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

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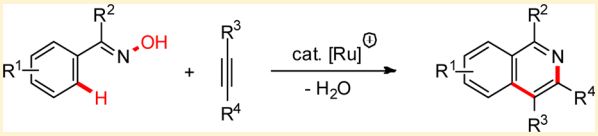
Supporting Information

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 antimalarial 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−H[4] 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-catalyzed[5] isoquinoline and pyridine syntheses.[6]

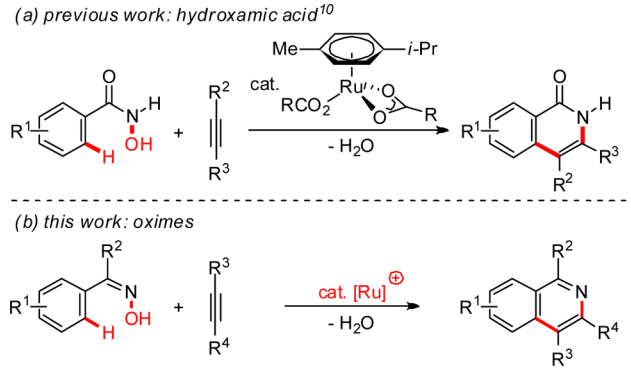
In 2011, we reported on the use of less-expensive ruthenium[7] complexes for oxidative annulations of alkynes by benzamides through C−H/N−H bond cleavages.[8] Notably, this approach proved more generally applicable.[9] Indeed, ruthenium(II) biscarboxylates[4b] also set the stage for redox-neutral dehydrative annulations of alkynes with free hydroxamic acids through C−H/N−O functionalizations to furnish isoquinolones (Scheme 1a).[10]

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-free[11] 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, KPF_6 gave rise to the most satisfactory results (entries 1−9),[12] while MeOH proved to be

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



the solvent of choice for the dehydrative annulation (entries 9−12). However, $[RuBr_2(p\text{-cymene})]_2$ delivered the desired isoquinoline **3aa** in a reduced yield as compared to a reaction with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst (entries 9, and 13). The high catalytic activity exerted by the KPF_6-derived ruthenium catalyst was suggestive of an in situ formation of a cationic ruthenium(II) species (vide infra).

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,

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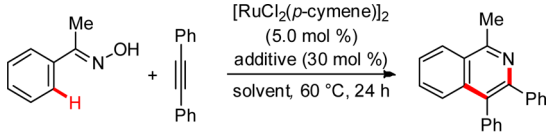
Table 1. Optimization of C−H/N−O Functionalization[a]

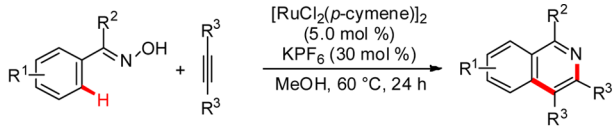


1a 2a 3aa

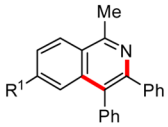
entry	additive	solvent	yield (%)
1	AgOAc	MeOH	9
2	CuOAc	MeOH	13[b]
3	CsOAc	MeOH	61
4	NaOAc	MeOH	39
5	KOPiv	MeOH	15
6	K_2CO_3	MeOH	9[b]
7	$AgSbF_6$	MeOH	38
8	$NaPF_6$	MeOH	67
9	**KPF_6**	**MeOH**	**81**
10	**KPF_6**	**MeOH**	**83**[c]
11	KPF_6	*t*-AmOH	9[b]
12	KPF_6	H_2O	30
13	KPF_6	MeOH	60[d]

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30 mol %), solvent (2 mL), 60 °C, isolated yields. [b]GC conversion. [c]4 Å mol. sieves (100 mg). [d]$[RuBr_2(p\text{-cymene})]_2$ (5.0 mol %).

