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Cationic Ruthenium Catalysts for Alkyne Annulations with Oximes by C–H/N–O Functionalizations

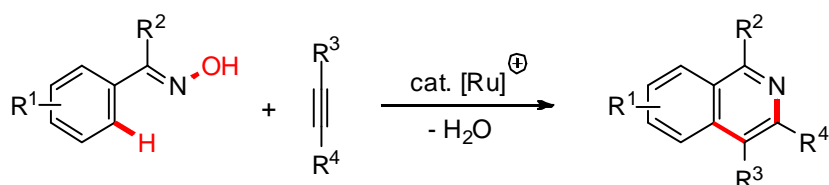
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Abstract: Cationic ruthenium(II) complexes enabled efficient redox-neutral annulations of alkynes with readily available oximes. The catalytic dehydrative C–H/N–O bond functionalization proved to be broadly applicable, and was shown to proceed through a reversible cyclometalation.

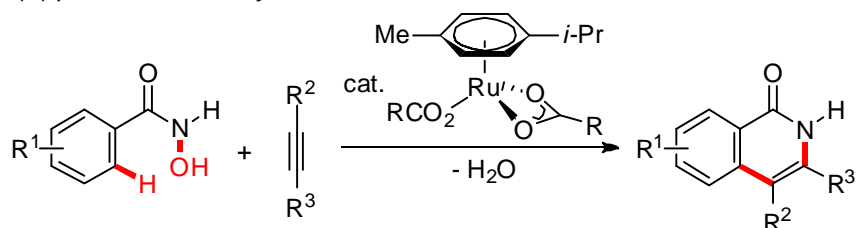
Introduction

The modular assembly of regioselectively decorated heterocycles is of central importance because of their prevalence in natural products and drugs.¹ Particularly, isoquinolines are key building blocks in organic synthesis, and represent structural motifs of alkaloids with, among others, cardiovascular, anti-inflammatory or anti-malarial bioactivities.² As a result, there is a continued strong demand for versatile isoquinoline syntheses. While transition metal-catalyzed annulations with prefunctionalized *ortho*-halo-substituted benzimines were previously developed,³ a more atom- and step-economical strategy was realized with methods that capitalize upon C–H⁴ bond activation. Hence, the research groups of Jun, Bergman and Ellman, Cheng, Fagnou, Satoh and Miura, Chiba, Rovis as well as Li exploited chelation assistance for rhodium-catalyzed⁵ isoquinoline and pyridine syntheses.⁶

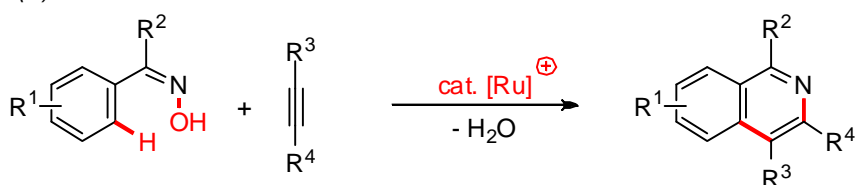
In 2011, we reported on the use of less-expensive ruthenium⁷ complexes for oxidative annulations of alkynes by benzamides through C–H/N–H bond cleavages.⁸ Notably, this approach proved more generally applicable.⁹ Indeed, ruthenium(II) biscoxylates^{4b} also set the stage for redox-neutral dehydrative annulations of alkynes with free hydroxamic acids through C–H/N–O functionalizations to furnish isoquinolones (Scheme 1a).¹⁰

Scheme 1. Ruthenium-Catalyzed C–H/N–O Functionalizations

(a) previous work: hydroxamic acid¹⁰



(b) this work: oximes

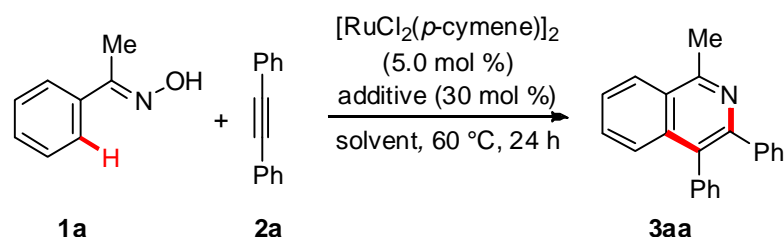


In consideration of the important bioactivities of substituted isoquinolines,¹⁻³ we consequently became attracted by utilizing ruthenium(II) complexes for step-economical isoquinoline syntheses in the absence of external oxidants (Scheme 1b), the results of which we report herein. In contrast to previous studies,^{9,10} we observed a remarkably high catalytic activity of carboxylate-free¹¹ cationic ruthenium(II) catalysts and obtained detailed mechanistic insight on reversible cyclometalations in dehydrative isoquinoline syntheses.

Results and Discussion

We initiated our studies by exploring representative metal carboxylates and solvents for the envisioned dehydrative annulation of alkyne **2a** by oxime **1a** (Table 1). Among various cocatalytic additives, KPF₆ gave rise to the most satisfactory results (entries 1–9),¹² while MeOH proved to be the solvent of choice for the dehydrative annulation (entries 9–12). However, [RuBr₂(*p*-cymene)]₂ delivered the desired isoquinoline **3aa** in a reduced yield as compared to a reaction with [RuCl₂(*p*-cymene)]₂ as the catalyst (entries 9, and 13). The high catalytic activity exerted by the KPF₆-derived ruthenium catalyst was suggestive of an in-situ formation of a cationic ruthenium(II) species (*vide infra*).

Table 1. Optimization of C–H/N–O Functionalization^a



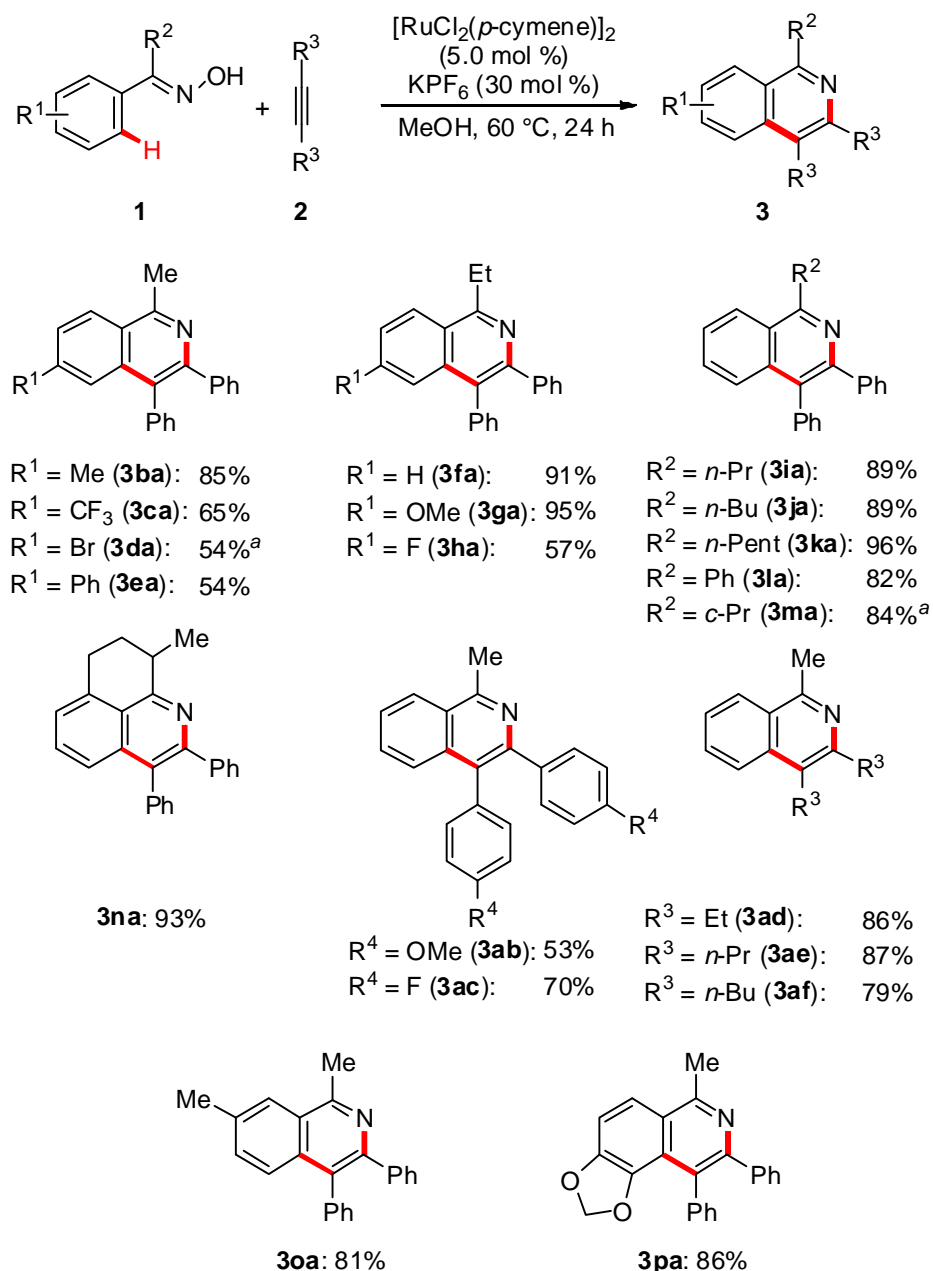
entry	additive	solvent	yield
1	AgOAc	MeOH	9%
2	CuOAc	MeOH	13% ^b
3	CsOAc	MeOH	61%
4	NaOAc	MeOH	39%
5	KOPiv	MeOH	15%
6	K ₂ CO ₃	MeOH	9% ^b
7	AgSbF ₆	MeOH	38%
8	NaPF ₆	MeOH	67%
9	KPF₆	MeOH	81%
10	KPF₆	MeOH	83% ^c
11	KPF ₆	<i>t</i> -AmOH	9% ^b
12	KPF ₆	H ₂ O	30%
13	KPF ₆	MeOH	60% ^d

^a Reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol %), additive (30 mol %), solvent (2 mL), 60 °C, isolated yields. ^b GC-conversion. ^c 4 Å-Mol. sieves (100 mg). ^d [RuBr₂(*p*-cymene)]₂ (5.0 mol %).

