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Synthesis of Isoquinoline Derivatives through Rhodium(III)-Catalyzed Reactions of Benzylamines with Non-Terminal Alkynes

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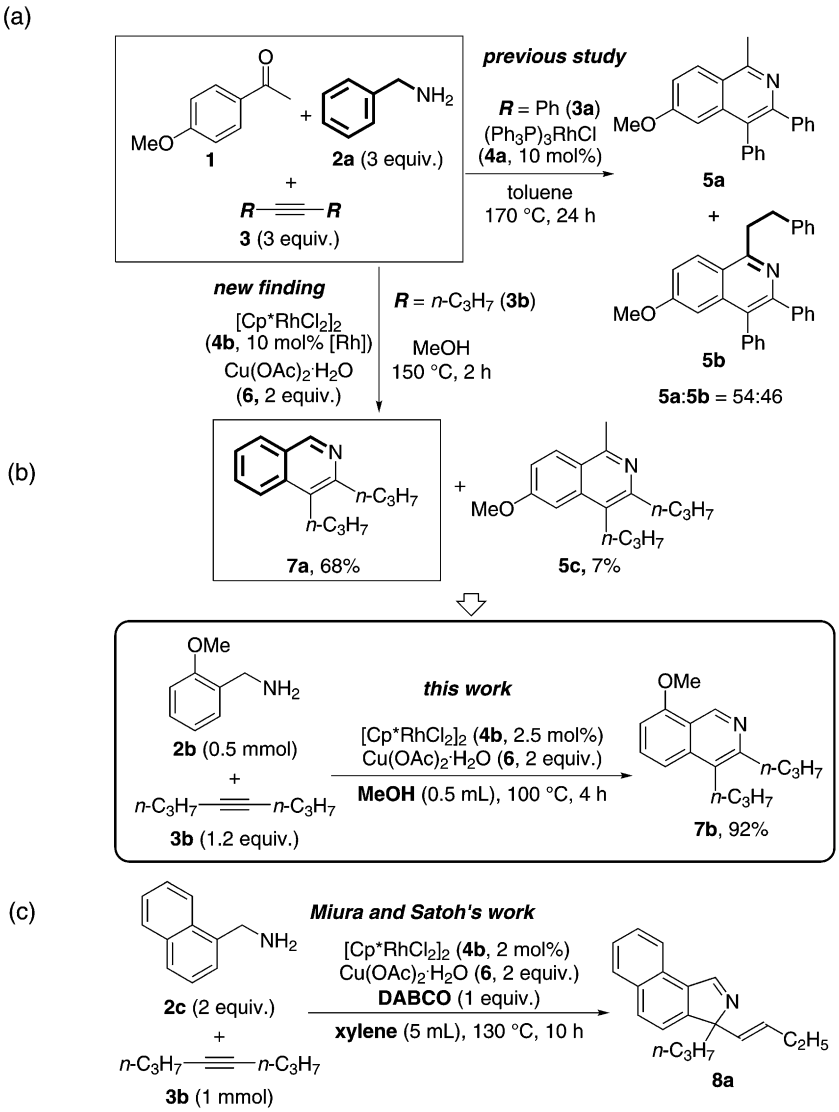
Abstract: A new rhodium(III)-catalyzed N-annulation reaction of benzylamines with internal alkynes has been developed. Observations made during these efforts suggest that the mechanistic pathway followed in this process involves direct participation of benzylamines without their preliminary oxidative dehydrogenation. Moreover, N-annulation reactions of primary benzylamines result in the formation of mixtures of isoquinolines and 8-vinylisoquinolines. Finally, secondary and tertiary benzylamines undergo rhodium(III)-catalyzed N-annulation reactions to generate the respective isoquinolinium and hydroisoquinolinium salt products.

Keywords: alkynes; amines; annulation; C–H activation; heterocycles

Introduction

New synthetic processes that rely on transition metal-catalyzed C–H bond activation are of current interests because they have the potential for forming carbon-carbon bonds in an atom economical manner.[1] Recent advances made in transition-metal catalyzed C–H bond activation reactions have led to the development of novel approaches to the preparation of N-heterocyclic compounds.[2] In particular, several recent studies have led to the development of methods for the synthesis of isoquinolines starting with a variety of different substances such as imines,[3] oximes[4] and azides.[5] In 2003, we described a Rh(I)-catalyzed one-pot method for the synthesis of isoquinolines that involves sequential *ortho*-alkenylation of *in situ* generated aromatic ketimines with alkynes followed by cyclization of the resulting *ortho*-vinyl aryl ketimines (Scheme 1a).[6] For example, *p*-methoxyacetophenone (**1**), benzylamine (**2a**) and alkynes **3a** were found to react in the presence of $(Ph_3P)_3RhCl$ (**4a**) to afford isoquinolines **5a** and **5b** in a nearly 1:1 ratio. Interestingly, when the same starting materials are treated with a different catalyst mixture comprised of $(Cp^*RhCl_2)_2$ (**4b**, 10 mol% [Rh]) and $Cu(OAc)_2 \cdot H_2O$ (**6**, 2 equiv.), the reaction proceeds to produce isoquinoline **7a** along with a trace amount of **5c** (Scheme 1b). These findings suggest that reactions of benzylamines with alkynes can be used for the synthesis of N-containing heterocyclic compounds.

In a related study, Miura et al. also observed that isoquinolines are generated in reactions of benzylamine with aryl-substituted alkynes promoted by $[Cp^*RhCl_2]_2$ (**4b**), $Cu(OAc)_2 \cdot H_2O$ (**6**, 2 equiv.) and DABCO in *o*-xylene.[7] However, these workers noted that isoquinolines are formed only in reactions of aryl-substituted alkynes and that aliphatic alkynes react to generate isoindole derivatives **8a** (Scheme 1c). In a recent effort, we found that isoquinolines are also generated even when aliphatic alkynes are used as substrates when a modified catalytic system is employed. In addition, we observed that this N-annulation reaction is highly sensitive to the conditions employed, such as the nature of the solvent and additives. In the study described below, we have demonstrated that by utilizing proper conditions, reactions of benzylamines with a variety of non-terminal alkynes serve as an ideal method for the preparation of isoquinoline derivatives. In addition, the studies have led to the proposal of a plausible mechanism for the N-annulation reaction, which can also be employed to transform *sec*- and *tert*-benzylamines to respective isoquinolinium and dihydroisoquinolinium salts.