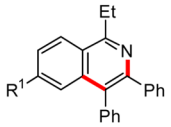
Scheme 2. Scope of Redox-Neutral Annulation with Oximes 1



1 2 3

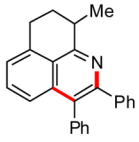


R^1 = Me (**3ba**): 85%
R^1 = CF_3 (**3ca**): 65%
R^1 = Br (**3da**): 54%[a]
R^1 = Ph (**3ea**): 54%

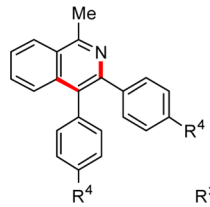


R^1 = H (**3fa**): 91%
R^1 = OMe (**3ga**): 95%
R^1 = F (**3ha**): 57%

R^2 = *n*-Pr (**3ia**): 89%
R^2 = *n*-Bu (**3ja**): 89%
R^2 = *n*-Pent (**3ka**): 96%
R^2 = Ph (**3la**): 82%
R^2 = *c*-Pr (**3ma**): 84%[a]

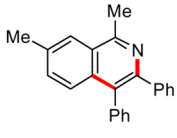


3na: 93%

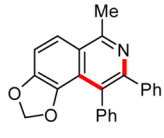


R^4 = OMe (**3ab**): 53%
R^4 = F (**3ac**): 70%

R^3 = Et (**3ad**): 86%
R^3 = *n*-Pr (**3ae**): 87%
R^3 = *n*-Bu (**3af**): 79%



3oa: 81%



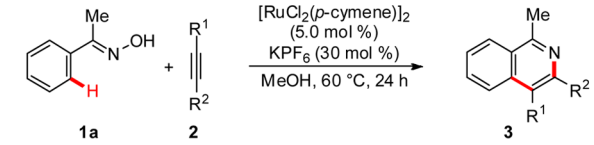
3pa: 86%

[a]In the presence of 4 Å mol. sieves.

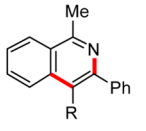
while oxime **1p** displaying a secondary directing group was functionalized at the sterically more congested C−2 position.

Importantly, intermolecular dehydrative annulations with challenging unsymmetrical alkynes **2** occurred with excellent regioselectivities (Scheme 3).[13] Hence, the cationic ruthenium-

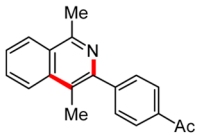
Scheme 3. Scope with Unsymmetrical Alkynes 2



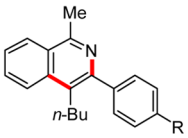
1a 2 3



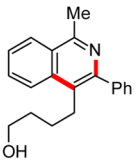
R = Me (**3ag**): 69%
R = Et (**3ah**): 63%
R = *n*-Hex (**3ai**): 52%



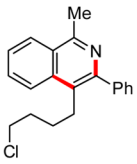
3aj: 70%



R = Me (**3ak**): 68%
R = Ph (**3al**): 51%
R = OMe (**3am**): 57%
R = F (**3an**): 60%
R = CO_2Et (**3ao**): 47%



3ap: 73%



3aq: 67%

(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.

Given the remarkable efficacy of the in situ generated ruthenium(II) catalyst, we subsequently probed the performance of preformed cationic complex $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (**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.

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).

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

Mechanistic studies with deuterated solvent MeOH-d_4 and isotopically labeled substrate **1a**-d_5 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 **3ae**-d_n when using MeOH-d_4 as the solvent (Scheme 7b).

On the basis of 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

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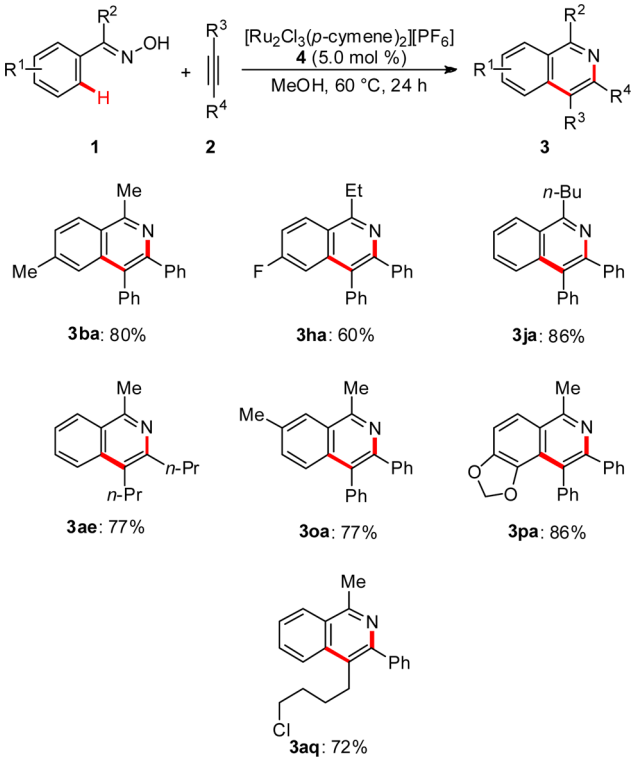
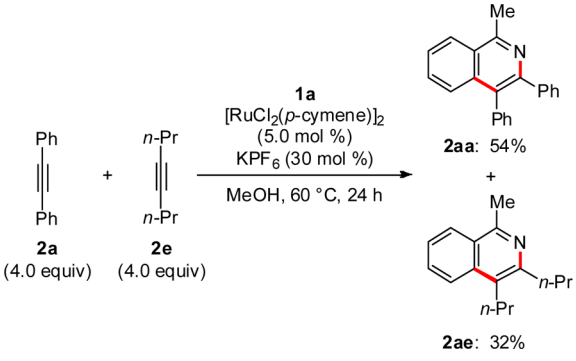
Scheme 4. Well-Defined Cationic Complex 4 as the Catalyst



