An Unprecedented Tandem Annulation of ω-Azido-1-alkynes with Diaryliodonium Salts: A Facile Synthesis of Polycyclic Quinolines

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Abstract: Polysubstituted quinolines are synthesized through an unprecedented cascade annulation of ω-azido-1-alkynes with diaryliodonium salts, which serve as C2-building blocks. The reaction proceeds smoothly and is catalyzed by Cu(I) catalysts to give various quinolines in good isolated yields with simple operation under mild conditions.

Key words: quinolines, azides, alkynes, copper catalyst, tandem annulation

Polycyclic quinolines are privileged scaffolds in many bioactive natural products and synthetic therapeutic agents, exemplified by the natural topoisomerase I inhibitors luotonin A (**1**) and camptothecin (**2**) with structures typical of pentacyclic quinoline (Figure 1).[1] Moreover, tacrine, a tricyclic quinoline (under the trade name of Cognex) was the first approved drug for the treatment of Alzheimer's disease as a centrally acting anticholinesterase and indirect cholinergic agonist.[2] Therefore, the development of new approaches toward polycyclic quinolines is highly desired in synthetic chemistry. Many methods have been developed for the construction of quinoline derivatives, which involve the classical Miller, Combes, Conrad–Limpach–Knorr, Niementowski, Pfitzinger, and Friedlander reactions, and also more recent approaches.[3] Among these methods, probably only Niementowski and Friedländer reactions are generally suitable to construct polycyclic quinolines.[4] Recently, we reported an efficient method to synthesize polycyclic quinolines with diaryliodonium salts and ω-cyano-1-alkynes, which are readily accessible linear molecules (Scheme 1, eq. 1).[5]

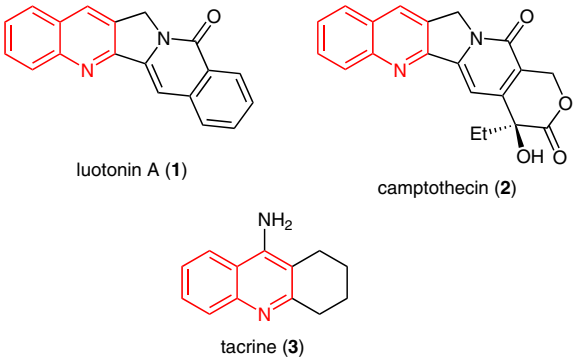
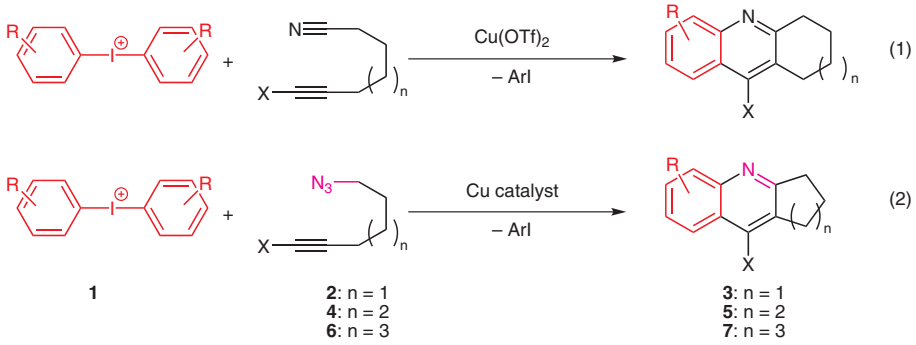


Figure 1 Luotonin A (**1**), camptothecin (**2**) and tacrine (**3**)

Diaryliodonium salts, $Ar_2I^+X^-$ have recently received considerable attention because of their use in the arylation of a wide range of nucleophiles to synthesize valuable aromatic compounds.[6] Our recent findings demonstrated that diaryliodonium salts could be used as C2 building blocks in organic reactions, and we disclosed their wider application in the synthesis of arenes and heteroarenes.[7] As a part of our ongoing project, herein, we would like to report a novel method to synthesize polycyclic quinolines through