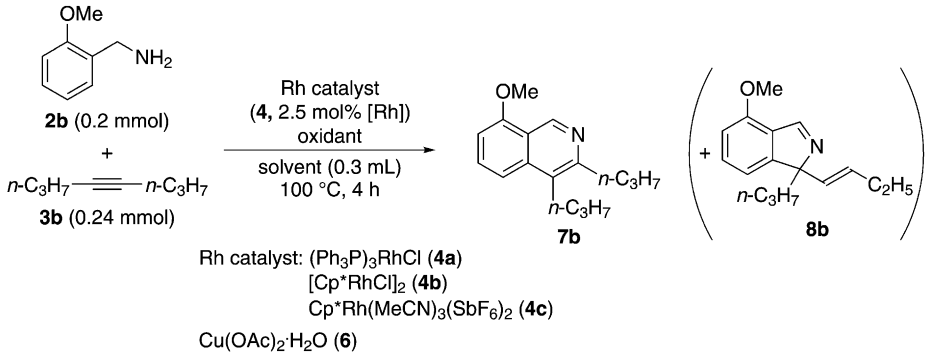
Scheme 1. Comparison of two sets of conditions for the preparation of isoquinolines by using (a) Rh(I) and (b) Rh(III)/Cu(II) catalysis. (c) Isoindole synthesis reported by Miura and Satoh.

Results and Discussion

N-Annulation Reaction of Primary Benzylamines with Alkynes: Optimization and Substrate Scope

The initial phase of this investigation focused on optimization of the N-heterocyclic annulation reaction using *o*-methoxybenzylamine (**2b**) and 4-octyne (**3b**) as substrates (Table 1). The reaction of **2b** with **3b**, carried out using $(Cp^*RhCl_2)_2$ (**4b**) as the catalyst and $Cu(OAc)_2{\cdot}H_2O$ (**6**) as the oxidant, was observed to give rise to isoquinoline **7b**. An exploration to determine the optimal amount of **6** required for this process, in which 0.5, 1.0, 1.5 and 2.0 equivalents of the oxidant were utilized (entries 1-4), showed that 2.0 equivalents led to the highest yielding reaction (entry 1), and the use of more than 2.0 equivalents of **6** did not increase the yield of the reaction. Moreover, this reaction does not occur when other oxidants such as $CuSO_4{\cdot}5H_2O$, $CuCl_2$, $K_2S_2O_8$, oxone and benzoquinone are used (entries 6–10). In contrast to the efficient process promoted by the cationic Rh(III) species $Cp^*Rh(MeCN)_3(SbF_6)_2$ (**4c**) (entry 11), the reaction did not take place when $(Ph_3P)_3RhCl$ (**4a**) was employed as the catalyst (entry 12).[8] A survey demonstrated that MeOH is a superior solvent for this reaction in contrast to others including *t*-BuOH, *o*-xylene, DMF, AcOH, and 1,2-DCE (entries 1, 13–19). In addition, reactions performed using *t*-BuOH and *o*-xylene as solvents produce mixtures of isoindole **8b** and isoquinoline **7b** (entries 13 and 14). The presence of DABCO (1 equiv.) in the reaction mixture does not lead to any improvement in the reaction efficiency (entry 15).[7] Finally, the reaction, performed with

Table 1. Optimization of the reaction conditions.



Entry	Metal catalyst	Oxidant	Solvent	Isolated yield of **7b** [%][a]
1	**4b**	**6** (2.0 equiv.)	MeOH	92
2	**4b**	**6** (1.5 equiv.)		54
3	**4b**	**6** (1.0 equiv.)		51
4	**4b**	**6** (0.5 equiv.)		32
5	**4b**	–		0
6	**4b**	$CuSO_4 \cdot 5H_2O$		9
7	**4b**	$CuCl_2$		trace
8	**4b**	$K_2S_2O_8$		trace
9	**4b**	oxone		trace
10	**4b**	BQ		trace
11	**4c**	**6** (2.0 equiv.)		80
12	**4a**	**6** (2.0 equiv.)		0
13	**4b**	**6**	*t*-BuOH	16 (2)[c]
14	**4b**	**6**	*o*-xylene	9 (10)[c]
15[b]	**4b**	**6**	*o*-xylene	7 (3)[c]
16[b]	**4b**	**6**	MeOH	87
17	**4b**	**6**	DMF	14
18	**4b**	**6**	AcOH	24
19	**4b**	**6**	1,2-DCE[c]	51

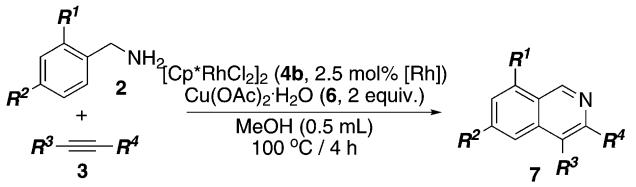
[a] Unless otherwise stated, the reactions give isoquinoline **7b** exclusively.
[b] The reaction was performed with DABCO (1 equiv.).
[c] Isolated yields of isoindole **8b** are given in parenthesis.
[d] 1,2-DCE = 1,2-dichloroethane.

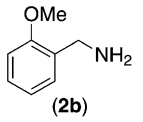
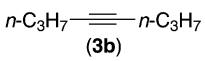
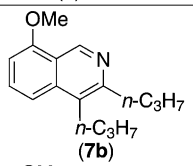
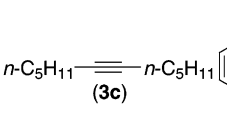
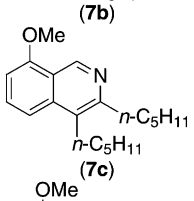
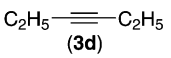
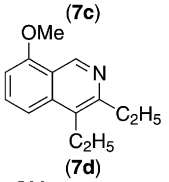
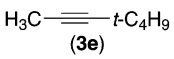
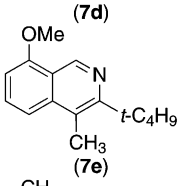
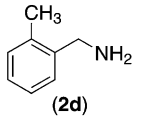
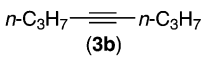
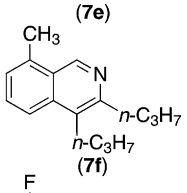
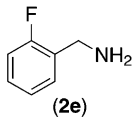
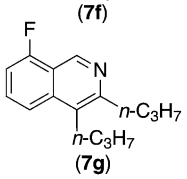
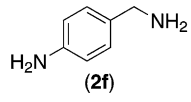
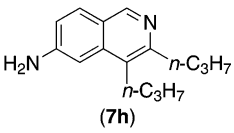
DABCO in methanol as solvent, gave isoquinoline **7b** exclusively without forming isoindole **8b** (entry 16).

The benzylamine **2** and alkyne **3** substrate scope of the N-annulation reaction was explored next (Table 2). Under the optimized conditions described above, reactions of *o*-methoxybenzylamine (**2b**) with a variety of internal alkynes take place smoothly to produce the corresponding isoquinoline products (entries 1–3). Interestingly, reaction of **2b** with the unsymmetrically alkyl-substituted alkyne **3e** generates the single isoquinoline regioisomer **7e** exclusively in a 51% isolated yield (entry 4). Analysis of NOESY NMR spectroscopic data showed that **7e** has the structure in which the bulky *tert*-butyl group is positioned adjacent to the isoquinoline ring to nitrogen (see the Supporting Information). Benzylamine substrates possessing electron-donating aryl substituents, such as methoxy, methyl and amino, were observed to react more efficiently than those that contain electron-withdrawing substituents (e.g., fluorine) (entries 1, 5–7). As expected, aniline and 2-phenethylamine do not undergo the N-annulation reactions owing presumably to difficulties associated with forming stable, intermediate 5-membered ring metallacyclic complexes.

