] Conversions are based on the crude $^1H$ NMR spectra.
[e] No reaction; an unidentified side product was observed.

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we envisaged a direct formation of isoquinoline *N*-oxides from *o*-alkynylbenzaldoximes would be possible via an appropriate electrophilic metal-catalyzed cyclization (Scheme 1).[9,10] Herein, we report examination of various conditions using electrophilic metals and development of a direct silver(I)-catalyzed route to isoquinoline-*N*-oxides. The current protocol is significantly more efficient than conventional basic or thermal condition in terms of the yield and mildness of reaction conditions.[11] It is of note that the current protocol is highly regio- (6-*endo*-*dig*) and chemoselective (N- vs. O-nucleophile) so that its scope nicely complements Pictet–Spengler or Bischler–Napieralski reactions for the synthesis of related heterocycles.

We set out our study by examination of various catalysts for the current reaction using **1a** (R = Ph) as substrate (Table 1). We first looked at various cationic Au(I) complexes. Use of $Au(PPh_3)Cl$ (5 mol%) in combination with equimolar AgOTf resulted in a sluggish reaction at room temperature and it took 12 hours at 70 °C for a complete conversion into **2a** (entry 1). There was a strong ligand dependency in Au(I)-catalyzed cyclization (entries 1–6, Table 1) and Au(IMes)Cl/AgOTf turned out to be the most efficient, delivering **2a** in 30 minutes at room temperature in a quantitative conversion (entry 6). We also looked at other electrophilic metals and group 11 metals. With $In(OTf)_3$ and $Zn(OTf)_2$, the reaction was much slower than Au(I) complexes, requiring higher temperature (entries 7 and 8). The Cu(II) and Cu(I) salts did not turn out effective at room temperature, producing byproducts (entries 9 and 10). Among Ag(I) salts (entries 11–13) examined, AgOTf (5 mol%)[9l] turned out to be as effective as Au(IMes)Cl/AgOTf under similar conditions: The cyclization was slightly faster than Au(I), although the isolated yield was somewhat lower (entry 9). Considering the benefit of cost effectiveness, we took AgOTf (entry 9) along with Au(IMes)OTf (entry 6) as our optimized condition.[12]

**Table 2** Scope of the Cyclization into Isoquinoline-*N*-oxides[14]

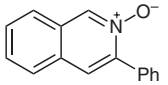
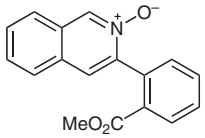
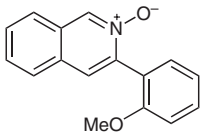
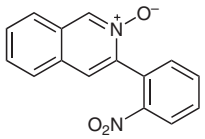
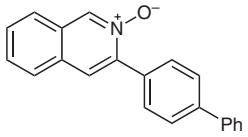
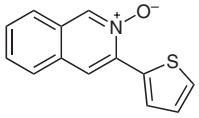
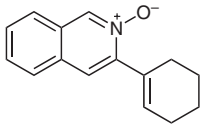
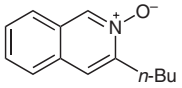
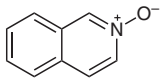
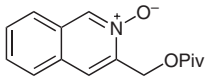
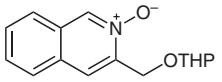
| Entry | Substrate (*R*) | Product | Conditions[a] (temp, time) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph<br>**1a** |  <br>**2a** | **A** (r.t., 0.5 h)<br>**B** (r.t., 0.5 h) | 96<br>85 |
| 2 | 3-$MeO_2CC_6H_4$<br>**1b** |  <br>**2b** | **A** (r.t., 1 h)<br>**B** (r.t., 2 h) | 95<br>95 |
| 3 | 3-$MeO_2C_6H_4$<br>**1c** |  <br>**2c** | **A** (r.t., 1.5 h)<br>**B** (r.t., 0.5 h) | 83<br>84 |
| 4 | 3-$O_2NC_6H_4$<br>**1d** |  <br>**2c** | **A** (70 °C, 72 h)<br>**B** (70 °C, 16 h) | 21<br>80 |
| 5 | Biphen-4-yl<br>**1e** |  <br>**2d** | **B** (r.t., 2.5 h) | 85 |
| 6 | Thien-2-yl<br>**1f** |  <br>**2f** | **A** (r.t., 5 h)<br>**B** (r.t., 1 h) | 64<br>75 |