Subsequently, we explored the scope of the optimized cationic ruthenium(II) complex in the redox-neutral annulation of alkynes **2** (Scheme 2). Thus, a variety of differently substituted isoquinolines **3ba**–**3ea** bearing valuable electrophilic functional groups was chemoselectively accessed. Furthermore, oximes **1** bearing sterically more demanding substituents furnished the desired products **3fa**–**3ma**, as did bicyclic substrate **1n**. The catalytic system was not restricted to tolane (**2a**), but allowed for the efficient conversion of different aryl- and alkyl-substituted alkynes **2b**–**2f** as well. Intramolecular

competition experiments with *meta*-substituted arenes **1o** and **1p** revealed a significant change in site-selectivity. Thus, isoquinoline **3oa** was generated through steric interactions, while oxime **1p** displaying a secondary directing group was functionalized at the sterically more congested C-2 position.

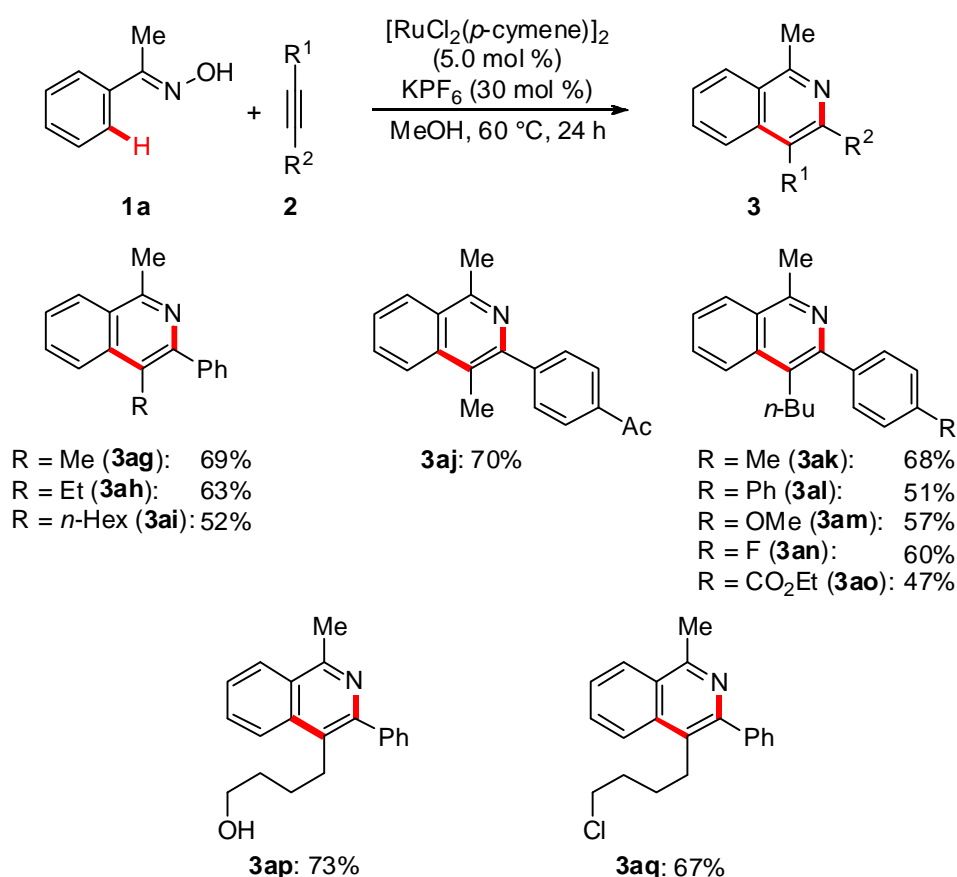
Scheme 2. Scope of Redox-Neutral Annulation with Oximes **1**



^a In the presence of 4Å-Mol. sieves.

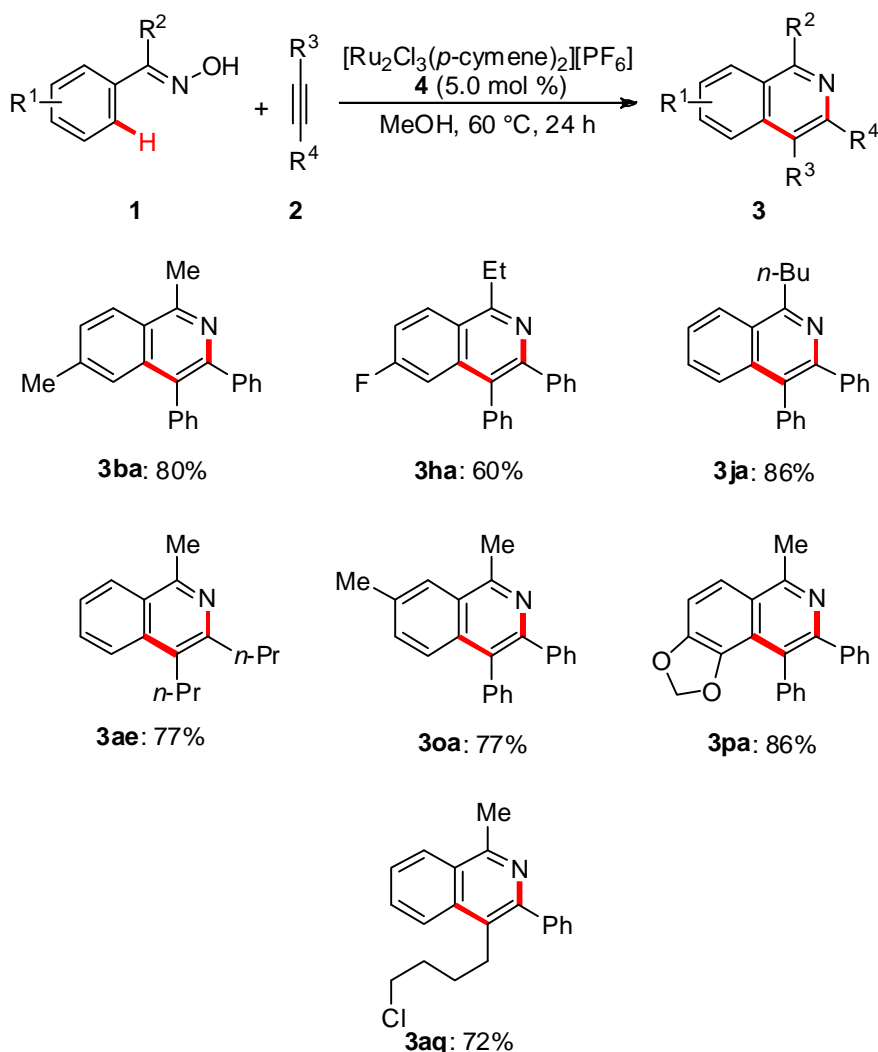
Importantly, intermolecular dehydrative annulations with challenging unsymmetrical alkynes **2** occurred with excellent regioselectivities (Scheme 3).¹³ Hence, the cationic ruthenium(II) complex furnished the 3-aryl-substituted isoquinolines **3ag–3aq** with high yields. Moreover, the catalyst proved tolerant of useful functional groups, such as esters, ketones, free hydroxyl groups as well as aryl and alkyl halides.

Scheme 3. Scope with Unsymmetrical Alkynes **2**



Given the remarkable efficacy of the in-situ generated ruthenium(II) catalyst, we subsequently probed the performance of preformed cationic complex $[\text{Ru}_2\text{Cl}_3(p\text{-cymene})_2][\text{PF}_6]$ (**4**)^{12,14} (Scheme 4). Importantly, well-defined complex **4** displayed an activity as well as chemo-, regio- and site-selectivity being comparable to the one displayed by the in-situ formed catalytic system.

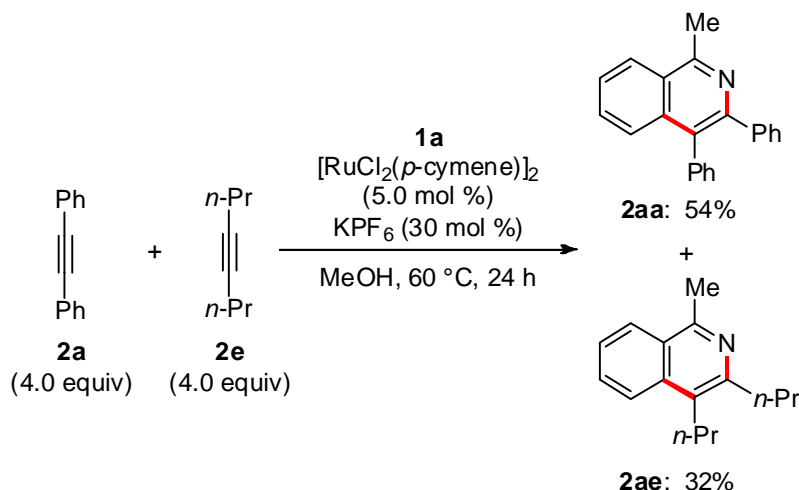
Scheme 4. Well-Defined Cationic Complex **4** as the Catalyst



Mechanistic Studies. Considering the high catalytic efficacy exerted by the optimized cationic catalyst, we became interested in delineating its mode of action. To this end, we performed

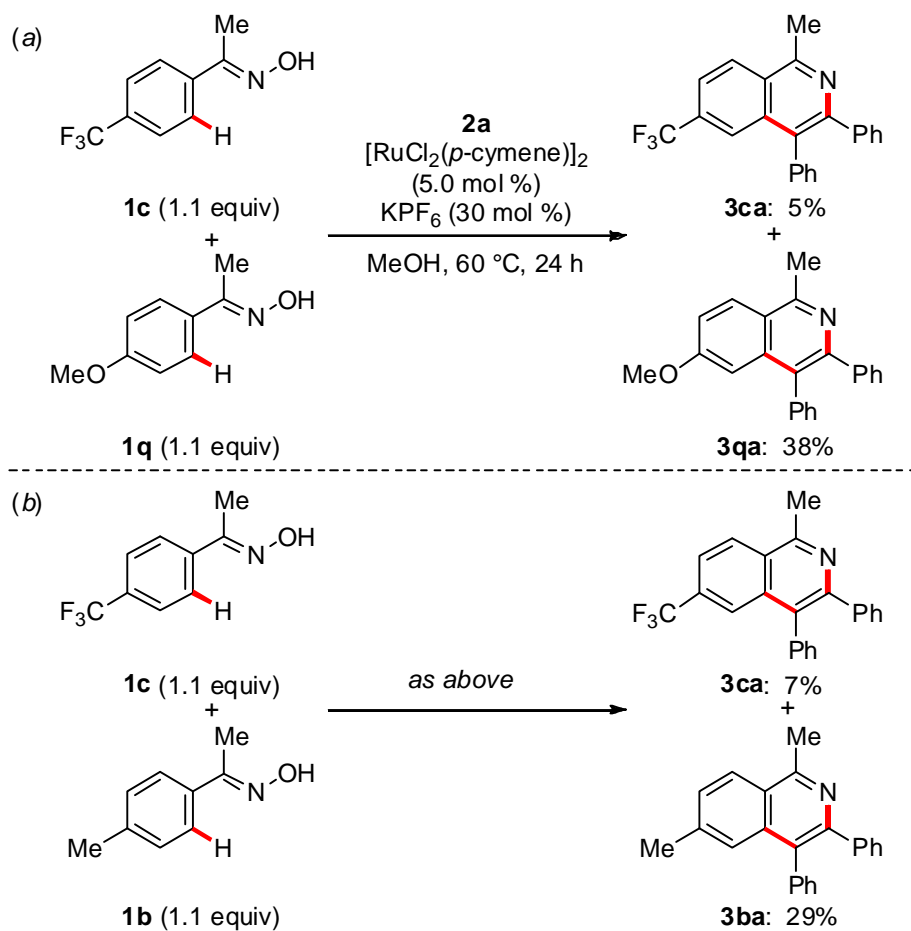
intermolecular competition experiments between different alkynes **2**, which revealed electron-deficient substrates to be more reactive (Scheme 5).