In further studies, we observed that reaction of benzylamine **2a** with 4-octyne (**3b**) promoted by $Cp^*Rh(MeCN)_3(SbF_6)_2$ (**4c**) and $Cu(OAc)_2 \cdot H_2O$ (**6**) at 100 °C for 4 h generates a 83:17 mixture of isoquinoline **7a** and 8-vinylisoquinoline **9a** in 84% isolated yield (Figure 1a). Interestingly, the **7**/**9** ratio is influenced by the nature of the substituents at the α-position of the benzylamine substrate.[9] For example, in contrast to the annulation reaction of **2a** which produces a minor amount of **9a**, reactions of benzylamines bearing methyl (**2g**), cyclohexyl (**2h**), *n*-hexyl (**2i**), and phenyl (**2j**) α-substituents generate major amounts of the corresponding 8-vinylisoquinolines **9** as reflected

Table 2. Substrate scope.



Entry	Amine (2)	Alkyne (3)	Isoquinoline (7)	Isolated yield [%]
1	 (2b)	 (3b)	 (7b)	92
2	 (3c)	 (7c)		89
3	 (3d)	 (7d)		87
4	 (3e)	 (7e)		51
5	 (2d)	 (3b)	 (7f)	71
6	 (2e)	 (7g)		35
7	 (2f)	 (7h)		88[a]

[a] Less than 3% of 8-vinylisoquinoline was observed.

in the finding that **2g**, **2h**, **2i** and **2j** produce **7** and **9** in respective ratios of 18/82 (**7i**/**9b**), 28/72 (**7j**/**9c**), 15/85 (**7k**/**9d**), and 7/93 (**7l**/**9e**) (Figure 1a). Thus, although not well understood at this point, the formation of 8-vinylisoquinolines **9** seems to become increasingly favoured as the steric bulk of the α-substituent on the benzylamine substrates increases. The **7**/**9** ratio is also influenced by reaction temperature (Figure 1b). Specifically, as the temperature is increased from 80 to 150 °C the ratio of **7a**/**9a** increases from 77/23 to 90/10, a trend that is also followed in the reaction of α-substituted benzylamine **2g** with alkyne **3b** (the **7i**/**9b** ratio changes from 9/91 to 35/65 with a temperature change from 80 to 150 °C). These results suggest that the N-annulation reaction favours the formation of the *ortho*-vinyl product at low temperatures while production of the isoquinoline products is favoured at high temperatures.

Mechanism of the N-Annulation Reaction of Primary Benzylamines with Alkynes

Two plausible mechanistic routes for this N-annulation reaction of primary benzylamines with alkynes are depicted in Scheme 2. In route A, benzylamine **2j** undergoes initial $Cu(OAc)_2$ (**6**) promoted dehydrogenation to form the benzophenone imine **10a**. In the absence of water, imine **10a** participates in a Rh(III)-catalyzed N-annulation reaction. In the other possible pathway (route B), **2j** undergoes direct N-annulation to form the dihydroisoquinoline **12a**, which upon oxidative dehydrogenation affords isoquinoline **7l**.

Several experiments were carried out in order to gain information that would enable a distinction between the two mechanistic pathways. To test whether the benzylamine substrate is first oxidized to afford the corresponding imine,[7] reaction of *N*-diphenylmethylamine (**2j**) with **6** (2 equiv.) at 100 °C was conducted in the presence of H_2O. This process was observed to form benzophenone (**11**) in 31% yield (Scheme 3a), and this result suggests that **2j** can be oxidized by **6** to give corresponding imine **10a**, which is readily hydrolyzed in H_2O to give **11**. In addition, we found that in contrast with the N-annulation of imine **10a** with alkyne **3b** promoted by **4c** and **6** in MeOH, which produces isoquinoline **7l** in 94% isolated yield, the same process conducted in H_2O generates a mixture of **7l** and benzophenone **11** in a 23:34 ratio (Scheme 3b). Moreover, reaction of benzylamine **2j** with **3b** in H_2O under otherwise identical conditions does not yield the hydrolysis product **11** but instead forms the vinylisoquinoline **9e** along with **7l** in a 73:21 ratio (Scheme 3c). Importantly, **9e** is not produced in the reaction of imine **10a** with **3b**. These observations suggest that reaction of **2j** with **3b** does not proceed through the intermediacy of imine **10a** and, as a result, the N-annulation process likely takes place through the mechanistic pathway portrayed in route B (Scheme 2).

Another interesting feature of the N-annulation reaction is the formation of 8-vinylisoquinoline products **9**, as exemplified by the observation that diphenylmethylamine (**2j**) reacts with **3b** under the optimized conditions to afford 8-vinylisoquinoline **9e** predominantly (Figure 1a). To explore this feature, the N-annulation reaction of diphenylmethylamine-*d* (**2j**-*d*)