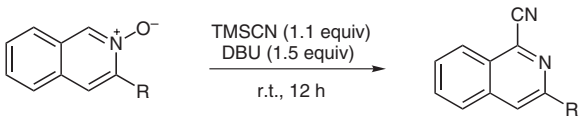
**Table 2** Scope of the Cyclization into Isoquinoline-*N*-oxides[14] (continued)

| Entry | Substrate (*R*) | Product | Conditions[a] (temp, time) | Yield (%)[b] |
|---|---|---|---|---|
| 7 | Cyclohexen-1-yl<br>**1g** |  <br>**2g** | **A** (70 °C, 5 h)<br>**B** (r.t., 0.5 h) | 91<br>89 |
| 8 | *n*-Bu<br>**1h** |  <br>**2h** | **A** (r.t., 0.5 h)<br>**B** (r.t., 0.5 h) | 92<br>97 |
| 9 | H<br>**1i** |  <br>**2i** | **A** (r.t., 1 h)<br>**B** (r.t., 0.5 h) | 94<br>97 |
| 10 | $CH_2OPiv$<br>**1j** |  <br>**2j** | **A** (70 °C, 12 h)<br>**B** (r.t., 1 h) | 83<br>86 |
| 11 | $CH_2OTHP$<br>**1k** |  <br>**2k** | **A** (70 °C, 12 h)<br>**B** (r.t., 0.5 h) | 53[c]<br>70 |

[a] Method A: Au(IMes)OTf (5 mol%) in $CH_2Cl_2$, Method B: AgOTf (5 mol%) in $CH_2Cl_2$.
[b] Isolated yield (%) after chromatography.
[c] THP-Deprotected alcohol (26%) was obtained along with **2k**.

With the optimization conditions above, a variety of substrates having aryl and alkyl R substituents were converted into the respective isoquinoline *N*-oxides in an efficient manner (Table 2). For example, **1b–d**, with different *ortho*-substituted aryl groups, underwent smooth conversion into isoquinoline-*N*-oxides **2b–d** (entries 2–4). Biphenyl, heteroaryl, and alkyl R groups were also well accommodated in the current reaction (entries 5–11). For substrate **1j**, a potentially competing [3,3]- or [2,3]-sigmatropic rearrangement of propargyl pivalate was effectively suppressed, delivering **2j** uneventfully. In general, both Au(I)- and Ag(I)-based catalysts performed similarly and Ag(I) catalyst shows better catalytic activity than Au(I) system when functional group compatibility becomes an issue (entry 4, 6, and 11). One problem of electrophilic metal catalysis could be functional group compatibility with acid-labile protecting group. A substrate with an acid-sensitive THP protecting group (**1k**, entry 11) under Au(I) catalysis (method A) led to 53% of **2k** with the formation of 26% of the corresponding alcohol. In contrast, the same substrate under Ag(I) catalysis (method B) led to 70% isolated yield of **2k** with only a trace amount of hydrolyzed byproduct, indicating a better functional-group compatibility of Ag(I) catalyst as compared to the Au(I)-based catalyst.

The thus-prepared isoquinoline-*N*-oxides allow for various subsequent transformations and one such opportunity is demonstrated in Scheme 2.[4,13] Isoquinoline-*N*-oxides **2a**, **2c**, and **2h** underwent smooth conversion into the respective 1-cyanoisoquinolines in generally good yields by treatment with TMSCN and DBU as base.




**2a**, R = Ph
**2c**, R = 2-MeOC$_6$H$_4$
**2h**, R = *n*-Bu

**3a**, 69%
**3c**, 67%
**3c**, 84%

**Scheme 2**

In summary, we report herein direct formation of isoquinoline-*N*-oxides from *o*-alkynylarylaldoximes under Au(I) and Ag(I) catalysis. The advantage of an Ag(I)-based system is demonstrated in substrates where coordinating atoms or acid-labile groups are involved. Future study in this laboratory will focus on the generation of chiral ligands based on the isoquinoline-*N*-oxides utilizing the current approach.