Scheme 5. Competition Experiment with Alkynes **2**

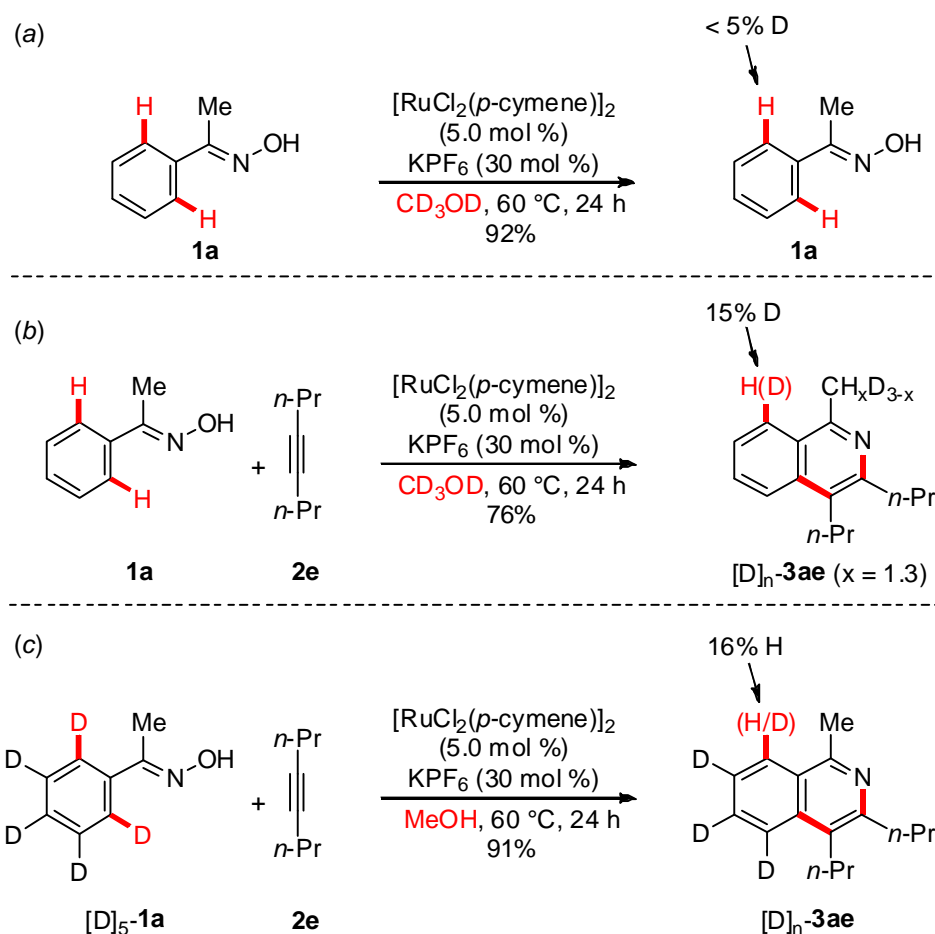


Moreover, intermolecular competition experiments with *para*-substituted oximes **1** highlighted electron-rich arenes to be preferentially converted (Scheme 6).

Scheme 6. Intermolecular Competition Experiments

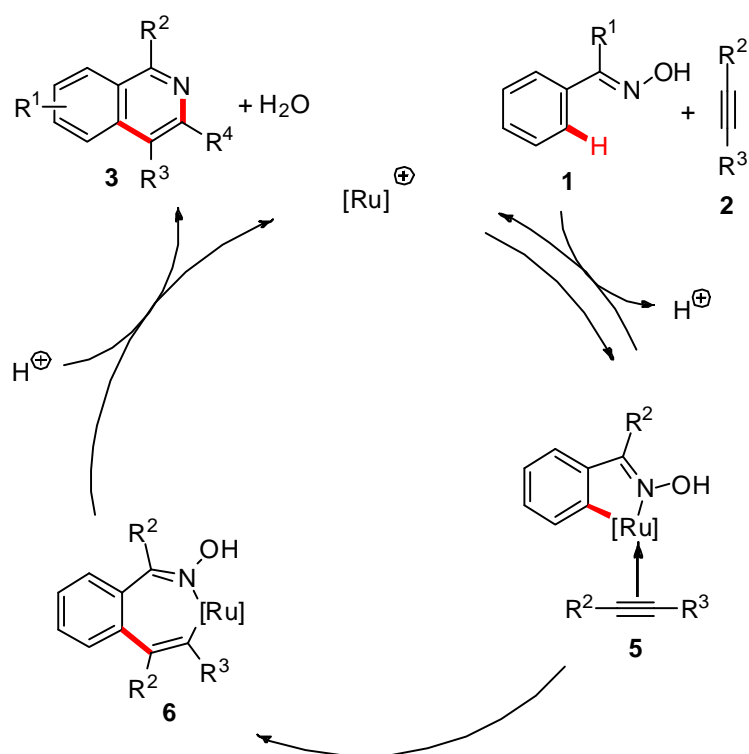


Mechanistic studies with deuterated solvent $[\text{D}]_4\text{-MeOH}$ and isotopically labeled substrate $[\text{D}]_5\text{-1a}$ showed a significant H/D scrambling, albeit solely occurring in the presence of an alkyne (Scheme 7). These observations were, hence, indicative of a reversible C–H bond metalation step by an alkyne-coordinated ruthenium complex, likely proceeding through base assistance. It is further noteworthy that deuterium was also incorporated into the methyl^{6f,15} group of product $[\text{D}]_n\text{-3ae}$ when using $[\text{D}]_5\text{-MeOH}$ as the solvent (Scheme 7b).

Scheme 7. Reactions with [D₄]-MeOH and Substrate [D₅]-**1a**

Based on these mechanistic studies we propose a catalytic cycle to involve an initial reversible base-assisted cycloruthenation with an alkyne-coordinated cationic complex, furnishing metalacycle **5**, presumably, *via* a S_EAr-type mechanism (Scheme 8). Subsequent migratory insertion of the alkyne **2** generates key intermediate **6**, while reductive elimination delivers product **3**. Finally, reoxidation by the internal oxidant *via* N–O bond cleavage regenerates the catalytically active species.

Scheme 8. Proposed Catalytic Cycle



Conclusions

In summary, we have reported on ruthenium-catalyzed redox-neutral annulations of alkynes by oximes through C–H/N–O functionalizations. Contrary to previous studies,^{9,10} carboxylate-free cationic ruthenium(II) catalysts were found to be most effective, which allowed for an expedient isoquinoline synthesis via reversible cyclometalation.

Experimental Section

General remarks. Catalytic reactions were carried out under a N₂ atmosphere using pre-dried glassware. H₂O was degassed and purged with N₂, DMF was dried and distilled over CaH₂, *t*-AmOH was dried and distilled over sodium, MeOH was dried and distilled over Mg(OMe)₂. All ketoximes **1** were synthesized according to a previously described procedure.¹⁶ Internal alkynes **2** were prepared according to previously described methods and were purified via Kugelrohr distillation.^{17,18} [Ru₂Cl₃(*p*-cymene)₂][PF₆] (**4**) was synthesized according to a previously reported procedure.¹² Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ¹H-NMR and GC-analysis. NMR spectra were recorded in the solvent indicated; chemical shifts (δ) are given in ppm. High resolution mass spectrometry (HRMS): FTICR.

Representative procedure for the Ruthenium-Catalyzed Synthesis of Isochinolines via Direct C–H/N–O Bond Functionalization, Synthesis of 1-Methyl-3,4-diphenylisoquinoline (3aa): A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), diphenylacetylene (**2a**) (178 mg, 1.00 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF₆ (28 mg, 0.15 mmol, 30 mol %) in MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **3aa** (119 mg, 81%) as a white solid (M.p.: 152–155 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.23–8.20 (m, 1H), 7.71–7.67 (m, 1H), 7.63–7.57 (m, 2H), 7.44–7.32 (m, 5H), 7.29–7.17 (m, 5H), 3.11 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.7 (C_q), 149.4 (C_q), 141.0 (C_q), 137.6 (C_q), 136.0 (C_q), 131.4 (CH), 130.2 (CH), 129.9 (CH), 129.1 (C_q), 128.1 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 126.1 (C_q), 125.5 (CH), 22.7 (CH₃). IR (ATR): 3025, 1567, 1389, 1334, 1072, 1026, 765, 695, 612, 563, 496 cm⁻¹. MS (EI) *m/z* (relative intensity) 295 (50) [M⁺], 294 (100), 278 (5), 252 (17), 177 (15), 146 (6), 43 (14). HR-MS (EI): *m/z* calcd for C₂₂H₁₇N 295.1361, found 295.1348. The spectral data are in accordance with those reported in the literature.¹⁹

1,6-Dimethyl-3,4-diphenylisoquinoline (3ba): The representative procedure was followed using **1b** (75 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **3ba** (131 mg, 85%) as a white solid (M.p.: 160–163 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.09 (d, *J* = 9.2 Hz, 1H), 7.44–7.39 (m, 2H), 7.39–7.30 (m, 5H), 7.25–7.14 (m, 5H), 3.05 (s, 3H), 2.43 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.3 (C_q), 149.5 (C_q), 141.1 (C_q), 140.1 (C_q), 137.7 (C_q), 136.2 (C_q), 131.4 (CH), 130.2 (CH), 128.7 (C_q), 128.6 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 125.4 (CH), 125.0 (CH), 124.5 (C_q), 22.6 (CH₃), 22.1 (CH₃). IR (ATR): 3062, 1495, 1444, 1385, 1336, 1071, 1029, 813, 767, 755, 696, 614 cm⁻¹. MS (EI) *m/z* (relative intensity) 309 (40) [M⁺], 308 (100), 293 (5), 265 (5), 252 (12), 146 (5), 43 (4). HR-MS (ESI): *m/z* calcd for C₂₃H₁₉N+H⁺ 310.1590, found 310.1592. The spectral data are in accordance with those reported in the literature.¹⁹