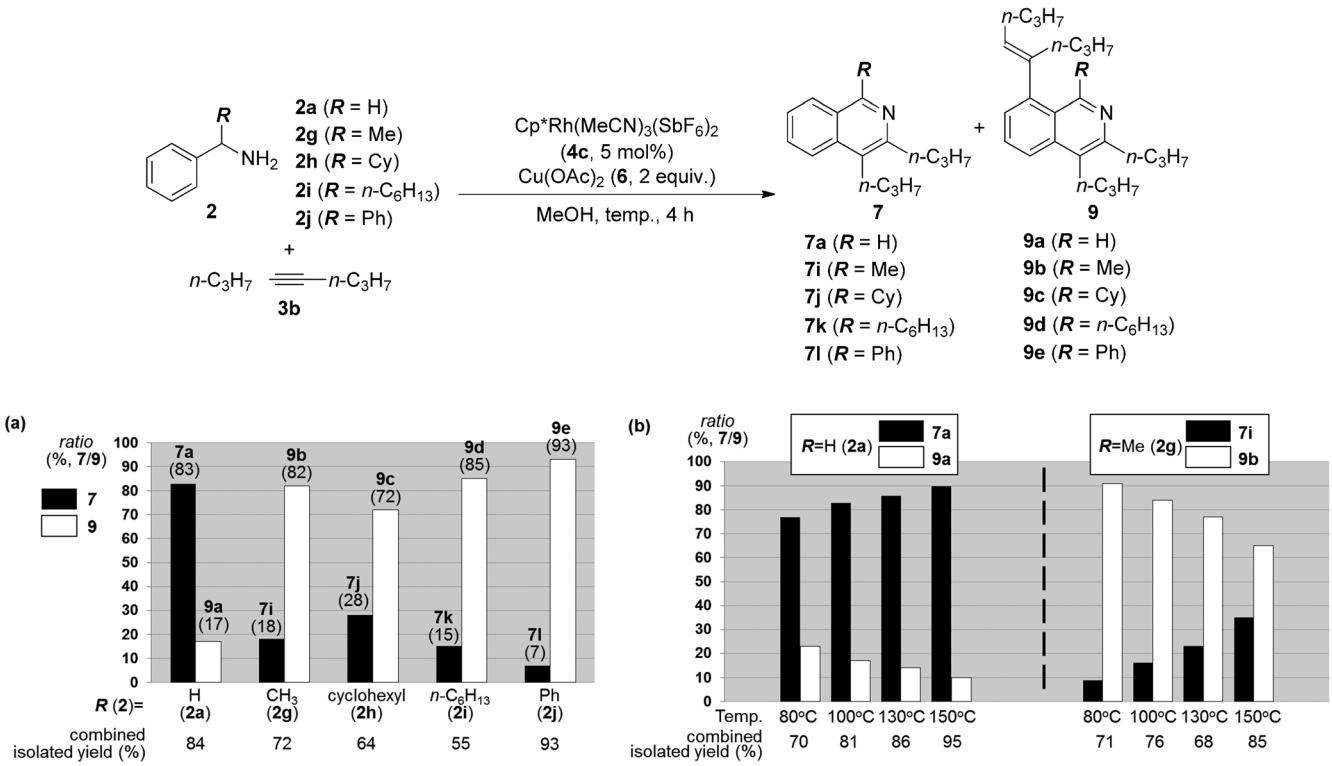
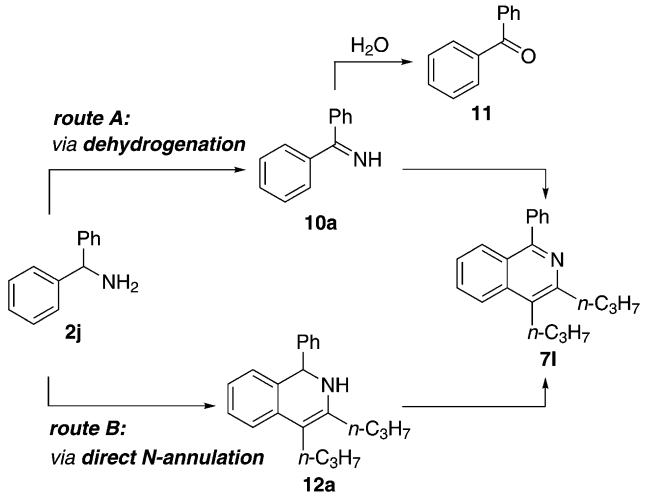


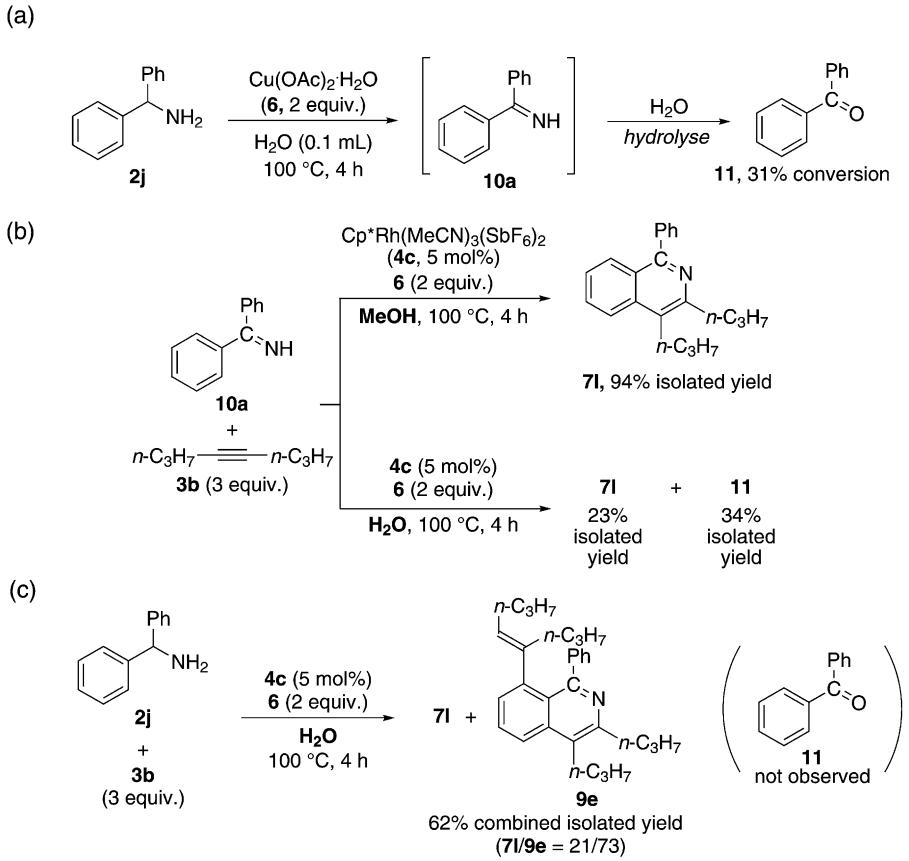
Figure 1. (a) Substituent effect of α-position on the formation of isoquinoline **7** and 8-vinylisoquinoline **9**. The reactions were performed at 100 °C. (b) Temperature dependence on the formation of **7** and **9**.



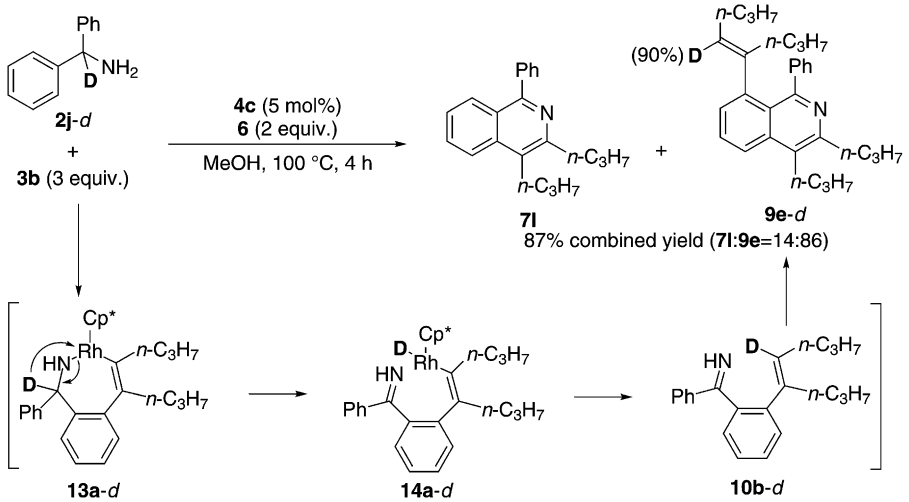
Scheme 2. Possible routes for N-annulation reaction of primary benzylamine **2j** with internal alkyne **3b**.

with **3b** was carried out in the presence of the typical catalytic system (Scheme 4). 8-Vinylisoquinoline **9e** formed in this process was found to have 90% deuterium enrichment in the exocyclic vinyl moiety. This result suggests that deuterium in the benzylic position of the amine is transferred to the vinyl position of the product by a pathway involving β-hydride elimination through migration of the benzylic hydrogen in rhodacyclic intermediate **13a** to the rhodium center in rhodium intermediate **14a**, followed by reductive elimination of rhodium in **14a** to produce the alkenyl-benzophenone imine **10b** (Scheme 4). Importantly, if the reaction were to have proceeded *via* a route involving oxidative transformation of benzylamine to the corresponding imine, the deuterium atom present in **2j**-*d* would not be transferred to the vinylic position of **9e**.