Scheme 1

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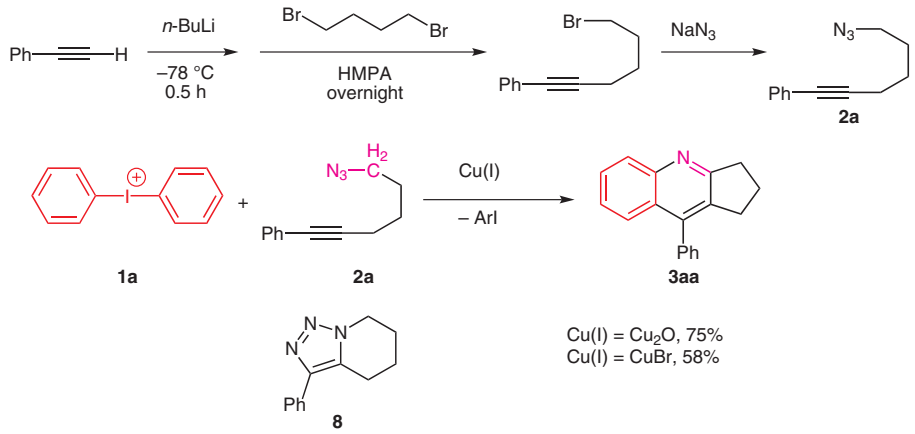
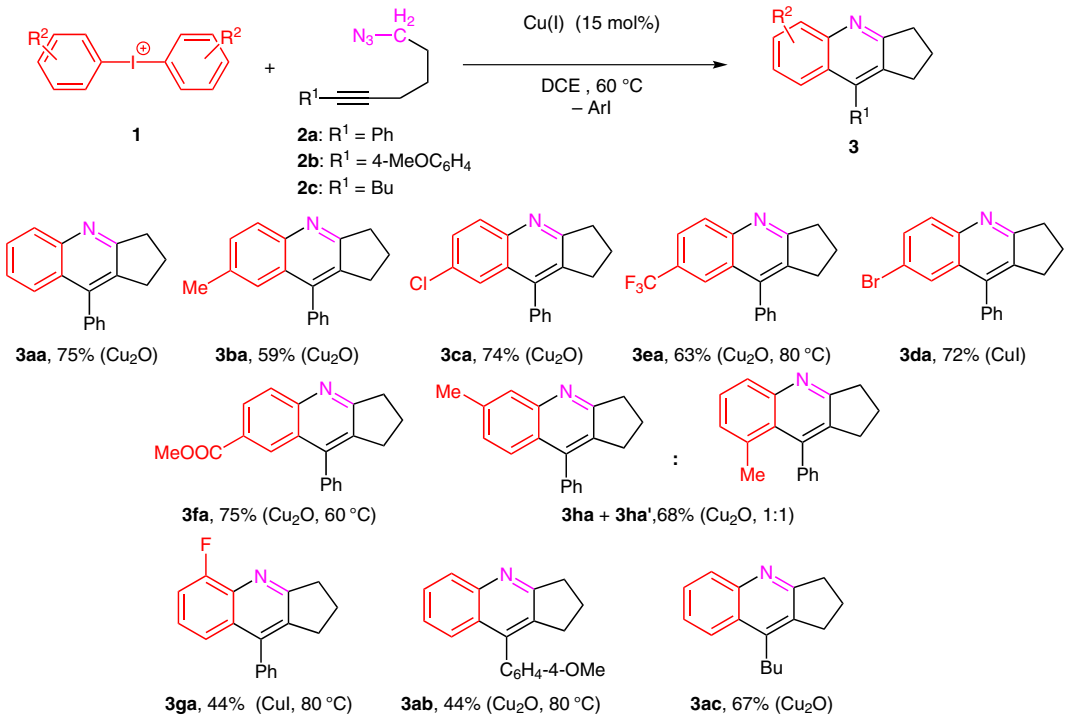