6-(Trifluoromethyl)-1-methyl-3,4-diphenylisoquinoline (3ca): The representative procedure was followed using **1c** (102 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ca** (118 mg, 65%) as an orange solid (M.p.: 109–114 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.31 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.40–7.33 (m, 5H), 7.23–7.16 (m, 5H), 3.10 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.8 (C_q), 150.9 (C_q), 140.4 (C_q), 136.5 (C_q), 135.4 (C_q), 131.5 (q, ²*J*_{C-F} = 32 Hz, C_q), 131.2 (CH), 130.2 (CH), 129.7 (C_q), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.0 (C_q), 126.8 (CH), 123.9 (q, ³*J*_{C-F} = 5 Hz, CH), 123.8 (d, ¹*J*_{C-F} = 272 Hz, C_q), 122.2 (q, ³*J*_{C-F} = 3 Hz, CH), 22.8 (CH₃). ¹⁹F-NMR (282 MHz, CDCl₃): δ = –62.9 (s). IR (ATR): 2958, 1555, 1336, 1305, 1257, 1176, 1155, 1134, 1082, 909, 769, 696, 618 cm⁻¹. MS (EI) *m/z* (relative intensity) 363 (50) [M⁺], 362 (100), 252 (8), 146 (5), 43 (5). HR-MS (EI): *m/z* calcd for C₂₃H₁₆F₃N 363.1235, found 363.1219. The spectral data are in accordance with those reported in the literature.²⁰

6-Bromo-1-methyl-3,4-diphenylisoquinoline (3da): The representative procedure was followed using **1d** (107 mg, 0.50 mmol) diphenylacetylene (**2a**) (178 mg, 1.00 mmol) and molecular sieves 4Å

(100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **3da** (102 mg, 54%) as a yellow solid (M.p.: 193–195 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.06 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.39–7.30 (m, 5H), 7.23–7.14 (m, 5H), 3.06 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.6 (C_q), 150.5 (C_q), 140.5 (C_q), 137.3 (C_q), 136.7 (C_q), 131.2 (CH), 130.0 (CH), 129.9 (CH), 128.3 (CH), 128.3 (CH), 128.2 (C_q), 127.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 125.0 (C_q), 124.5 (C_q), 22.8 (CH₃). IR (ATR): 3064, 1597, 1561, 1481, 1445, 1386, 1329, 1259, 1071, 1029, 751, 697 cm⁻¹. MS (EI) *m/z* (relative intensity) 374 (100) [M+H⁺], 293 (26), 252 (28), 189 (15), 146 (14), 43 (56). HR-MS (ESI): *m/z* calcd for C₂₂H₁₆BrN+H⁺ 374.0539, found 374.0538. The spectral data are in accordance with those reported in the literature.²⁰

1-Methyl-3,4,6-triphenylisoquinoline (3ea): The representative procedure was followed using **1e** (106 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **3ea** (101 mg, 54%) as a pale orange solid (M.p.: 176–178 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.28 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.87 (s, 1H), 7.86 (d, *J* = 8.2, 1.8 Hz, 1H), 7.62–7.53 (m, 2H), 7.49–7.14 (m, 14H), 3.11 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.5 (C_q), 150.0 (C_q), 142.5 (C_q), 141.0 (C_q), 140.4 (C_q), 137.5 (C_q), 136.3 (C_q), 131.4 (CH), 130.2 (CH), 129.3 (C_q), 128.9 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.2 (CH), 126.2 (CH), 125.2 (C_q), 124.0 (CH), 22.7 (CH₃). IR (ATR): 3058, 1611, 1567, 1434, 1339, 955, 893, 831, 760, 751, 690, 611 cm⁻¹. MS (EI) *m/z* (relative intensity) 371 (68) [M⁺], 370 (100), 354 (3), 327 (5), 292 (2), 252 (4), 77 (3). HR-MS (EI): *m/z* calcd for C₂₈H₂₁N 371.1674, found 371.1657. The spectral data are in accordance with those reported in the literature.²⁰

1-Ethyl-3,4-diphenylisoquinoline (3fa): Representative procedure A was followed using **1f** (75 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **3fa** (141 mg, 91%) as a pale brown solid (M.p.: 113–115 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.29–8.20 (m, 1H), 7.70–7.62 (m, 1H), 7.61–7.50 (m, 2H), 7.42–7.30 (m, 5H), 7.26–7.12 (m, 5H), 3.44 (q, *J* = 7.6 Hz, 2H), 1.53 (t, *J* = 7.6 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ =

162.2 (C_q), 149.2 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.7 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.4 (CH), 126.4 (CH), 125.3 (C_q), 125.1 (CH), 28.8 (CH₂), 13.9 (CH₃). IR (ATR): 2935, 1552, 1445, 1382, 1260, 1072, 1028, 753, 694, 607, 561 cm⁻¹. MS (EI) *m/z* (relative intensity) 309 (55) [M⁺], 308 (100), 293 (14), 280 (8), 252 (5), 146 (5), 69 (6). HR-MS (EI): *m/z* calcd for C₂₃H₁₉N 309.1517, found 309.1505. The spectral data are in accordance with those reported in the literature.¹⁹

1-Ethyl-6-methoxy-3,4-diphenylisoquinoline (3ga): The representative procedure was followed using **1g** (94 mg, 0.52 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ga** (168 mg, 95%) as a pale yellow solid (M.p.: 158–161 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.14 (d, *J* = 9.2 Hz, 1H), 7.40–7.28 (m, 5H), 7.26–7.11 (m, 6H), 6.91 (d, *J* = 2.6 Hz, 1H), 3.71 (s, 3H), 3.37 (q, *J* = 7.6 Hz, 2H), 1.50 (t, *J* = 7.6 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 161.6 (C_q), 160.3 (C_q), 150.0 (C_q), 141.3 (C_q), 138.4 (C_q), 138.0 (C_q), 131.3 (CH), 130.3 (CH), 128.3 (C_q), 128.2 (CH), 127.5 (CH), 127.0 (CH), 127.0 (CH), 126.8 (CH), 121.0 (C_q), 119.0 (CH), 104.6 (CH), 55.1 (CH₃), 28.8 (CH₂), 14.1 (CH₃). IR (ATR): 2970, 1617, 1574, 1454, 1411, 1232, 1146, 1018, 757, 699, 662, 527 cm⁻¹. MS (EI) *m/z* (relative intensity) 339 (55) [M⁺], 338 (100), 323 (5), 295 (10), 280 (12), 267 (7), 239 (8). HR-MS (EI): *m/z* calcd for C₂₄H₂₁NO 339.1623, found 339.1613.

1-Ethyl-6-fluoro-3,4-diphenylisoquinoline (3ha): The representative procedure was followed using **1h** (83 mg, 0.50 mmol) and diphenyl acetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 15/1 → 12/1) yielded **3ha** (94 mg, 57%) as a white solid (M.p.: 141–142 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.27 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.45–7.10 (m, 12H), 3.42 (q, *J* = 7.5 Hz, 2H), 1.53 (t, *J* = 7.5 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 163.0 (d, ¹*J*_{C-F} = 245 Hz, C_q), 162.0 (C_q), 150.7 (C_q), 140.8 (C_q), 138.4 (d, ³*J*_{C-F} = 10 Hz, C_q), 137.3 (C_q), 131.2 (CH), 130.3 (CH), 128.7 (d, ⁴*J*_{C-F} = 5 Hz, C_q), 128.4 (CH), 128.2 (d, ³*J*_{C-F} = 10 Hz, CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 122.5 (d, ⁴*J*_{C-F} = 1 Hz, C_q), 116.6 (d, ²*J*_{C-F} = 25 Hz, CH), 110.0 (d, ²*J*_{C-F} = 22 Hz, CH), 28.9 (CH₂),

13.9 (CH₃). ¹⁹F-NMR (282 MHz, CDCl₃): δ = -107.9 (s). IR (ATR): 2973, 1619, 1573, 1447, 1386, 1182, 1072, 876, 788, 753, 697 cm⁻¹. MS (EI) *m/z* (relative intensity) 327 (53) [M⁺], 326 (100), 311 (12), 298 (10), 98 (10), 74 (6), 57 (10), 43 (20). HR-MS (ESI): *m/z* calcd for C₂₃H₁₈FN+H⁺ 328.1496, found 328.1498.

3,4-Diphenyl-1-*n*-propylisoquinoline (3ia): The representative procedure was followed using **1i** (82 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **3ia** (144 mg, 89%) as a yellow solid (M.p.: 118–120 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.23–8.14 (m, 1H), 7.64–7.56 (m, 1H), 7.54–7.45 (m, 2H), 7.37–7.22 (m, 5H), 7.20–7.05 (m, 5H), 3.32 (t, *J* = 7.7 Hz, 2H), 1.95 (dt, *J* = 7.7, 7.3 Hz 2H), 1.08 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 161.3 (C_q), 149.3 (C_q), 141.1 (C_q), 137.8 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 126.3 (CH), 125.6 (C_q), 125.2 (CH), 37.7 (CH₂), 23.2 (CH₂), 14.5 (CH₃). IR (ATR): 3063, 2962, 1612, 1568, 1550, 1444, 1385, 1087, 1031, 757, 697 cm⁻¹. MS (EI) *m/z* (relative intensity) 323 (22) [M⁺], 295 (100), 308 (16), 252 (7). HR-MS (EI): *m/z* calcd for C₂₄H₂₁N-H⁺ 322.1596, found 322.1607.