Based on the evidence gained in the experiments described above, it is possible to propose the mechanistic pathway shown in Scheme 5 for N-annulation reactions of benzylamines and alkynes that produce isoquinoline derivatives. The catalytic cycle is initiated by Rh insertion into the N–H bond of the benzylamine **2j** to form the Rh-complex **15a**, which does not undergo elimination to form the corresponding imine. Subsequent C–H bond activation at the *ortho*-position of phenyl group in **15a** gives rise to the 5-membered rhodacycle **16a**, which then participates in alkyne coordination followed by carbometallation to afford the 7-membered rhodacycle **13a**. Reductive elimination in **13a** leads to formation of dihydroisoquinoline **12a**, which is then dehydrogenated by **6** to generate isoquinoline **7l**. In the pathway for production of 8-vinylisoquinoline **9e**, β-hydride elimination in rhodacycle **13a** followed by reductive elimination of the formed vinyl rhodium intermediate **14a** takes place to generate imine **10b**. N–H bond cleavage in

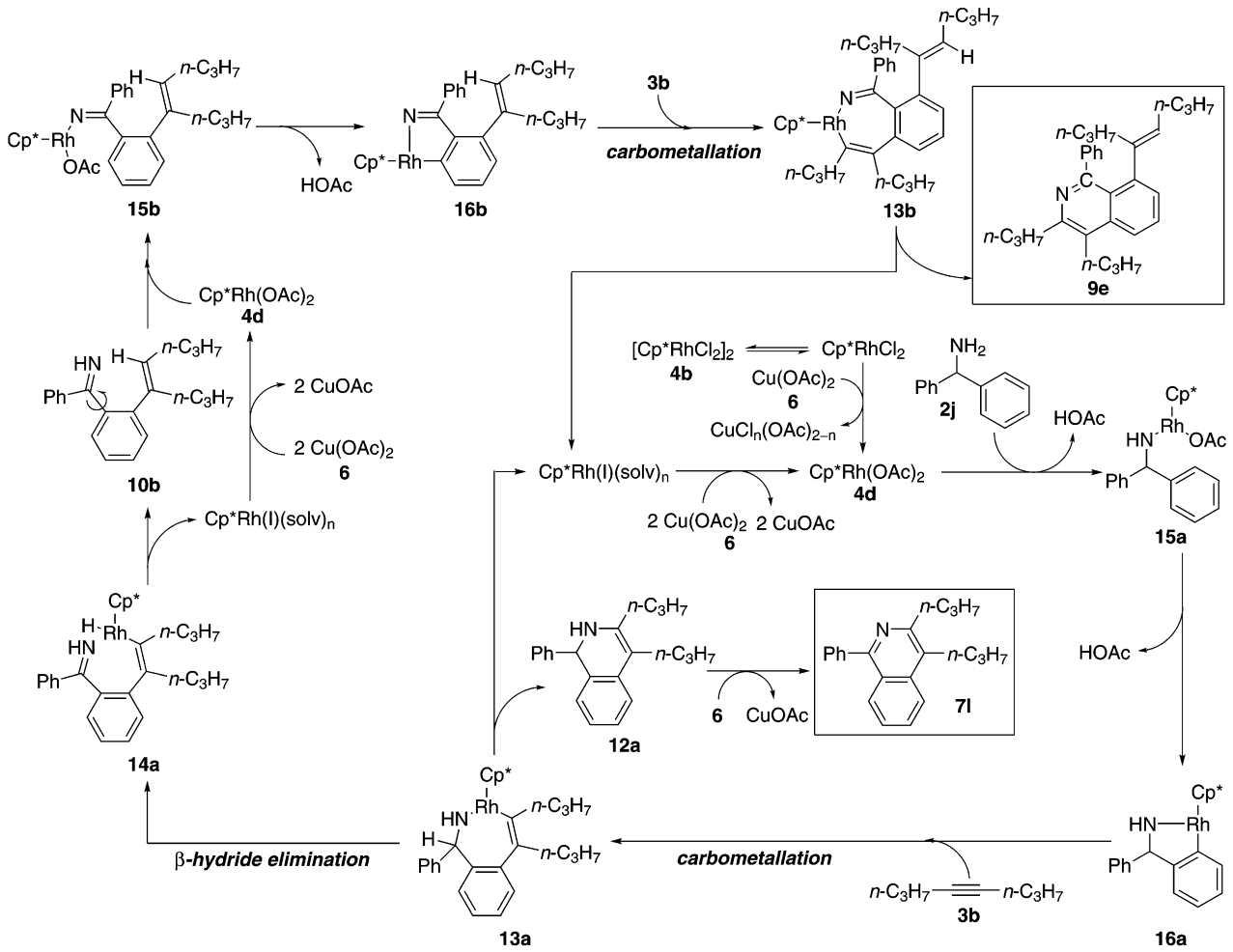


Scheme 3. (a) Experimental evidence for oxidation of benzylamine by $Cu(OAc)_2$ (**6**). (b) N-Annulation reaction of benzophenone imine (**10a**) and **3b** in MeOH (*up*) or H_2O solvent (*down*). (c) N-Annulation reaction of diphenylmethanamine (**2j**) and **3b** in H_2O solvent.



Scheme 4. Possible routes for N-annulation reaction of primary benzylamine **2j**-*d* with internal alkyne **3b**.

10b promoted by **4d** affords the imino-Rh intermediate **15b**, which then undergoes chelation-assisted C–H bond cleavage at *ortho*-phenyl position to give rhodacyclic **16b**. Alkyne coordination and subsequent carbometallation gives rise to the seven-membered rhodacyclic **13b**, which participates in reductive elimination to form the 8-vinylisoquinoline product **9e** along with a Rh(I) species. Oxidation of the formed Rh(I) complex by **6** regenerates the active Rh(III) catalyst **4d**.[3a]



Scheme 5. Proposed mechanistic pathway of N-annulation reaction using benzylamine and alkyne to produce isoquinoline **7l** and 8-vinylisoquinoline **9e**.