Scheme 2 The synthesis of starting material **2a** and its reaction with **1a**

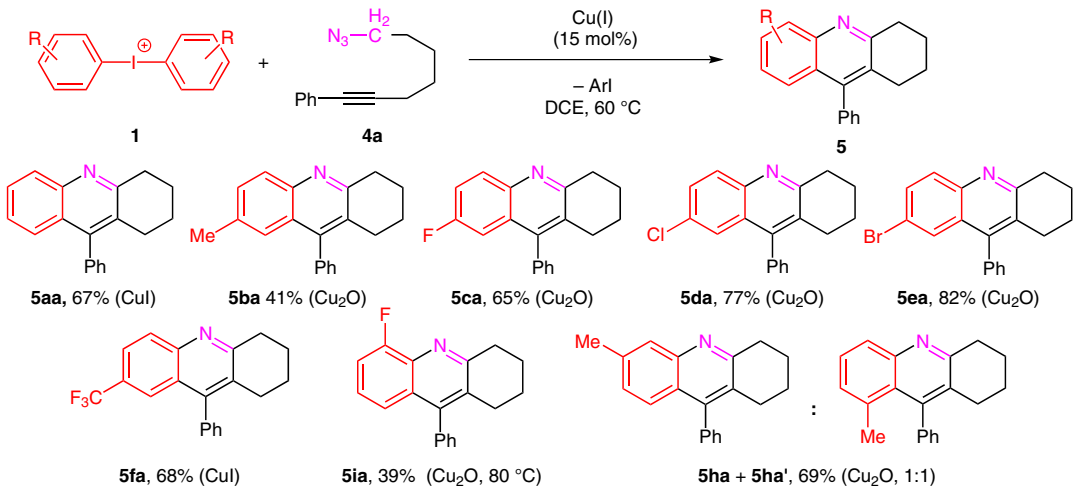
an unprecedented cascade annulation of ω-azido-1-alkynes with diaryliodonium salts, which also served as C2 building blocks (Scheme 1, eq. 2).

We first examined the reaction of diphenyliodonium triflate (**1a**) with ω-azido-1-phenyl-1-hexyne (**2a**), which was easily prepared by an azidation reaction followed by an ethynylation reaction of 1,4-dibromobutane (Scheme 2; for details, see the Supporting Information). The reaction of **1a** with **2a** proceeded smoothly when catalyzed by Cu_2O (10 mol%) in 1,2-dichloroethane (DCE) at 60 °C to give five-membered-ring fused quinoline **3aa** (4-phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline) in 75% isolated yield;[8] where two hydrogen atoms of the azido methylene group were lost during the reaction.[9] When Cu_2O was replaced by CuBr (10 mol%) as the catalyst, **3aa** was isolated in 58% yield. However, with $Cu(OTf)_2$ (10 mol%) as the catalyst, dipolar cycloaddition product **8** was obtained as the major product (48%).[10] When **8** was isolated and then treated with **1a** and Cu_2O under the standard conditions for a further 8 h, no quinoline product was detected, and the triazole was found to decompose.

Inspired by this result, diphenyliodonium salts **1**, with a range of substituents, were further examined in the reaction with **2a**; all worked well to give expected fused quinolines (2,3-dihydro-1*H*-cyclopenta[*b*]quinoline; Scheme 3). The reaction of diphenyliodonium salts **1** with *para*-substituents including 4-methyl, 4-chloro, 4-bromo, 4-trifluoromethyl, and 4-methoxycarbonyl groups provided fused quinolines **3ba**–**fa** in higher yields than substrates with an *ortho*-substituent (**3ga**). A mixture of regioiso-



Scheme 3 The synthesis of 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline **3** from the reaction of **1** and ω-azido-1-hexyne



Scheme 4 The synthesis of tetrahydroacridine **5** from the reaction of **1** and **4a**

mers **3ha**/**3ha′** (ratio 1:1) was obtained when di(*m*-tolyl)iodonium salt was used. ω-Azido-1-anisol-1-hexyne (**2b**) and ω-azido-5-decyne (**2c**) also reacted with diphenyliodonium (**1a**) and afforded the corresponding products **3ab** and **3ac** in satisfactory yields.