Scheme 5. Competition Experiment with Alkynes 2



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.

CONCLUSIONS

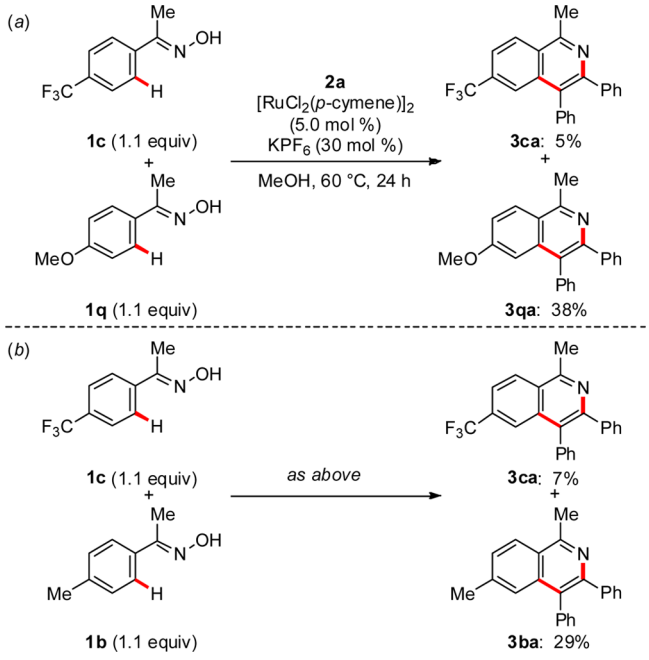
In summary, we have reported on ruthenium-catalyzed redox-neutral annulations of alkynes by oximes through C−H/N−O functionalizations. Contrary to previous studies,[9,10] carboxylate-free cationic ruthenium(II) catalysts were found to be most effective, which allowed for an expedient isoquinoline synthesis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

EXPERIMENTAL SECTION

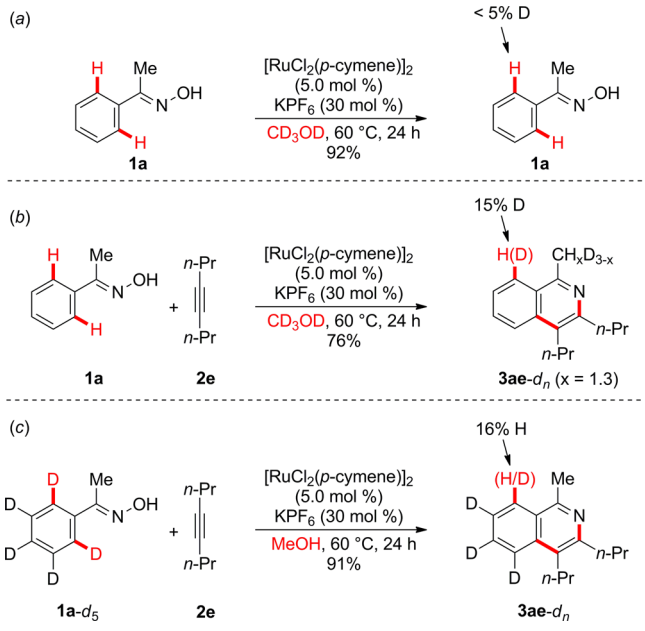
General Remarks. Catalytic reactions were carried out under a N_2 atmosphere using predried glassware. H_2O was degassed and purged with N_2, DMF was dried and distilled over CaH_2, *t*-AmOH was dried and distilled over sodium, and MeOH was dried and distilled over $Mg(OMe)_2$. All ketoximes **1** were 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] $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (**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), $[RuCl_2(p\text{-cymene})]_2$ (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