1-*n*-Butyl-3,4-diphenylisoquinoline (3ja): The representative procedure was followed using **1j** (89 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **3ja** (151 mg, 89%) as a yellow solid (M.p.: 78–80 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.27–8.21 (m, 1H), 7.69–7.64 (m, 1H), 7.60–7.54 (m, 2H), 7.40–7.31 (m, 5H), 7.26–7.15 (m, 5H), 3.42 (t, *J* = 8.0 Hz, 2H), 2.02–1.90 (m, 2H), 1.58 (dt, *J* = 7.7, 7.3 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 161.5 (C_q), 149.3 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.8 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 125.4 (C_q), 125.2 (CH), 35.5 (CH₂), 32.1 (CH₂), 23.1 (CH₂), 14.1 (CH₃). IR (ATR): 3061, 2958, 2876, 1611, 1504, 1442, 1382, 1337, 1172, 1073, 763, 697 cm⁻¹. MS (EI) *m/z*

(relative intensity) 337 (6) [M^+], 295 (100), 308 (10), 252 (6). HR-MS (EI): m/z calcd for $C_{25}H_{23}N-H^+$ 336.1752, found 336.1747. The spectral data are in accordance with those reported in the literature.²¹

1-*n*-Pentyl-3,4-diphenylisoquinoline (3ka): The representative procedure was followed using **1k** (96 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **3ka** (168 mg, 96%) as a yellow oil. 1H -NMR (300 MHz, $CDCl_3$): δ = 8.31–8.19 (m, 1H), 7.71–7.63 (m, 1H), 7.61–7.53 (m, 2H), 7.42–7.28 (m, 5H), 7.27–7.12 (m, 5H), 3.40 (t, J = 7.5 Hz, 2H), 2.07–1.89 (m, 2H), 1.66–1.37 (m, 4H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 149.3 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.3 (CH), 125.5 (C_q), 125.2 (CH), 35.8 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR (ATR): 3058, 2927, 2858, 1613, 1551, 1504, 1443, 1383, 1073, 1030, 763, 696, 612, 566 cm^{-1} . MS (EI) m/z (relative intensity) 351 (5) [M^+], 322 (10), 308 (12), 295 (100), 252 (5), 216 (5). HR-MS (EI): m/z calcd for $C_{26}H_{25}N$ 351.1987, found 351.1998.

1,3,4-Triphenylisoquinoline (3la): The representative procedure was followed using **1l** (99 mg, 0.50 mmol) and diphenylacetylene (**2l**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **3la** (147 mg, 82%) as a pale yellow solid (M.p.: 181–184 °C). 1H -NMR (300 MHz, $CDCl_3$): δ = 8.20 (dm, J = 8.5 Hz, 1H), 7.84 (dd, J = 8.0, 1.6 Hz, 2H), 7.74 (dm, J = 8.7 Hz, 1H), 7.67–7.10 (m, 15H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 159.9 (C_q), 149.6 (C_q), 140.9 (C_q), 139.8 (C_q), 137.5 (C_q), 136.9 (C_q), 131.3 (CH), 130.4 (CH), 130.2 (CH), 129.9 (CH), 129.7 (C_q), 128.5 (CH), 128.3 (CH), 128.3 (CH), 127.5 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 126.6 (CH), 126.0 (CH), 125.4 (C_q). IR (ATR): 3054, 1540, 1494, 1442, 1384, 1336, 1073, 1030, 980, 761, 700, 668, 633, 567 cm^{-1} . MS (EI) m/z (relative intensity) 357 (50) [M^+], 356 (100), 278 (11), 252 (10), 177 (5). HR-MS (EI): m/z calcd for $C_{27}H_{19}N$ 357.1517, found 357.1493. The spectral data are in accordance with those reported in the literature.¹⁹

1-Cyclopropyl-3,4-diphenylisoquinoline (3ma): The representative procedure was followed using **1m** (81 mg, 0.50 mmol), diphenylacetylene (**2a**) (178 mg, 1.00 mmol) and molecular sieves 4Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 200/1) yielded **3ma** (135 mg, 84%) as a yellow solid (M.p.: 148–150 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.50 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.69–7.62 (m, 1H), 7.62–7.51 (m, 2H), 7.42–7.27 (m, 5H), 7.27–7.21 (m, 2H), 7.20–7.08 (m, 3H), 2.89–2.74 (m, 1H), 1.44–1.32 (m, 2H), 1.18–1.05 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ = 160.6 (C_q), 148.7 (C_q), 141.2 (C_q), 138.0 (C_q), 136.1 (C_q), 131.4 (CH), 130.4 (CH), 129.6 (CH), 128.2 (CH), 128.0 (C_q), 127.3 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 126.3 (C_q), 126.2 (CH), 124.8 (CH), 13.6 (CH), 9.4 (CH₂). IR (ATR): 3055, 1611, 1568, 1547, 1444, 1410, 1318, 1261, 1075, 1014, 767, 694 cm⁻¹. MS (EI) *m/z* (relative intensity) 321 (68) [M⁺], 320 (100), 278 (5), 243 (8), 152(5), 43 (13). HR-MS (EI): *m/z* calcd for C₂₄H₁₉N-H⁺ 320.1439, found 320.1438. The spectral data are in accordance with those reported in the literature.²²

9-Methyl-2,3-diphenyl-8,9-dihydro-7H-benzo[de]quinoline (3na): The representative procedure was followed using **1n** (88 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **3na** (157 mg, 93%) as a yellow solid (M.p.: 145–147 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 7.51–7.46 (m, 2H), 7.45–7.28 (m, 7H), 7.25–7.12 (m, 4H), 3.54–3.41 (m, 1H), 3.36–3.24 (m, 1H), 3.23–3.11 (m, 1H), 2.43–2.31 (m, 1H), 2.12–1.99 (m, 1H), 1.63–1.56 (d, *J* = 7.1, 3H). ¹³C-NMR (75 MHz, C₂D₂Cl₄, 100 °C): δ = 162.0 (C_q), 148.7 (C_q), 141.3 (C_q), 138.0 (C_q), 138.0 (C_q), 136.2 (C_q), 131.2 (CH), 130.3 (CH), 129.3 (CH), 128.4 (C_q), 127.9 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 124.3 (CH), 123.3 (CH), 123.0 (C_q), 37.4 (CH), 30.8 (CH₂), 27.8 (CH₂), 19.6 (CH₃). IR (ATR): 2929, 1604, 1577, 1442, 1377, 1306, 1178, 1071, 1023, 767, 699 cm⁻¹. MS (EI) *m/z* (relative intensity) 335 (91) [M⁺], 334 (100), 320 (50), 241 (8), 43 (13). HR-MS (EI): *m/z* calcd for C₂₅H₂₁N-H⁺ 334.1596, found 334.1608.

3,4-Bis(4-methoxyphenyl)-1-methylisoquinoline (3ab): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)acetylene (**2b**) (238 mg, 1.00 mmol).

Purification by column chromatography (*n*-hexane/EtOAc: 10/1 → 8/1) yielded **3ab** (95 mg, 53%) as an orange solid (M.p.: 106–110 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.20–8.11 (m, 1H), 7.73–7.62 (m, 1H), 7.60–7.49 (m, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.04 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 158.6 (C_q), 158.5 (C_q), 157.3 (C_q), 149.1 (C_q), 136.4 (C_q), 133.6 (C_q), 132.4 (CH), 131.5 (CH), 129.9 (C_q), 129.7 (CH), 128.2 (C_q), 126.2 (CH), 126.1 (CH), 125.9 (C_q), 125.5 (CH), 113.7 (CH), 113.1 (CH), 55.2 (CH₃), 55.1 (CH₃), 22.7 (CH₃). IR (ATR): 2937, 2838, 1604, 1510, 1287, 1243, 1170, 1027, 837, 814, 760, 598, 557, 530 cm⁻¹. MS (EI) *m/z* (relative intensity) 355 (80) [M⁺], 354 (100), 340 (10), 311 (20), 296 (5), 268 (15), 239 (4), 226 (4), 43 (3). HR-MS (EI): *m/z* calcd for C₂₄H₂₁NO₂ 355.1572, found 355.1539. The spectral data are in accordance with those reported in the literature.²³

3,4-Bis(4-fluorophenyl)-1-methylisoquinoline (3ac): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)acetylene (**2c**) (214 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **3ac** (116 mg, 70%) as an orange oil. ¹H-NMR (300 MHz, CDCl₃): δ = 8.23–8.15 (m, 1H), 7.65–7.55 (m, 3H), 7.37–7.27 (m, 2H), 7.22–7.12 (m, 2H), 7.11–7.00 (m, 2H), 6.95–6.84 (m, 2H), 3.06 (s, 3H). ¹³C-NMR (126 MHz, CDCl₃): δ = 161.9 (d, ¹*J*_{C-F} = 247 Hz, C_q), 161.8 (d, ¹*J*_{C-F} = 247 Hz, C_q), 157.9 (C_q), 148.5 (C_q), 136.8 (d, ⁴*J*_{C-F} = 3 Hz, C_q), 135.9 (C_q), 133.2 (d, ⁴*J*_{C-F} = 4 Hz, C_q), 132.8 (d, ³*J*_{C-F} = 8 Hz, CH), 131.9 (d, ³*J*_{C-F} = 8 Hz, CH), 130.1 (CH), 128.0 (C_q), 126.6 (CH), 126.1 (C_q), 125.8 (CH), 125.5 (CH), 115.4 (d, ²*J*_{C-F} = 21 Hz, CH), 114.6 (d, ²*J*_{C-F} = 21 Hz, CH), 22.8 (CH₃). ¹⁹F-NMR (282 MHz, CDCl₃): δ = -114.6 (tt, *J* = 8.8, 5.6 Hz), -115.2 (tt, *J* = 8.7, 5.5 Hz). IR (ATR): 3035, 1603, 1508, 1390, 1334, 1221, 1154, 1093, 907, 836, 759, 728, 594, 560, 547 cm⁻¹. MS (EI) *m/z* (relative intensity) 331 (55) [M⁺], 330 (100), 315 (4), 288 (15), 268 (4). HR-MS (EI): *m/z* calcd for C₂₂H₁₅F₂N 331.1173, found 331.1150.