Encouraged by the successful preparation of five-membered-ring fused quinolines, we next examined the preparation of their six-membered counterparts (tetrahydroacridine) by using diaryliodonium salts and ω-azido-1-heptyne **4a**, which was easily prepared as described for **2a** with a similar method (Scheme 4). Diphenyliodonium (**1a**) reacted with ω-azido-1-heptyne **4a** to give fused quinoline **5aa** in 67% isolated yield.[11] The reaction of diphenyliodonium salts **1** with *para*-substituents including 4-methyl, 4-fluoro, 4-chloro, 4-bromo, and 4-trifluoromethyl groups provided fused quinolines **5aa**–**fa** in higher yields than obtained with an *ortho*-substituted substrate (**5ia**). A mixture of regioisomer **5ha**/**5ha′** (ratio 1:1) was obtained when di(*m*-tolyl)iodonium salt was used. Besides characterization by NMR and MS, the

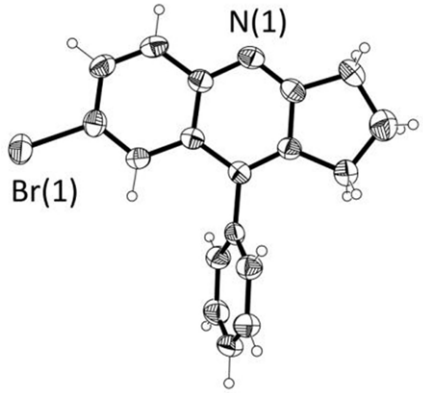
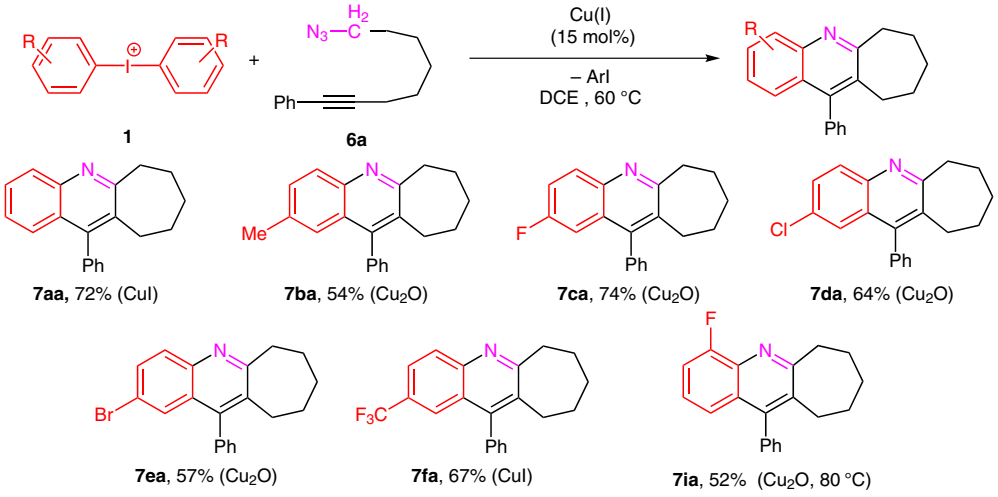


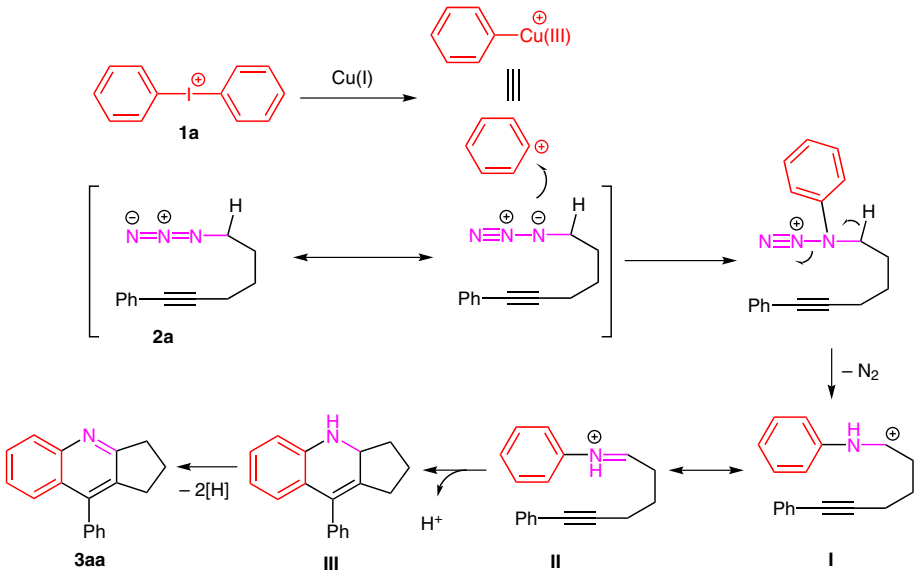
Figure 2 Single-crystal structure of **5ea**

structure of **5ea** was unambiguously confirmed by XRD analysis (Figure 2).[12]