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## References and Notes


(1) (a) Larock, R. C. In *Acetylene Chemistry*; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, **2005**, 51–99. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

(2) (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (b) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (c) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (d) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537. (e) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503.

(3) (a) Su, S.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (b) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243.

(4) Addition of amine nucleophile: (a) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554. (b) Outurier, M.; Caron, L.; Tumidajski, S.; Jones, K.; White, T. D. *Org. Lett.* **2006**, *8*, 1929. (c) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127. Rearrangement into isoquinolone: (d) Robison, M. M.; Robison, B. L. *J. Org. Chem.* **1957**, *21*, 1337. 1,3-Dipolar cycloaddition: (e) Zhao, B.-X.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2973. Ni-Catalyzed alkenylation: (f) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 8872.

(5) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (c) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. (d) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674. (e) Hrdina, R.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2007**, *349*, 822.

(6) (a) Collado, D.; Perez-Inestrosa, E.; Suau, R. *J. Org. Chem.* **2003**, *68*, 3574. (b) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Desvergne, J.-P.; Bouas-Laurent, H. *Org. Lett.* **2002**, *4*, 855. (c) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Navarrete, J. T. L. *Tetrahedron* **2006**, *62*, 2927. (d) Durmaz, Y. Y.; Yilmaz, G.; Yagci, Y. *J. Polym. Sci., Part A.: Polym. Chem.* **2007**, *45*, 423.

(7) For catalytic oxidation of isoquinolines using $H_2O_2$ as stoichiometric oxidant, see: (a) Copéret, C.; Adolfsson, H.; Chiang, J. P.; Yudin, A. K.; Sharpless, K. *J. Org. Chem.* **1998**, *63*, 1740. (b) Prasad, M. R.; Kamalakar, G.; Madhavi, G.; Kulkarni, S. J.; Raghavan, K. V. *Chem. Commun.* **2000**, 1577.

(8) Yeom, H.-S.; Lee, E.-S.; Shin, S. *Synlett* **2007**, 2292.

(9) For metal-catalyzed approaches to other isoquinoline derivatives, see (selected examples) for Pd: (a) Ban, Y.; Wakamatsu, T.; Mori, M. *Heterocycles* **1977**, *6*, 1711. (b) Tietze, L. F.; Schimpf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1089. (c) Larock, R. C.; Yum, E. K.; Doty, M. J.; Shan, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (e) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1553. (f) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (g) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (h) Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett.* **2000**, *41*, 1215. (i) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (j) Cho, C. S.; Patel, D. B. *J. Mol. Catal. A: Chem.* **2006**, *260*, 105. (k) Oikawa, M.; Takeda, Y.; Naito, S.; Hashizume, D.; Koshino, H.; Sasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4255. For Ag: (l) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. For Au: (m) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521.

(10) For metal-catalyzed tandem cyclization–addition of 2-alkynyl benzaldimines, see for Ag: (a) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439. (b) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 5526. For Cu/Zn: (c) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611. For In: (d) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3822. Without catalyst: (e) Asao, N.; Iso, K.; Yudha, S. S. *Org. Lett.* **2006**, *8*, 4149. Organocatalyzed: (f) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959.

(11) For previous stoichiometric base-promoted cyclization, see: (a) Sakamoto, T.; Numata, A.; Kondo, Y. *Chem. Pharm. Bull.* **2000**, *48*, 669. (b) Sakamoto, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311. Thermal cyclization: (c) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793.

(12) One of the referees suggested the possibility of TfOH (generated by hydrolysis of metal triflates) acting as acid catalyst. When **1a** was treated with 10% of TfOH in $CH_2Cl_2$, a slow decomposition was observed but none of the isoquinoline-*N*-oxide was observed in this case.

(13) Miyashita, A.; Kawashima, T.; Iijima, C.; Higashino, T. *Heterocycles* **1992**, *33*, 211.