N-Annulation Reactions of Secondary Benzylamines with Alkynes to Produce Isoquinolinium Salts

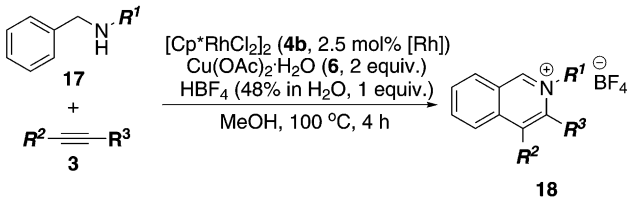
N-Alkylisoquinolinium salts are important building blocks in the synthesis of natural product.[10] Earlier, Cheng et al. described a procedure for the synthesis of isoquinolinium salts that involved a one-pot 3-component N-annulation reaction of aldehydes, primary amines and alkynes.[10a] In our effort, we observed that N-annulation reactions of secondary benzylamines and non-terminal alkynes using the optimized catalyst system were not successful. However, the addition of HBF_4 to the reaction mixtures results in efficient reactions that produce *N*-alkylisoquinolinium salts. For example, reaction of *N*-methylbenzylamine (**17a**) with alkyne **3a** in the presence of a mixture of **4b** and **6**, and HBF_4 (1 equiv.) produces the *N*-methylisoquinolinium BF_4 salt **18a** in a 93% isolated yield (Table 3, entry 1). Various secondary amines (**17b–d**) were found to react with aliphatic and aromatic alkynes **3a**, **3b** and **3f** to produce the corresponding isoquinolinium salts **18b–f** in high to moderate yields (entries 2–6).

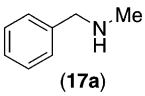
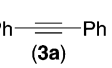
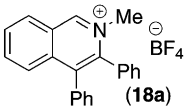
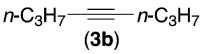
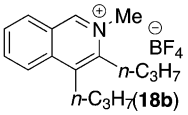
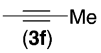
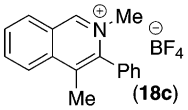
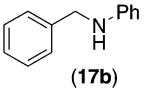
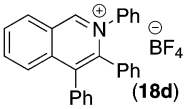
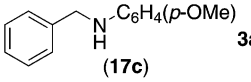
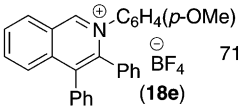
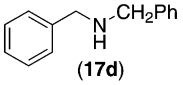
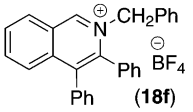
The mechanism for the N-annulation reaction of secondary benzylamines is similar to that operating in reactions of primary benzylamines (Scheme 6). In the pathway, initial N–H bond cleavage of the secondary benzylamine **17a** by **4d** forms intermediate **15c**. *ortho*-C–H bond insertion then gives rise to 5-membered rhodacycle **16c**, which undergoes alkyne coordination followed by carbometallation to afford the 7-membered rhodacycle **13b**. Reductive elimination in **13b** results in the formation of dihydroisoquinoline **12b**. Finally, $Cu(OAc)_2$ (**6**)/HBF_4-promoted aromatization of **12b** affords the isoquinolinium salt **18a**.

N-Annulation Reactions of Tertiary Benzylamines with Alkynes to Produce Dihydroisoquinolinium Salts

The possible participation of tertiary benzylamines in the N-annulation reaction was explored because these

Table 3. The reaction of secondary benzylamine **17** with alkyne **3**.[a]



Entry	Amine (17)	Alkyne (3)	Product (18)	Yield [%][a]
1	 (17a)	 (3a)	 (18a)	93 (96)
2	17a	 (3b)	 (18b)	89 (94)
3	17a	 (3f)	 (18c)	86 (92)
4	 (17b)	3a	 (18d)	75 (82)
5	 (17c)	3a	 (18e)	71 (79)
6	 (17d)	3a	 (18f)	50 (72)

[a] Isolated yield. Conversion yields, determined by ^{1}H NMR with using mesitylene as an internal standard, are given in parentheses.

substrates are unique in that they do not contain N–H bonds. Interestingly, when subjected to the optimized reaction conditions *N*,*N*-dimethylbenzylamine (**19a**) and 3-hexyne (**3d**) react to form 2,2-dimethyl-3,4-dipropyl-1,2-dihydroisoquinolin-2-ium hexafluorophosphate (**20a**) in a 69% isolated yield (Scheme 7a).[11,12] The mechanism for the generation of the hydroisoquinolinium salt (Scheme 7b) is similar to that followed in reactions of primary and secondary benzylamines. It is interesting to note that reaction of *N*,*N*-dibenzylmethylamine (**19b**) with **3d** under the optimized catalytic conditions produces *N*-methylisoquinolinium salt (**18g**, 27% yield, Scheme 8), which lacks the benzyl group present in the amine substrate. The formation of **18g** in this process suggests that the initially formed tetraalkylammonium cation **20b** undergoes dehydrobenzylation promoted by **6** and KPF_6 as a consequence of stabilization offered by the formation of the aromatic isoquinolium ring system.

Conclusions

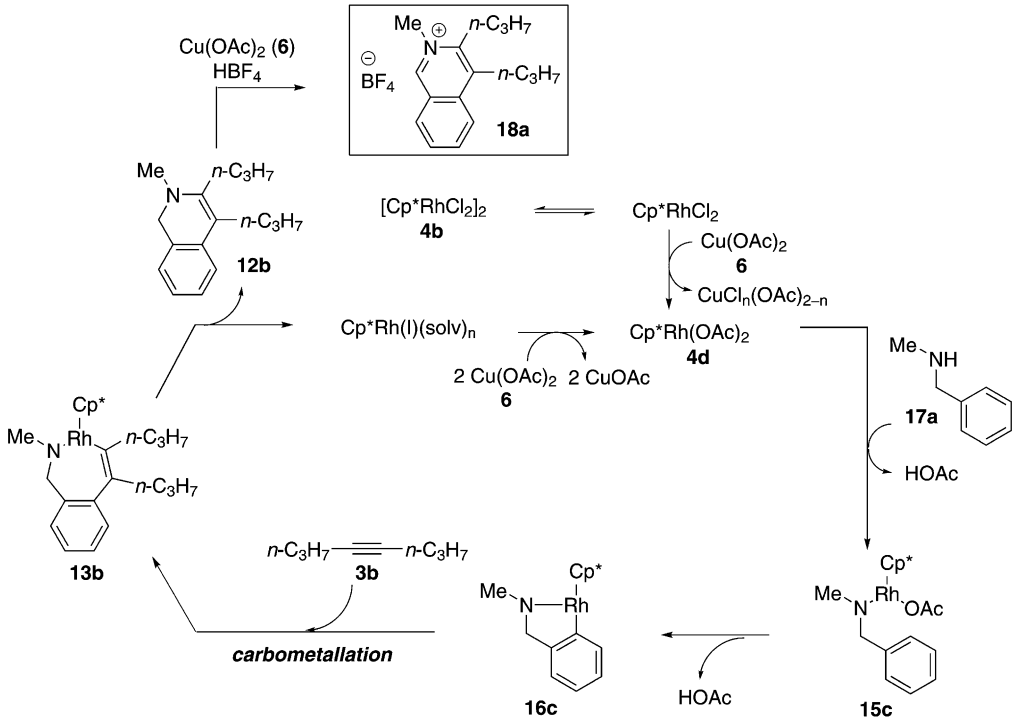
The investigation described above has led to the development of a Rh(III)-catalyzed N-annulation process that serves as a method for the facile and direct synthesis of isoquinoline derivatives from benzylamines and internal alkynes. Observations made in this effort show that the benzylamine substrate directly participates in the N-annulation reaction without undergoing initial dehydrogenation to form an imine. Instead, the reaction proceeds through initial N–H bond insertion by the Rh(III) catalyst, followed by *ortho*-C–H bond activation to generate an *ortho*-vinyl rhodium(III) intermediate. Carbometallation of internal alkyne and reductive elimination of carbometallated rhodium(III) complex produces the corresponding dihydroisoquinoline and Rh(I) species. In this reaction, the oxidant Cu(II) serves the dual role of promoting aromatization of the dihydroisoquinoline and oxidizing Rh(I) to regenerate the catalytically active Rh(III) species.