Scheme 6. Intermolecular Competition Experiments



Scheme 7. Reactions with MeOH-d_4 and Substrate 1a-d_5



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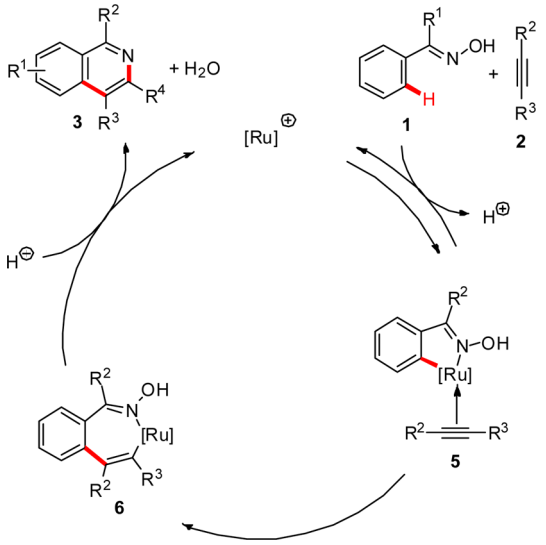
Scheme 8. Proposed Catalytic Cycle



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 (mp 152−155 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3); 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 $C_{22}H_{17}N$ 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 (mp 160−163 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3), 22.1 (CH_3); 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 $C_{23}H_{19}N$ + 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 (mp 109−114 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.8 (C_q), 150.9 (C_q), 140.4 (C_q), 136.5 (C_q), 135.4 (C_q), 131.5 (q, $^2J_{C-F}$ = 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, $^3J_{C-F}$ = 5 Hz, CH), 123.8 (d, $^1J_{C-F}$ = 272 Hz, C_q), 122.2 (q, $^3J_{C-F}$ = 3 Hz, CH), 22.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) 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 $C_{23}H_{16}F_3N$ 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 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **3da** (102 mg, 54%) as a yellow solid (mp 193−195 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3); 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 $C_{22}H_{16}BrN$ + 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 (mp 176−178 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3); 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 $C_{28}H_{21}N$ 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 (mp 113−115 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 13.9 (CH_3); 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 $C_{23}H_{19}N$ 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 (mp 158−161 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3), 28.8 (CH_2), 14.1 (CH_3); 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 $C_{24}H_{21}NO$ 339.1623, found 339.1613.

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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 (mp 141−142 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.0 (d, $^1J_{C-F}$ = 245 Hz, C_q), 162.0 (C_q), 150.7 (C_q), 140.8 (C_q), 138.4 (d, $^3J_{C-F}$ = 10 Hz, C_q), 137.3 (C_q), 131.2 (CH), 130.3 (CH), 128.7 (d, $^4J_{C-F}$ = 5 Hz, C_q), 128.4 (CH), 128.2 (d, $^3J_{C-F}$ = 10 Hz, CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 122.5 (d, $^4J_{C-F}$ = 1 Hz, C_q), 116.6 (d, $^2J_{C-F}$ = 25 Hz, CH), 110.0 (d, $^2J_{C-F}$ = 22 Hz, CH), 28.9 (CH_2), 13.9 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) 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 $C_{23}H_{18}FN$ + 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 (mp 118−120 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 23.2 (CH_2), 14.5 (CH_3); 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 $C_{24}H_{21}N$ − 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 (mp 78−80 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{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), 128.8 (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 (CH_2), 32.1 (CH_2), 23.1 (CH_2), 14.1 (CH_3); 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: ^{1}H 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 (mp 181−184 °C): ^{1}H 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 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 200/1) yielded **3ma** (135 mg, 84%) as a yellow solid (mp 148−150 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2); 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 $C_{24}H_{19}N$ − 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-7*H*-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 (mp 145−147 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 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 (CH_2), 27.8 (CH_2), 19.6 (CH_3); 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 $C_{25}H_{21}N$ − 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 (mp 106−110 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_3), 55.1 (CH_3), 22.7 (CH_3); 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 $C_{24}H_{21}NO_2$ 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: ^{1}H NMR (300 MHz, $CDCl_3$) δ =