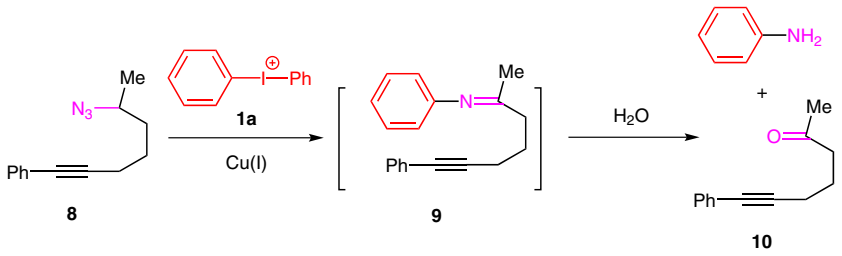
Finally, we prepared seven-membered-ring fused quinolines (7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline,



Scheme 5 The synthesis of 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline **7** from the reaction of **1** and **6a**



Scheme 6 A mechanistic proposal for the reaction of **1a** and **2a**



Scheme 7 Indirect evidence for the proposed pathway

Scheme 5) by using diaryliodonium salts and ω-azido-1-octyne **6a**, which was easily prepared as described for **2a**. Diphenyliodonium **1a** reacted with ω-azido-1-octyne **6a** to give fused quinoline **7aa** in 72% isolated yield.[13] The reaction of diphenyliodonium salts **1** with *para*-substituents including 4-methyl, 4-fluoro, 4-chloro, 4-bromo, and 4-trifluoromethyl groups provided fused quinolines **7aa**–**fa** in higher yields than obtained with *ortho*-substituted substrate **7ia**.

It was reported that alkyl azides reacted with electrophiles to generate electrophilic species upon N_2 elimination.[9] Therefore, a similar process likely takes place in our case to give intermediate **I** when ω-azido-1-alkyne (exemplified as **2a**) reacts with a phenyl cationic species, which is presumably generated from diphenyliodonium salt and copper catalyst (Scheme 6).[14] Intermediate **I** is naturally phenyl iminium salt and chemically equal to intermediate **II**. Intermediate **II** easily undergoes electrophilic cyclization to give quinoline backbone **III**, resembling a classic Povarov reaction. [15] The dehydrogenation-aromatization of intermediate **III** would give the product **3aa**. As indirect evidence for this pathway, when azido-1-alkyne **8** was reacted with **1a**, no quinoline derivative was observed but imine **9** and oxo-alkyne **10** was observed after the mixture was hydrolyzed (Scheme 7).

In conclusion, we have developed a concise construction of polycyclic quinolines through tandem annulation of ω-azido-1-alkynes with diaryliodonium salts. The process produces polycyclic quinolines in one step with readily available, linear staring materials and catalyst. Interestingly, diaryliodonium salts with Cu catalyst initiated the electrophilic attack on the azido group and served as a C2 unit in the products. Moreover, an azido methylene moiety was transferred into the -N=C- moiety of the product, and two hydrogen atoms were removed from the structure. Further design and synthesis of bioactive and natural molecules with this new strategy are in progress.