(14) **Representative Preparatory Procedure for Isoquinoline *N*-oxide 2a (Method B)**

To a solution of oxime **1a** (20 mg, 0.090 mmol) in $CH_2Cl_2$ (1 mL) was added AgOTf (1.2 mg, 0.0045 mmol) and the mixture was stirred at r.t. for 30 min. The solvent was removed and the residue was purified by silica gel chromatography ($CH_2Cl_2$–MeOH, 10:1) to give 17.0 mg (85%) of **2a** as a white solid (method A). To a mixture of Au(IMes)Cl (5 mol%) and AgOTf (5 mol%) in $CH_2Cl_2$ (ca. 0.1 M) at r.t. was added substrate. Otherwise, a similar procedure to method B was followed.

Compound **2a**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 7.93–7.76 (m, 4 H), 7.76–7.67 (m, 1 H), 7.67–7.54 (m, 2 H), 7.54–7.38 (m, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 147.8, 137.7, 133.5, 130.4, 130.1, 129.9, 129.74, 129.70, 129.5, 128.9, 127.3, 125.5, 125.1. HRMS: *m/z* calcd for $C_{30}H_{22}N_2O_2Na$ [2 M + Na]: 465.1573; found: 465.1546.

Compound **2d**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1 H), 8.18 (d, *J* = 8.2 Hz, 1 H), 7.90–7.82 (m, 2 H), 7.82–7.73 (m, 2 H), 7.71–7.60 (m, 3 H), 7.54 (d, *J* = 7.3 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 149.9, 145.9, 137.0, 134.2, 132.9, 131.2, 130.2, 129.8, 129.7, 128.6, 127.5, 125.5, 125.0, 124.4. HRMS: *m/z* calcd for $C_{30}H_{20}N_2O_6Na$ [2 M + Na]: 555.1275; found: 555.1280.

Compound **2g**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 7.80–7.64 (m, 2 H), 7.60 (s, 1 H), 7.58–7.48 (m, 2 H), 6.09 (m, 1 H), 2.75–2.43 (m, 2 H), 2.40–2.18 (m, 2 H), 1.94–1.62 (m, 4 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 151.0, 137.2, 134.7, 131.8, 130.0, 129.3, 129.2, 129.1, 127.0, 125.0, 123.7, 27.2, 26.2, 22.9, 22.4. HRMS: *m/z* calcd for $C_{30}H_{30}N_2O_2Na$ [2 M + Na]: 473.2199; found: 473.2180.

Compound **2k**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 7.93 (s, 1 H), 7.88–7.78 (m, 1 H), 7.78–7.66 (m, 1 H), 7.66–7.52 (m, 2 H), 5.15 (d of AB, *J* = 16.5 Hz, 1 H), 4.92 (d of AB, *J* = 16.5 Hz, 1 H), 4.878 (t, *J* = 3.5 Hz, 1 H), 4.02–3.82 (m, 1 H), 3.48–3.70 (m, 1 H), 2.10–1.50 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 146.7, 136.9, 129.8, 129.5, 129.3, 129.0, 127.3, 125.3, 121.6, 99.8, 64.1, 63.3, 31.2, 26.0, 20.3. HRMS: *m/z* calcd for $C_{30}H_{34}N_2O_6Na$ [2 M + Na]: 541.2309; found: 541.2309.

**General Experimental Procedure for Cyanation of 2h into 3h**

To a solution of **2h** (19 mg, 0.094 mmol) in THF (1 mL) at

r.t. was added DBU (21 μL, 0.142 mmol) and TMSCN (14 μL, 0.104 mmol), and the mixture was stirred at r.t. overnight. The mixture was directly loaded onto a silica gel column and eluted with EtOAc–hexane (1:10) to give 16.7 mg (84%) of 1-cyano-3-*n*-butyl-isoquinoline (**3h**) as a yellow solid.

Compound **3h**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.0 Hz, 1 H), 7.94–7.82 (d, *J* = 8.0 Hz, 1 H), 7.82–7.65 (m, 3 H), 2.98 (t, *J* = 7.3 Hz, 2 H), 1.80 (quin, *J* = 7.3 Hz, 2 H), 1.42 (sext, *J* = 7.3 Hz, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.6, 137.3, 134.8, 132.1, 129.4, 128.5, 127.5, 125.8, 122.9, 116.7, 38.1, 32.6, 23.0, 14.5.