Importantly, N-annulation reactions of primary benzylamines result in the formation of mixtures of isoquinolines and 8-vinylisoquinolines. Furthermore, secondary and tertiary benzylamines also participate in the N-annulation process to generate isoquinolinium and hydroisoquinolinium salts, respectively.

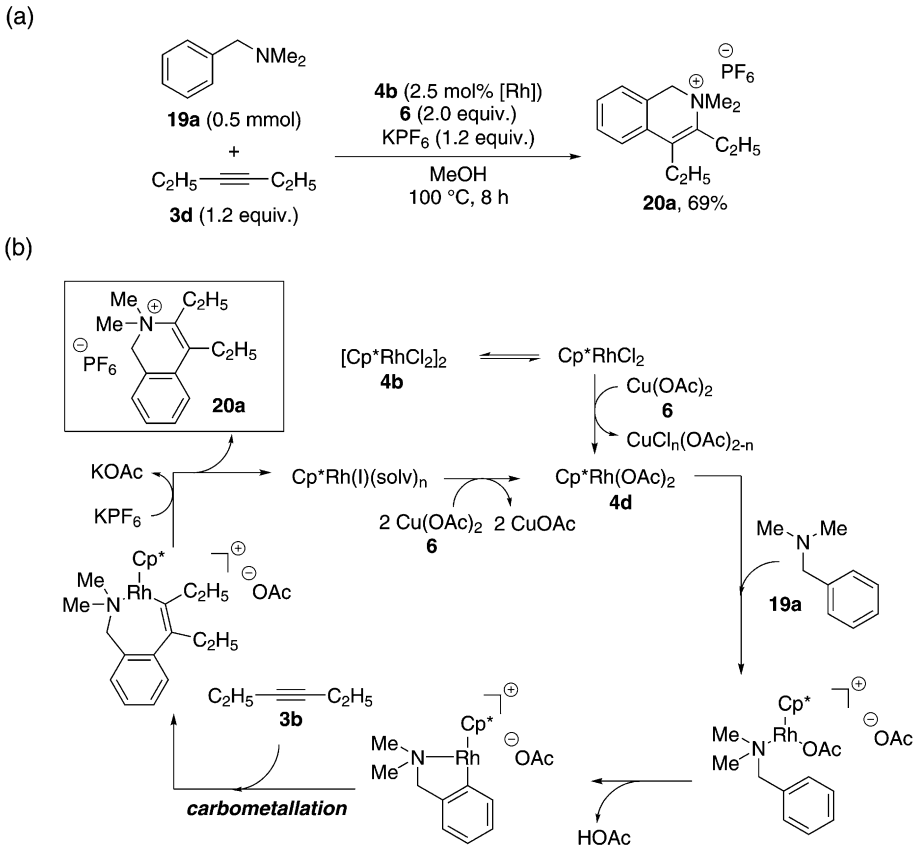
Experimental Section

General Remarks

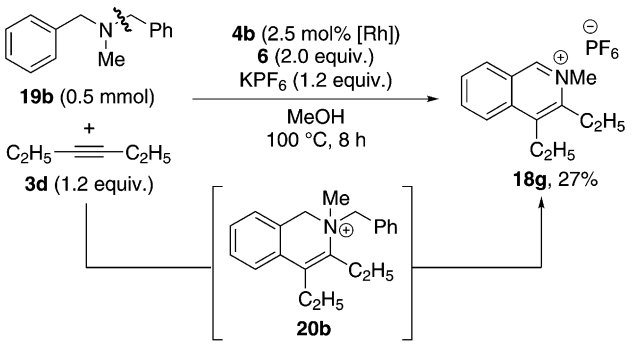
Flash column chromatography was performed using E. Merck 230–400 mesh silica gel and column chromatography was monitored by using analytical thin-layer chromatography (TLC) carried out on 0.25 Merck silica gel plates (60F-254) using UV light as a visualizing agent, *p*-anisaldehyde, ninhydrin and $KMnO_4$ solution as staining solutions, and heat as developing agent. Gas chromatographic analyses were performed using an Agilent 7890A instrument with an FID detector and an Agilent HP-5 capillary column. GC/MS analyses were performed on an Agilent 5975C instrument with an Agilent HP-5 MS column. IR spectra were recorded using a Bruker Vertex 70 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Advance II/DPX 400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometers with chemical shifts reported relative to residual deuterated solvent peaks. ^{1}H NMR spectra are referenced to $CDCl_3$ (for ^{1}H, $\delta = 7.26$), CD_2Cl_2 (for ^{1}H, $\delta = 5.34$) as internal standard, and are reported as follows: chemical shift multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{13}C NMR spectra are referenced to the residual $CDCl_3$ (for ^{13}C, $\delta = 77.26$), CD_2Cl_2 (for ^{13}C, $\delta = 54.00$) as internal standard. ^{11}B NMR spectra were referenced to external $BF_3{\cdot}OEt_2$ (0.0 ppm) with a negative sign indicating an up-field shift. ^{19}F NMR spectra are referenced to external $CFCl_3$ (0.0 ppm). High-resolution mass spectrometric analyses were carried out at the NCIRF Seoul National Universi-



Scheme 6. Proposed mechanism for N-annulation reaction of secondary benzylamine **17a** with internal alkyne **3b**.



Scheme 7. (a) N-Annulation reaction of tertiary benzylamine **19a** and **3d** in the presence of **4b**, **6** and KPF_6. (b) Proposed mechanism for N-annulation reaction of tertiary benzylamine **19a** with internal alkyne **3d**.



Scheme 8. N-Annulation reaction of tertiary benzylamine **19b** and **3d** in the presence of **4b**, **6** and KPF_6.

ty. Most commercially available reagent grade chemicals (**1**, **2a**, **2b**, **2d–g**, **2j**, **3a–f**, **6**, **10a**, **17a–d** and **19a**) were purchased from Aldrich Chemical Company, TCI, ACROS and Burdick & Jackson, and used as received unless otherwise stated. Reagents (**2h** and **2i**,[13] **2j-*d***,[14] and **19b**[15]) were prepared according to the literature procedures. Complexes $[Cp^*RhCl_2]_2$ (**4b**)[16] and $Cp^*Rh(MeCN)_3(SbF_6)_2$ (**4c**)[17] were prepared using literature procedures and stored in a refrigerator under an N_2 atmosphere.