Acknowledgment

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(8) **Preparation of 3aa; Typical Procedure:** 6-Azido-1-phenyl-1-hexyne (**2a**; 0.3 mmol, 59.7 mg) was added to a solution of diphenyliodonium trifluoromethanesulfonate (**1a**; 0.6 mmol, 258 mg) and Cu_2O (0.045 mmol, 6.5 mg) in anhydrous DCE (2.0 mL) under a N_2 atmosphere. The reaction mixture was stirred at 60 °C for 24 h, and then poured into a mixture of sat. aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, washed with sat. aq $NaHCO_3$ (2 × 5 mL), and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided 9-phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**3aa**; 55 mg, 75% isolated yield) as a yellow solid. This product has been reported previously.[5] **9-Phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (3aa):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 8.8, 1.0 Hz, 1 H), 7.66–7.58 (m, 2 H), 7.56–7.42 (m, 3 H), 7.42–7.32 (m, 3 H), 3.24 (t, *J* = 7.7 Hz, 2 H), 2.91 (t, *J* = 7.4 Hz, 2 H), 2.17 (quint, *J* = 7.5 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.68, 148.1, 142.8, 136.9, 133.8, 129.4 (2×CH), 129.0, 128.6 (2×CH), 128.4, 128.1, 126.3, 125.8, 125.6, 35.4, 30.5, 23.7. GC-MS: *m*/*z* calcd for $C_{18}H_{15}N$: 245; found: 245.

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(11) **Preparation of 5aa; Typical Procedure:** 7-Azido-1-phenyl-1-heptyne (**4a**; 0.3 mmol, 63.9 mg) was added to a solution of diphenyliodonium trifluoromethanesulfonate (**1a**; 0.6 mmol, 258 mg) and Cu_2O (0.045 mmol, 6.5 mg) in anhydrous DCE (2.0 mL) under a N_2 atmosphere. The reaction mixture was stirred at 60 °C for 24 h, and then poured into a mixture of sat. aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, washed with sat. aq $NaHCO_3$ (2 × 5 mL), and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided 9-phenyl-1,2,3,4-tetrahydroacridine (**5aa**; 52 mg, 67% isolated yield) as a yellow solid. This product has been reported[5] previously. **9-Phenyl-1,2,3,4-tetrahydroacridine (5aa):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.5 Hz, 1 H), 7.60 (ddd, *J* = 8.3, 5.1, 3.1 Hz, 1 H), 7.55–7.42 (m, 3 H), 7.35–7.27 (m, 2 H), 7.23 (dd, *J* = 8.0, 1.4 Hz, 2 H), 3.20 (t, *J* = 6.6 Hz, 2 H), 2.60 (t, *J* = 6.5 Hz, 2 H), 2.02–1.88 (m, 2 H), 1.84–1.70 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 146.6, 146.4, 137.3, 129.2 (2×CH), 128.7 (2×CH), 128.5, 128.5, 127.8, 126.8, 125.9, 125.5, 34.4, 28.2, 23.2, 23.1. GC-MS: *m*/*z* calcd for $C_{19}H_{17}N$: 259; found: 259.

(12) CCDC-1019165 (**3da**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) **Preparation of 7aa; Typical Procedure:** 8-Azido-1-phenyl-1-octyne (**6a**; 0.3 mmol, 68.1 mg) was added to a solution of diphenyliodonium trifluoromethanesulfonate (**1a**; 0.6 mmol, 258 mg) and Cu_2O (0.045 mmol, 6.5 mg) in anhydrous DCE (2.0 mL) under a N_2 atmosphere. The reaction mixture was stirred at 60 °C for 24 h, and then poured into a mixture of sat. aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, washed with sat. aq $NaHCO_3$ (2 × 5 mL), and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided 11-phenyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline (**7aa**; 59 mg, 72% isolated yield) as a yellow solid. This product has been reported[5] previously. **11-Phenyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline (7aa)**: ^{1}H NMR (301 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.3 Hz, 1 H), 7.60 (ddd, *J* = 8.3, 6.5,

1.8 Hz, 1 H), 7.55–7.42 (m, 3 H), 7.36–7.27 (m, 2 H), 7.26–7.19 (m, 2 H), 3.32–3.23 (m, 2 H), 2.73–2.66 (m, 2 H), 1.91–1.77 (m, 4 H), 1.67–1.53 (m, 2 H). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 165.0, 146.0, 145.6, 137.8, 134.0, 129.6 (2×CH), 128.8, 128.6 (2×CH), 128.3, 127.8, 127.1, 126.5, 125.7, 40.4, 32.1, 30.9, 28.7, 27.2. GC-MS: *m*/*z* calcd for $C_{20}H_{19}N$: 273; found: 273.

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