3,4-Diethyl-1-methylisoquinoline (3ad): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 3-hexyne (**2d**) (82 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ad** (86 mg, 86%) as a pale yellow solid (M.p.: 54–57 °C). ¹H-NMR (300

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3 MHz, CDCl₃): δ = 8.06 (ddd, J = 8.5, 1.3, 0.8 Hz, 1H), 7.96 (dt, J = 8.5, 0.8 Hz, 1H), 7.64 (ddd, J = 8.5,
4 6.8, 1.3 Hz, 1H), 7.48 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 3.03 (q, J = 7.7 Hz, 2H), 2.95 (q, J = 7.7 Hz, 2H),
5 2.90 (s, 3H), 1.33 (t, J = 7.7 Hz, 3H), 1.27 (t, J = 7.7 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 155.7
6 (C_q), 152.5 (C_q), 135.1 (C_q), 129.4 (CH), 127.1 (C_q), 126.1 (CH), 126.0 (C_q), 125.2 (CH), 123.3 (CH),
7 28.5 (CH₂), 22.3 (CH₃), 20.6 (CH₂), 15.2 (CH₃), 14.9 (CH₃). IR (ATR): 2963, 1614, 1566, 1451, 1391,
8 1311, 1054, 963, 769, 692, 616 cm⁻¹. MS (EI) m/z (relative intensity) 199 (31) [M⁺], 198 (100), 184
9 (23), 170 (9), 128 (10), 115 (20), 77 (8), 69 (8). HR-MS (EI): m/z calcd for C₁₄H₁₇N 199.1361, found
10 199.1355. The spectral data are in accordance with those reported in the literature.¹⁹

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22 **1-Methyl-3,4-di-*n*-propylisoquinoline (3ae):** The representative procedure was followed using **1a**
23 (68 mg, 0.50 mmol) and 4-octyne (**2e**) (110 mg, 1.00 mmol). Purification by column chromatography
24 (*n*-hexane/EtOAc: 12/1) yielded **3ae** (99 mg, 87%) as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ =
25 8.06 (dd, J = 8.5, 0.8 Hz, 1H), 7.94 (dd, J = 8.5, 0.8 Hz, 1H), 7.3 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.47
26 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 3.01–2.92 (m, 2H), 2.92–2.84 (m, 2H), 2.89 (s, 3H), 1.84–1.72 (m, 2H),
27 1.71–1.58 (m, 2H), 1.07 (t, J = 6.7 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ =
28 155.6 (C_q), 151.7 (C_q), 135.4 (C_q), 129.3 (CH), 126.1 (C_q), 126.1 (CH), 126.0 (C_q), 125.2 (CH), 123.5
29 (CH), 37.4 (CH₂), 29.8 (CH₂), 24.2 (CH₂), 23.8 (CH₂), 22.4 (CH₃), 14.6 (CH₃), 14.4 (CH₃). IR (ATR):
30 2957, 2870, 1617, 1568, 1454, 1391, 1333, 1027, 754, 614 cm⁻¹. MS (EI) m/z (relative intensity) 227
31 (40) [M⁺], 212 (80), 198 (100), 184 (50), 171 (55), 128 (23), 115 (16), 77 (6), 43 (31). HR-MS (EI): m/z
32 calcd for C₁₆H₂₁N 227.1674, found 227.1669. The spectral data are in accordance with those reported in
33 the literature.¹⁹

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50 **3,4-Di-*n*-butyl-1-methylisoquinoline (3af):** The representative procedure was followed using **1a**
51 (68 mg, 0.50 mmol) and 5-decyne (**2f**) (138 mg, 1.00 mmol). Purification by column chromatography
52 (*n*-hexane/EtOAc: 12/1) yielded **3af** (101 mg, 79%) as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ =
53 8.05 (dd, J = 8.5, 1.0 Hz, 1H), 7.94 (dd, J = 8.5, 1.0 Hz, 1H), 7.62 (ddd, J = 7.8, 6.8, 1.1 Hz, 1H), 7.46
54 (ddd, J = 7.8, 6.8, 1.1 Hz, 1H), 3.04–2.86 (m, 4H), 2.90 (s, 3H), 1.79–1.65 (m, 2H), 1.65–1.40 (m, 6H),
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0.99 (t, $J = 7.1$ Hz, 3H), 0.97 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 155.5$ (C_q), 151.7 (C_q), 135.3 (C_q), 129.3 (CH), 126.1 (C_q), 126.0 (CH), 126.0 (C_q), 125.1 (CH), 123.4 (CH), 35.2 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 27.4 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 22.3 (CH_3), 14.1 (CH_3), 13.9 (CH_3). IR (ATR): 2955, 2858, 1617, 1568, 1504, 1441, 1391, 1336, 1028, 754, 614 cm^{-1} . MS (EI) m/z (relative intensity) 255 (8) [M^+], 240 (9), 226 (31), 213 (28), 198 (45), 184 (28), 171 (100), 128 (12), 115 (6), 43 (11). HR-MS (EI): m/z calcd for $\text{C}_{18}\text{H}_{25}\text{N}$ 255.1987, found 255.1992.

1,7-Dimethyl-3,4-diphenylisoquinoline (3oa): The representative procedure was followed using **1o** (75 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3oa** (125 mg, 81%) as a pale orange solid (M.p.: 134–139 °C). ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.96$ (dq, $J = 1.8, 0.9$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.45–7.30 (m, 6H), 7.26–7.14 (m, 5H), 3.06 (s, 3H), 2.57 (s, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 156.9$ (C_q), 148.6 (C_q), 141.0 (C_q), 137.7 (C_q), 136.3 (C_q), 134.1 (C_q), 132.0 (CH), 131.3 (CH), 130.2 (CH), 129.0 (C_q), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.2 (C_q), 126.0 (CH), 124.4 (CH), 22.7 (CH_3), 21.8 (CH_3). IR (ATR): 3023, 2914, 1551, 1504, 1442, 1386, 1321, 1073, 1027, 831, 767, 755, 696, 567 cm^{-1} . MS (EI) m/z (relative intensity) 309 (65) [M^+], 100 (100), 293 (8), 265 (5), 252 (15), 146 (5), 43 (6). HR-MS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{N} + \text{H}^+$ 310.1590, found 310.1592. The spectral data are in accordance with those reported in the literature.²⁴

5,6-(Methylenedioxy)-1-methyl-3,4-diphenylisoquinoline (3pa): The representative procedure was followed using **1p** (100 mg, 0.50 mmol) and diphenylacetylene (**2a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1 \rightarrow 8/1 \rightarrow 6/1 \rightarrow 2/1) yielded **3pa** (164 mg, 86%) as a white solid (M.p.: 251–254 °C). ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.82$ (d, $J = 8.8$ Hz, 1H), 7.37–7.06 (m, 11H), 5.83 (s, 2H), 2.99 (s, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 157.7$ (C_q), 150.2 (C_q), 147.6 (C_q), 141.7 (C_q), 140.8 (C_q), 138.4 (C_q), 131.1 (CH), 130.2 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 124.8 (C_q), 123.2 (C_q), 122.5 (C_q), 120.9 (CH), 110.8 (CH), 101.4 (CH_2), 23.4 (CH_3). IR (ATR): 2899, 1626, 1549, 1512, 1432, 1383, 1353, 1279, 1209, 1119, 1049, 891, 794, 760, 744, 698, 644 cm^{-1} .

MS (EI) m/z (relative intensity) 339 (100) [M^+], 338 (98), 310 (18), 292 (14), 278 (9), 267 (6), 239 (6), 176 (5), 139 (9), 77 (7), 43 (8). HR-MS (EI): m/z calcd for $C_{23}H_{17}NO_2$ 339.1259, found 339.1252.

1,4-Dimethyl-3-phenylisoquinoline (3ag): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-phenyl-1-propyne (**3g**) (116 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ag** (81 mg, 69%) as a red solid (M.p.: 83–87 °C). 1H -NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.5, 0.9 Hz, 1H), 8.04 (dd, J = 8.5, 0.9 Hz, 1H), 7.73 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.64–7.54 (m, 3H), 7.52–7.45 (m, 2H), 7.42–7.33 (m, 1H), 2.98 (s, 3H), 2.59 (s, 3H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 155.8 (C_q), 150.6 (C_q), 141.5 (C_q), 136.2 (C_q), 129.8 (CH), 129.8 (CH), 128.0 (CH), 127.4 (CH), 126.2 (CH), 126.1 (C_q), 126.0 (CH), 124.1 (CH), 122.1 (C_q), 22.5 (CH_3), 15.4 (CH_3). IR (ATR): 2947, 1683, 1561, 1504, 1437, 1388, 1336, 1159, 1020, 760, 699, 603, 539 cm^{-1} . MS (EI) m/z (relative intensity) 233 (50) [M^+], 232 (100), 217 (10), 202 (4), 189 (7), 128 (5), 115 (8), 77 (6), 43 (11). HR-MS (EI): m/z calcd for $C_{17}H_{15}N$ 233.1204, found 233.1186. The spectral data are in accordance with those reported in the literature.¹⁹

4-Ethyl-1-methyl-3-phenylisoquinoline (3ah): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-phenyl-1-butyne (**2h**) (130 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ah** (78 mg, 63%) as a pale yellow solid (M.p.: 117–120 °C). 1H -NMR (300 MHz, $CDCl_3$): δ = 8.17 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H), 8.07 (dd, J = 8.6, 1.0 Hz, 1H), 7.73 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.59 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.54–7.33 (m, 5H), 2.99 (q, J = 7.5 Hz, 2H), 2.97 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 155.8 (C_q), 150.7 (C_q), 141.8 (C_q), 135.1 (C_q), 129.8 (CH), 129.2 (CH), 128.5 (C_q), 128.1 (CH), 127.4 (CH), 126.7 (C_q), 126.3 (CH), 126.1 (CH), 124.1 (CH), 22.5 (CH_3), 21.6 (CH_2), 15.7 (CH_3). IR (ATR): 2963, 1562, 1435, 1390, 1333, 1162, 1027, 861, 771, 748, 685, 620, 590 cm^{-1} . MS (EI) m/z (relative intensity) 247 (54) [M^+], 246 (100), 231 (21), 217 (10), 202 (6), 189 (5), 128 (5), 115 (7), 77 (6). HR-MS (EI): m/z calcd for $C_{18}H_{17}N$ 247.1361, found 247.1349. The spectral data are in accordance with those reported in the literature.¹⁹

4-*n*-Hexyl-1-methyl-3-phenylisoquinoline (3ai): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-phenyl-1-octyne (**2i**) (186 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ai** (79 mg, 52%) as an orange oil and **3ai'** (9 mg, 6%) as an orange oil. ¹H-NMR (300 MHz, CDCl₃): δ = 8.15 (ddd, *J* = 8.4, 1.3, 0.8 Hz, 1H), 8.05 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.53–7.34 (m, 5H), 3.01–2.89 (m, 2H), 2.97 (s, 3H), 1.70–1.56 (m, 2H), 1.38–1.14 (m, 6H), 0.84 (t, *J* = 6.7 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 155.7 (C_q), 150.9 (C_q), 141.9 (C_q), 135.4 (C_q), 129.7 (CH), 129.3 (CH), 128.1 (CH), 127.4 (C_q), 127.3 (CH), 126.6 (C_q), 126.2 (CH), 126.1 (CH), 124.2 (CH), 31.4 (CH₂), 31.2 (CH₂), 29.5 (CH₂), 28.5 (CH₂), 22.5 (CH₂), 22.5 (CH₃), 14.0 (CH₃). IR (ATR): 2924, 2856, 1614, 1562, 1504, 1436, 1391, 1333, 1029, 755, 698, 616, 592 cm⁻¹. MS (EI) *m/z* (relative intensity) 303 (35) [M⁺], 260 (10), 246 (50), 217 (15), 189 (5). HR-MS (EI): *m/z* calcd for C₂₂H₂₅N 303.1987, found 303.1982.