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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); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.9 (d, $^1J_{C-F}$ = 247 Hz, C_q), 161.8 (d, $^1J_{C-F}$ = 247 Hz, C_q), 157.9 (C_q), 148.5 (C_q), 136.8 (d, $^4J_{C-F}$ = 3 Hz, C_q), 135.9 (C_q), 133.2 (d, $^4J_{C-F}$ = 4 Hz, C_q), 132.8 (d, $^3J_{C-F}$ = 8 Hz, CH), 131.9 (d, $^3J_{C-F}$ = 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, $^2J_{C-F}$ = 21 Hz, CH), 114.6 (d, $^2J_{C-F}$ = 21 Hz, CH), 22.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) 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 $C_{22}H_{15}F_2N$ 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 (mp 54−57 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 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, 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), 2.90 (s, 3H), 1.33 (t, J = 7.7 Hz, 3H), 1.27 (t, J = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.7 (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), 28.5 (CH_2), 22.3 (CH_3), 20.6 (CH_2), 15.2 (CH_3), 14.9 (CH_3); IR (ATR) 2963, 1614, 1566, 1451, 1391, 1311, 1054, 963, 769, 692, 616 cm^{-1}; MS (EI) m/z (relative intensity) 199 (31) [M$^+$], 198 (100), 184 (23), 170 (9), 128 (10), 115 (20), 77 (8), 69 (8); HR-MS (EI) m/z calcd for $C_{14}H_{17}N$ 199.1361, found 199.1355. The spectral data are in accordance with those reported in the literature.[19]

1-Methyl-3,4-di-*n*-propylisoquinoline (3ae). The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 4-octyne (**2e**) (110 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3ae** (99 mg, 87%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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 (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), 1.71−1.58 (m, 2H), 1.07 (t, J = 6.7 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 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 (CH), 37.4 (CH_2), 29.8 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 22.4 (CH_3), 14.6 (CH_3), 14.4 (CH_3); IR (ATR) 2957, 2870, 1617, 1568, 1454, 1391, 1333, 1027, 754, 614 cm^{-1}; MS (EI) m/z (relative intensity) 227 (40) [M$^+$], 212 (80), 198 (100), 184 (50), 171 (55), 128 (23), 115 (16), 77 (6), 43 (31); HR-MS (EI) m/z calcd for $C_{16}H_{21}N$ 227.1674, found 227.1669. The spectral data are in accordance with those reported in the literature.[19]

3,4-Di-*n*-butyl-1-methylisoquinoline (3af). The representative procedure was followed using **1a** (68 mg, 0.50 mmol) and 5-decyne (**2f**) (138 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **3af** (101 mg, 79%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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 (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), 0.99 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 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 $C_{18}H_{25}N$ 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 (mp 134−139 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 $C_{23}H_{19}N$ + 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 → 8/1 → 6/1 → 2/1) yielded **3pa** (164 mg, 86%) as a white solid (mp 251−254 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 (mp 83−87 °C): ^{1}H 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 (mp 117−120 °C): ^{1}H 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: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.7 (C_q), 150.9 (C_q), 141.9 (C_q),

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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 (CH_2), 31.2 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 22.5 (CH_3), 14.0 (CH_3); 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 $C_{22}H_{25}N$ 303.1987, found 303.1982.

3-*n*-Hexyl-1-methyl-4-phenylisoquinoline (3ai′). Data: ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 22.5 (CH_2), 22.5 (CH_3), 14.0 (CH_3); 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 $C_{22}H_{25}N$ 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 (mp 149−153 °C): ^1H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) δ = 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 $C_{19}H_{17}NO$ 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, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 $C_{21}H_{23}N$ 289.1830, found 289.1833.

3-*n*-Butyl-1-methyl-4-(*p*-tolyl)isoquinoline (3ak′). Data: ^1H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 (mp 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 $C_{21}H_{23}NO$ 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-fluoroyphenyl)-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 (mp 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, $^1J_{C-F}$ = 246 Hz, C_q), 155.9 (C_q), 149.8 (C_q), 137.9 (d, $^4J_{C-F}$ = 3 Hz, C_q), 135.3 (C_q), 131.0 (d, $^3J_{C-F}$ = 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, $^2J_{C-F}$ = 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 $C_{20}H_{20}FN$ 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, 712, 616 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 347 (64) [M^+], 318 (100), 304 (15), 290 (14), 276 (8), 260 (25), 244

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(11), 231 (61), 216 (11), 202 (10), 189 (5), 115 (5), 43 (18); HR-MS (EI) m/z calcd for $C_{23}H_{25}NO_2$ 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 (mp 96−101 °C): ^{1}H 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), 1.75−45 (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 $C_{20}H_{21}NO$ 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: ^{1}H 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 $C_{20}H_{20}ClN$ 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), $[RuCl_2(p\text{-cymene})]_2$ (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), $[RuCl_2(p\text{-cymene})]_2$ (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 (mp 175−177 °C).