3-*n*-Hexyl-1-methyl-4-phenylisoquinoline (3ai'): ¹H-NMR (300 MHz, CDCl₃): δ = 8.14–8.07 (m, 1H), 7.53–7.38 (m, 5H), 7.37–7.30 (m, 1H), 7.30–7.22 (m, 2H), 2.99 (s, 3H), 2.69–2.58 (m, 2H), 1.77–1.55 (m, 2H), 1.28–1.08 (m, 6H), 0.79 (t, *J* = 7.0 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 157.4 (C_q), 151.7 (C_q), 137.9 (C_q), 136.0 (C_q), 130.4 (CH), 129.5 (CH), 128.9 (C_q), 128.3 (CH), 127.3 (CH), 125.8 (CH), 125.6 (CH), 125.4 (C_q), 125.3 (CH), 35.7 (CH₂), 31.6 (CH₂), 30.4 (CH₂), 29.3 (CH₂), 22.5 (CH₂), 22.5 (CH₃), 14.0 (CH₃). IR (ATR): 2925, 2855, 1713, 1563, 1505, 1442, 1392, 1336, 1028, 758, 699, 626, 599 cm⁻¹. MS (EI) *m/z* (relative intensity) 303 (4) [M⁺], 288 (4), 274 (5), 260 (15), 246 (20), 232 (100), 217 (10), 189 (8), 43 (7). HR-MS (EI): *m/z* calcd for C₂₂H₂₅N 303.1987, found 303.1976.

1-{4-(1,4-Dimethylisoquinolin-3-yl)phenyl}ethanone (3aj): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-{4-(prop-1-yn-1-yl)phenyl}ethanone (**2j**) (158 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **3aj** (97 mg, 70%) as a yellow solid (M.p.: 149–153 °C). ¹H-NMR (300 MHz, CDCl₃): δ = 8.17 (ddd, *J* = 8.3, 1.3, 0.7 Hz, 1H), 8.09–8.04 (m, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.76 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.69 (d,

$J = 8.5$ Hz, 2H), 7.63 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 2.98 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 197.9$ (C_q), 156.2 (C_q), 149.3 (C_q), 146.3 (C_q), 136.1 (C_q), 135.9 (C_q), 130.2 (CH), 130.0 (CH), 128.1 (CH), 126.7 (CH), 126.3 (C_q), 126.1 (CH), 124.1 (CH), 122.6 (C_q), 26.7 (CH_3), 22.5 (CH_3), 15.3 (CH_3). IR (ATR): 2920, 1681, 1605, 1565, 1261, 1012, 957, 853, 834, 762, 733, 599, 540 cm^{-1} . MS (EI) m/z (relative intensity) 275 (59) [M^+], 274 (100), 231 (27), 217 (8), 188 (6), 129 (5), 115 (5), 43 (13). HR-MS (EI): m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}$ 275.1310, found 275.1299.

4-*n*-Butyl-1-methyl-3-(*p*-tolyl)isoquinoline (3ak): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-(*p*-tolyl)-1-hexyne (**2k**) (172 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ak** (98 mg, 68%) as an orange oil and **3ak'** (11 mg, 8%) as an orange oil. ^1H -NMR (300 MHz, CDCl_3): $\delta = 8.14$ (dd, $J = 8.6, 0.9$ Hz, 1H), 8.04 (dt, $J = 8.6, 0.9$ Hz, 1H), 7.70 (ddd, $J = 8.3, 6.8, 1.3$ Hz, 1H), 7.56 (ddd, $J = 8.3, 6.8, 1.2$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 3.03–2.91 (m, 2H), 2.95 (s, 3H), 2.41 (s, 3H), 1.70–1.56 (m, 2H), 1.34 (dt, $J = 7.3, 7.3$ Hz, 2H), 0.86 (t, $J = 7.3$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 155.6$ (C_q), 150.9 (C_q), 139.0 (C_q), 136.9 (C_q), 135.4 (C_q), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.2 (C_q), 126.5 (C_q), 126.2 (CH), 126.0 (CH), 124.2 (CH), 33.4 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.5 (CH_3), 21.2 (CH_3), 13.8 (CH_3). IR (ATR): 2955, 2923, 2869, 1614, 1563, 1513, 1438, 1391, 1333, 1026, 825, 755, 726, 615, 587, 539, 497 cm^{-1} . MS (EI) m/z (relative intensity) 289 (50) [M^+], 260 (70), 246 (100), 231 (30), 216 (8), 202 (10), 115 (5), 43 (11). HR-MS (EI): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{N}$ 289.1830, found 289.1833.

3-*n*-Butyl-1-methyl-4-(*p*-tolyl)isoquinoline (3ak'): ^1H -NMR (300 MHz, CDCl_3): $\delta = 8.13$ –8.05 (m, 1H), 7.51–7.43 (m, 2H), 7.39–7.32 (m, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 2.98 (s, 3H), 2.70–2.61 (m, 2H), 2.45 (s, 3H), 1.70–1.55 (m, 2H), 1.31–1.16 (m, 2H), 0.78 (t, $J = 7.3$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 157.2$ (C_q), 151.8 (C_q), 136.8 (C_q), 136.2 (C_q), 134.8 (C_q), 130.3 (CH), 129.4 (CH), 129.0 (CH), 128.9 (C_q), 125.9 (CH), 125.6 (CH), 125.4 (C_q), 125.3 (CH), 35.5 (CH_2), 32.7 (CH_2), 22.7 (CH_2), 22.5 (CH_3), 21.3 (CH_3), 13.9 (CH_3). IR (ATR): 2955, 2924, 1614, 1563, 1517, 1439, 1391, 1336, 1107, 1024, 965, 817, 758, 613 cm^{-1} . MS (EI) m/z (relative intensity) 289 (5) [M^+], 274

(10), 260 (15), 246 (100), 231 (15), 216 (5), 202 (8), 189 (6), 122 (5), 43 (12). HR-MS (EI): m/z calcd for $C_{21}H_{23}N$ 289.1830, found 289.1822.

3-([1,1'-Biphenyl]-4-yl)-4-*n*-butyl-1-methylisoquinoline (3al): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1,1'-biphenyl-1-hexyne (**2l**) (234 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3al** (90 mg, 51%) as a pale yellow solid (M.p.: 129–130 °C). 1H -NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.78–7.55 (m, 8H), 7.51–7.43 (m, 2H), 7.41–7.33 (m, 1H), 3.10–2.96 (m, 2H), 2.99 (s, 3H), 1.76–1.60 (m, 2H), 1.38 (dt, J = 7.4, 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 155.9 (C_q), 150.5 (C_q), 141.1 (C_q), 140.9 (C_q), 140.1 (C_q), 135.4 (C_q), 129.7 (CH), 129.7 (CH), 128.7 (CH), 127.4 (C_q), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.6 (C_q), 126.2 (CH), 126.1 (CH), 124.2 (CH), 33.5 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.5 (CH_3), 13.8 (CH_3). IR (ATR): 2926, 2870, 1563, 1436, 1387, 1334, 1006, 927, 814, 761, 732, 692, 598, 485 cm^{-1} . MS (EI) m/z (relative intensity) 351 (25) [M^+], 322 (45), 308 (100), 231 (6), 77 (10). HR-MS (EI): m/z calcd for $C_{26}H_{25}N$ 351.1987, found 351.1979.

4-*n*-Butyl-1-methyl-3-(4-methoxyphenyl)isoquinoline (3am): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-(4-methoxyphenyl)-1-hexyne (**2m**) (188 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3am** (87 mg, 57%) as a red oil. 1H -NMR (300 MHz, $CDCl_3$): δ = 8.14 (ddd, J = 8.4, 1.3, 0.7 Hz, 1H), 8.03 (dd, J = 8.6, 0.7 Hz, 1H), 7.70 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.56 (ddd, J = 8.2, 6.8, 1.1 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.06–2.90 (m, 2H), 2.95 (s, 3H), 1.71–1.54 (m, 2H), 1.35 (dd, J = 7.3 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ = 158.9 (C_q), 155.6 (C_q), 150.5 (C_q), 135.4 (C_q), 134.4 (C_q), 130.5 (CH), 129.6 (CH), 127.2 (C_q), 126.5 (C_q), 126.2 (CH), 125.9 (CH), 124.1 (CH), 113.5 (CH), 55.3 (CH_3), 33.4 (CH_2), 28.3 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 13.8 (CH_3). IR (ATR): 2957, 2926, 2868, 1609, 1567, 1512, 1463, 1436, 1391, 1376, 1291, 1250, 1176, 1021, 836,

753, 615, 588, 574, 541 cm^{-1} . MS (EI) m/z (relative intensity) 305 (72) [M^+], 276 (71), 262 (100), 247 (35), 230 (6), 218 (23), 43 (8). HR-MS (EI): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{NO}$ 305.1780, found 305.1771.

4-*n*-Butyl-3-(4-fluorophenyl)-1-methylisoquinoline (3an): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 1-(4-fluorophenyl)-1-hexyne (**2n**) (176 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3an** (88 mg, 60%) as a pale brown solid (M.p.: 58–60 °C). ^1H -NMR (300 MHz, CDCl_3): δ = 8.15 (ddd, J = 8.4, 1.3, 0.7 Hz, 1H), 8.04 (dd, J = 8.4, 0.7 Hz, 1H), 7.72 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.58 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.51–7.41 (m, 2H), 7.20–7.07 (m, 2H), 3.01–2.89 (m, 2H), 2.95 (s, 3H), 1.67–1.53 (m, 2H), 1.40–1.25 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3): δ = 162.3 (d, $^1J_{\text{C-F}}$ = 246 Hz, C_q), 155.9 (C_q), 149.8 (C_q), 137.9 (d, $^4J_{\text{C-F}}$ = 3 Hz, C_q), 135.3 (C_q), 131.0 (d, $^3J_{\text{C-F}}$ = 8 Hz, CH), 129.9 (CH), 127.5 (C_q), 126.7 (C_q), 126.3 (CH), 126.3 (CH), 124.2 (CH), 115.0 (d, $^2J_{\text{C-F}}$ = 21 Hz, CH), 33.3 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 13.7 (CH_3). ^{19}F -NMR (282 MHz, CDCl_3): δ = –115.3 (tt, J = 8.8, 5.5 Hz). IR (ATR): 2931, 2868, 1603, 1434, 1387, 1335, 1218, 1091, 837, 761, 727, 711, 616 cm^{-1} . MS (EI) m/z (relative intensity) 293 (40) [M^+], 264 (36), 250 (100), 235 (15), 220 (4), 207 (4), 147 (4). HR-MS (EI): m/z calcd for $\text{C}_{20}\text{H}_{20}\text{FN}$ 293.1580, found 293.1584.

Ethyl 4-(4-*n*-butyl-1-methylisoquinolin-3-yl)benzoate (3ao): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and ethyl 4-(hex-1-yn-1-yl)benzoate (**2o**) (230 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ao** (81 mg, 47%) as a red oil. ^1H -NMR (300 MHz, CDCl_3): δ = 8.15 (dd, J = 8.6, 0.9 Hz, 1H), 8.13 (d, J = 8.1 Hz, 2H), 8.04 (dd, J = 8.6, 0.9 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.64–7.54 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 3.00–2.86 (m, 2H), 2.95 (s, 3H), 1.65–1.53 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.30 (dt, J = 7.4, 7.4 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3): δ = 166.6 (C_q), 156.1 (C_q), 149.7 (C_q), 146.4 (C_q), 135.2 (C_q), 129.9 (CH), 129.4 (CH), 129.4 (CH), 129.3 (C_q), 127.6 (C_q), 126.8 (C_q), 126.5 (CH), 126.2 (CH), 124.2 (CH), 60.9 (CH_2), 33.4 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 14.3 (CH_3), 13.7 (CH_3). IR (ATR): 2957, 2871, 1713, 1611, 1563, 1508, 1391, 1366, 1267, 1174, 1098, 1019, 866, 757, 600 cm^{-1} .

712, 616 cm^{-1} . MS (EI) m/z (relative intensity) 347 (64) [M^+], 318 (100), 304 (15), 290 (14), 276 (8), 260 (25), 244 (11), 231 (61), 216 (11), 202 (10), 189 (5), 115 (5), 43 (18). HR-MS (EI): m/z calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_2$ 347.1885, found 347.1870.

4-(4-Hydroxy-*n*-butyl)-1-methyl-3-phenylisoquinoline (3ap): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 6-phenylhex-5-yn-1-ol (**2p**) (174 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **3ap** (106 mg, 73%) a pale brown solid (M.p.: 96–101 °C). ^1H -NMR (300 MHz, CDCl_3): δ = 8.17 (dd, J = 8.5, 1.3, 0.8 Hz, 1H), 8.06 (dd, J = 8.5, 0.8 Hz, 1H), 7.73 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.59 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.52–7.34 (m, 5H), 3.48 (t, J = 6.5 Hz, 2H), 3.06–2.90 (m, 2H), 2.97 (s, 3H), 1.75–1.45 (m, 5H). ^{13}C -NMR (75 MHz, CDCl_3): δ = 156.0 (C_q), 151.0 (C_q), 141.7 (C_q), 135.3 (C_q), 130.0 (CH), 129.3 (CH), 128.1 (CH), 127.4 (CH), 126.9 (C_q), 126.6 (C_q), 126.3 (CH), 126.2 (CH), 124.1 (CH), 62.2 (CH_2), 32.5 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 22.4 (CH_3). IR (ATR): 3273, 2936, 2863, 1615, 1564, 1444, 1395, 1335, 1141, 1053, 1030, 982, 759, 707, 628 cm^{-1} . MS (EI) m/z (relative intensity) 291 (50) [M^+], 246 (68), 232 (100), 217 (14), 202 (6), 189 (7), 115 (5), 77 (5), 43 (6). HR-MS (EI): m/z calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$ 291.1623, found 291.1623.

4-(4-Chloro-*n*-butyl)-1-methyl-3-phenylisoquinoline (3aq): The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 6-chloro-1-phenylhexyne (**2q**) (193 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3aq** (104 mg, 67%) as a yellow oil. ^1H -NMR (300 MHz, CDCl_3): δ = 8.16 (ddd, J = 8.4, 1.3, 0.8 Hz, 1H), 8.04 (dd, J = 8.4, 0.8 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.59 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.53–7.34 (m, 5H), 3.42 (t, J = 6.2 Hz, 2H), 3.03–2.95 (m, 2H), 2.97 (s, 3H), 1.86–1.68 (m, 4H). ^{13}C -NMR (75 MHz, CDCl_3): δ = 156.1 (C_q), 151.1 (C_q), 141.6 (C_q), 135.2 (C_q), 129.9 (CH), 129.2 (CH), 128.2 (CH), 127.5 (CH), 126.6 (C_q), 126.4 (C_q), 126.3 (CH), 126.2 (CH), 124.0 (CH), 44.4 (CH_2), 32.3 (CH_2), 28.1 (CH_2), 27.5 (CH_2), 22.5 (CH_3). IR (ATR): 2953, 1614, 1561, 1504, 1437, 1391, 1331, 1027, 756, 699, 648,

616, 592 cm^{-1} . MS (EI) m/z (relative intensity) 309 (41) [M^+], 246 (95), 232 (100), 217 (16), 202 (6), 189 (6), 115 (6), 77 (5). HR-MS (EI): m/z calcd for $\text{C}_{20}\text{H}_{20}\text{ClN}$ 309.1284, found 309.1297.

Competition Experiment with Alkynes 2 (Scheme 5). A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), diphenylacetylene (**2a**) (356 mg, 2.00 mmol), 4-octyne (**2e**) (220 mg, 2.00 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) in MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **2aa** (80 mg, 54%) as a white solid and **2ae** (36 mg, 32%) as a yellow oil.

Competition Experiment with Oximes 1c and 1q (Scheme 6a). A mixture of oxime **1c** (118 mg, 0.55 mmol), oxime **1q** (91 mg, 0.55 mmol), diphenylacetylene (**2a**) (89 mg, 0.5 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) in MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ca** (8 mg, 5%) as an orange solid and **3qa** (62 mg, 38%) as a pale yellow solid (M.p.: 175–177 °C).

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (3qa): ^1H -NMR (300 MHz, CDCl_3): δ = 8.09 (d, J = 9.1 Hz, 1H), 7.38–7.28 (m, 5H), 7.25–7.13 (m, 6H), 6.91 (d, J = 2.6 Hz, 1H), 3.71 (s, 3H), 3.01 (s, 3H). ^{13}C -NMR (75 MHz, CDCl_3): δ = 160.5 (C_q), 156.9 (C_q), 150.1 (C_q), 141.2 (C_q), 138.0 (C_q), 137.8 (C_q), 131.2 (CH), 130.2 (CH), 128.5 (C_q), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 121.8 (C_q), 118.6 (CH), 104.4 (CH), 55.2 (CH_3), 22.6 (CH_3). IR (ATR): 2923, 1618, 1500, 1410, 1273, 1229, 1205, 1070, 1024, 853, 823, 767, 696, 611 cm^{-1} . MS (EI) m/z (relative intensity) 325 (55) [M^+], 324 (100), 281 (32), 239 (6), 139 (5), 43 (10). HR-MS (EI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{NO}$ 325.1467, found 325.1471. The spectral data are in accordance with those reported in the literature.¹⁹

Competition Experiment with Oximes 1c and 1b (Scheme 6b). A mixture of oxime **1c** (118 mg, 0.55 mmol), oxime **1b** (82 mg, 0.55 mmol), diphenylacetylene (**2a**) (89 mg, 0.5 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF₆ (28 mg, 0.15 mmol, 30 mol %) in MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ca** (13 mg, 7%) as an orange solid and **3ba** (45 mg, 29%) as a pale orange solid.

Reaction of oxime 1a in [D₄]-MeOH (Scheme 7a). A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF₆ (28 mg, 0.15 mmol, 30 mol %) in [D₄]-MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (50 mL) and H₂O (20 mL) were added and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were dried over Na₂SO₄. Evaporation of the solvents yielded **1a** (62 mg, 92%) with less than 5% deuterium incorporation in the *ortho*-position estimated by ¹H-NMR-spectroscopy.

Reaction of substrates 1a and 2e in [D₄]-MeOH (Scheme 7b). A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), 4-octyne (**2e**) (110 mg, 1.00 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF₆ (28 mg, 0.15 mmol, 30 mol %) in [D₄]-MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ae** (86 mg, 76%) with 15% deuterium incorporation in the *ortho*-position and 57% deuterium incorporation at the Methyl-Group as estimated by ¹H-NMR-spectroscopy.

Reaction of substrates [D]₅-1a and 2e (Scheme 7c). A mixture of [D]₅-acetophenone oxime ([D]₅-**1a**) (70 mg, 0.50 mmol), 4-octyne (**2e**) (110 mg, 1.00 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF₆ (28 mg, 0.15 mmol, 30 mol %) in MeOH (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the remaining residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D]₄-

3ae (107 mg, 91%) as a yellow oil with 16% hydrogen incorporation in the *ortho*-position as estimated by ¹H-NMR-spectroscopy. ¹H-NMR (300 MHz, CDCl₃): δ = 3.07–2.81 (m, 4H), 2.89 (s, 3H), 1.86–1.72 (m, 2H) 1.73–1.59 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 155.5 (C_q), 151.5 (C_q), 135.2 (C_q), 128.8 (t, *J* = 24 Hz, CD), 126.0 (C_q), 125.8 (C_q), 125.2 (t, *J* = 24 Hz, CD), 124.6 (t, *J* = 24 Hz, CD), 123.1 (t, *J* = 24 Hz, CD), 37.4 (CH₂), 29.7 (CH₂), 24.1 (CH₂), 23.8 (CH₂), 22.3 (CH₃), 14.5 (CH₃), 14.3 (CH₃). IR (ATR): 2957, 2930, 2871, 1593, 1555, 1451, 1402, 1376, 1307, 1275, 1089, 878, 647, 559 cm⁻¹. MS (EI) *m/z* (relative intensity) 231 (65) [M⁺], 216 (100), 201 (82), 184 (73), 175 (88), 160 (23), 145 (13), 131 (33), 118 (20), 92 (10), 79 (10), 41 (10). HR-MS (ESI): *m/z* calcd for C₁₆H₁₇D₄N+H⁺ 232.1998, found 232.1998.

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Associated Content

Supporting Information Available: Copies of ¹H and ¹³C NMR spectra for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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