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (3qa). Data: ^{1}H 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 $C_{23}H_{19}NO$ 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), $[RuCl_2(p\text{-cymene})]_2$ (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** (13 mg, 7%) as an orange solid and **3ba** (45 mg, 29%) as a pale orange solid.

Reaction of Oxime 1a in MeOH-d_4 (Scheme 7a). A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) in MeOH-d_4 (2.00 mL) was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (50 mL) and H_2O (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 Na_2SO_4. Evaporation of the solvents yielded **1a** (62 mg, 92%) with less than 5% deuterium incorporation in the *ortho*-position estimated by ^{1}H NMR spectroscopy.

Reaction of Substrates 1a and 2e in MeOH-d_4 (Scheme 7b). A mixture of acetophenone oxime (**1a**) (68 mg, 0.50 mmol), 4-octyne (**2e**) (110 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) in MeOH-d_4 (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 ^{1}H NMR spectroscopy.

Reaction of Substrates 1a-d_5 and 2e (Scheme 7c). A mixture of acetophenone oxime-d_5 (**1a**-d_5) (70 mg, 0.50 mmol), 4-octyne (**2e**) (110 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (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 **3ae**-d_4 (107 mg, 91%) as a yellow oil with 16% hydrogen incorporation in the *ortho*-position as estimated by ^{1}H NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 29.7 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.3 (CH_3), 14.5 (CH_3), 14.3 (CH_3); 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 $C_{16}H_{17}D_4N + H^+$ 232.1998, found 232.1998.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000.

(2) Alajarín, R.; Burgos, C. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 3, pp 1527−1629.

(3) A review: Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147−182.

(4) Illustrative reviews on C−H bond functionalizations: (a) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778−1791. (b) *Acc. Chem. Res.* **2012**, *45*, Special Issue (6), "C−H Functionalization". (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215−1292. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (f) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503−4513. (g) *Chem. Rev.* **2010**, *110*, Special Issue (2), "Selective Functionalization of C−H Bonds". (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677−685 and references cited therein.

(5) For representative recent reviews, see: (a) Zhu, C.; Wang, R.; Falck, J. R. *Chem.—Asian J.* **2012**, *7*, 1502−1504. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (c) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212−11222. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655.

(6) Illustrative examples: (a) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *77*, 2501−2507. (b) Jayakumar, J.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 197−200. (c) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927−5931. (d) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719−723. (e) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846−11848. (f) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141−4143. (g) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050−12051. (h) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325−328. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645−3651. (j) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, C. J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759−2761 and references cited therein.

(7) Recent reviews: (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403−1413. (b) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211−229. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877.

(8) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379−6382.

(9) For selected subsequent reports, see: (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278−3281. (b) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153−4155. (c) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573−12577. (d) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930−933. (e) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177−180. (f) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030−2032. (g) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764−767. (h) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478−3481. (i) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736−739. (j) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416−3419 and references cited therein. See also: (k) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245−2253.

(10) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548−6551.

(11) A very recent, independent report on the use of *neutral* ruthenium(II) complexes in related *carboxylate-assisted* C−H bond transformations: Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032−3035.

(12) For direct alkenylations with a KPF_6-derived ruthenium catalyst, see: Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728−731.

(13) Terminal alkynes provided only unsatisfactorily low yields of the desired products, both when using KPF_6 or representative carboxylates as the additives.

(14) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233−241.

(15) For related *acetate*-assisted *stoichiometric* transformations, see: Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics* **2009**, *28*, 433−440.

(16) Zhang, G.; Wen, X.; Wang, Y.; Mo, W.; Ding, C. *J. Org. Chem.* **2011**, *76*, 4665−4668.

(17) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070−14072.

(18) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199−3202.

(19) Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem.* **2009**, *74*, 9359−9364.

(20) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688−5691.

(21) Shih, W.-C.; Teng, C.-C.; Parthasarathy, K.; Cheng, C.-H. *Chem.—Asian J.* **2012**, *7*, 306−313.

(22) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159−6168.

(23) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794−5800.

(24) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719−723.