6-Methoxy-1-methyl-3,4-dipropylisoquinoline (5c): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 9.1$ Hz, 1H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.12 (dd, $J = 9.1$ Hz, 2.4 Hz, 1H), 3.94 (s, 3H), 2.94–2.87 (m, 4H), 2.85 (s, 3H), 1.81–1.72 (m, 2H), 1.72–1.62 (m, 2H), 1.08 (t, $J = 7.3$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.5$, 155.2, 152.3, 137.5, 128.2, 125.7, 121.9, 117.4, 102.4, 55.4, 37.6, 30.1, 24.0, 23.8, 22.2, 14.8, 14.6; IR ($CDCl_3$): $\nu = 3099$, 2959, 2871, 1925, 1678, 1573, 1506, 1463, 1263, 1235, 1157, 1029, 779, 703 cm^{-1}; HR-MS(EI+): $m/z = 257.1780$, calcd for $C_{17}H_{23}NO$ $[M]^+$ 257.1780.

Typical Procedure for Preparing Isoquinoline 7b in the Presence of 4b/6 (Table 2)

To a 1 mL pressure vial was added *o*-methoxybenzylamine (**2b**, 68.6 mg, 0.5 mmol), 4-octyne (**3b**, 66.1 mg, 0.6 mmol), $[Cp^*RhCl_2]_2$ (**4b**, 3.7 mg, 0.00625 mmol), $Cu(OAc)_2{\cdot}H_2O$ (**6**, 200 mg, 1.0 mmol) and methanol (500 μL). The mixture was stirred at 100 °C for 4 h. After cooling, the mixture was subjected to column chromatography (*n*-hexane:ethyl acetate = 2:1) on silica gel to give 8-methoxy-3,4-dipropylisoquinoline (**7b**) as a pale yellow oil; yield: 112.0 mg (92%).

3,4-Dipropylisoquinoline (7a) [CAS No. 1185276-02-1]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.08$ (s, 1H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 3.01 (t, $J = 7.8$ Hz, 2H), 2.95 (t, $J = 7.5$ Hz, 2H), 1.86–1.77 (m, 2H), 1.73–1.63 (m, 2H), 1.09 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.0$, 150.2, 135.5, 130.1, 128.3, 128.2, 127.3, 125.8, 123.1, 37.4, 30.0, 24.2, 23.8, 14.8, 14.5.

8-Methoxy-3,4-dipropylisoquinoline (7b): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.46$ (s, 1H), 7.55–7.47 (m, 2H), 6.77 (d, $J = 7.3$ Hz, 1H), 3.98 (s, 3H), 2.98–2.91 (m, 4H), 1.84–1.75 (m, 2H), 1.70–1.61 (m, 2H), 1.09–1.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.1$, 153.7, 145.1, 136.8, 130.4, 127.7, 119.5, 115.3, 103.8, 55.7, 37.6, 30.3, 24.2, 23.8, 14.8, 14.5; IR ($CDCl_3$): $\nu = 3073$, 2959, 2871, 1620, 1574, 1489, 1388, 1263, 1060, 792 cm^{-1}; HR-MS (EI$^+$): $m/z = 243.1622$, calcd. for $C_{16}H_{21}NO$ $[M]^+$: 243.1623.

8-Methoxy-3,4-dipentylisoquinoline (7c): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.46$ (s, 1H), 7.56–7.47 (m, 2H), 6.78 (d, $J = 7.44$ Hz, 1H), 3.98 (s, 3H), 2.99–2.92 (m, 4H), 1.80–1.72 (m, 2H), 1.66–1.59 (m, 2H), 1.51–1.33 (m, 8H), 0.94–0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.2$, 153.9, 145.1, 136.8, 130.5, 127.8, 119.5, 115.2, 103.8, 55.7, 35.6, 32.6, 32.3, 30.7, 30.4, 28.3, 22.9, 22.7, 14.3, 14.2; IR ($CDCl_3$): $\nu = 3073$, 2956, 2929, 2870, 2858, 1775, 1621, 1574, 1488, 1414, 1262, 1063, 756 cm^{-1}; HR-MS (EI$^+$): $m/z = 299.2247$, calcd. for $C_{20}H_{29}NO$ $[M]^+$: 299.2249.

3,4-Diethyl-8-methoxyisoquinoline (7d): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.47$ (s, 1H), 7.56–7.49 (m, 2H), 6.77 (d, $J = 6.8$ Hz, 1H), 3.98 (s, 3H), 3.05–2.96 (m, 4H), 1.35 (t, $J = 7.5$ Hz, 3H), 1.27 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.2$, 154.6, 145.3, 136.5, 130.5, 128.7, 119.6, 115.0, 103.8, 55.7, 28.6, 21.2, 15.2, 15.8; IR ($CDCl_3$): $\nu = 3073$, 2935, 1873, 1722, 1492, 1414, 1197, 1154, 965, 719 cm^{-1}; HR-MS (FAB$^+$): $m/z = 216.1388$, calcd. for $C_{14}H_{17}NO$ $[M+H]^+$: 216.1310.

3-*tert*-Butyl-8-methoxy-4-methylisoquinoline (7e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.47$ (s, 1H), 7.54 (d, $J = 4.3$ Hz, 2H), 6.80 (t, $J = 4.2$ Hz, 1H), 4.00 (s, 3H), 2.77 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$, 157.0, 143.5, 138.6, 130.2, 123.4, 119.1, 115.1, 103.8, 55.8, 38.8, 31.1, 16.7; IR ($CDCl_3$): $\nu = 3049$, 2955, 1775, 1703, 1577, 1456, 1364, 1224, 1167, 1052, 754 cm^{-1}; HR-MS (EI$^+$): $m/z = 229.1470$, calcd. for $C_{15}H_{19}NO$ $[M]^+$: 229.1467.

8-Methyl-3,4-dipropylisoquinoline (7f): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.29$ (s, 1H), 7.81 (d, $J = 8.6$ Hz, 1H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.26 (d, $J = 7.0$ Hz, 1H), 3.02–2.93 (m, 4H), 2.74 (s, 3H), 1.87–1.77 (m, 2H), 1.72–1.62 (m, 2H), 1.09 (t, $J = 7.3$ Hz, 3H), 1.04 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.9$, 146.9, 135.9, 135.7, 129.8, 128.4, 126.7, 126.3, 121.5, 37.5, 30.2, 24.3, 23.7, 18.9, 14.8, 14.5; IR ($CDCl_3$): $\nu = 3070$, 3043, 2959, 2871, 1721, 1614, 1580, 1454, 1380, 1341, 1088, 973, 756 cm^{-1}; HR-MS (EI$^+$): $m/z = 227.1675$, calcd. for $C_{16}H_{21}N$ $[M]^+$: 227.1674.

8-Fluoro-3,4-dipropylisoquinoline (7g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.35$ (s, 1H), 7.71 (d, $J = 8.6$ Hz, 1H), 7.59–7.54 (m, 1H), 7.10 (t, $J = 8.9$ Hz, 1H), 3.00–2,92 (m, 4H), 1.84–1,75 (m, 2H), 1.70–1.61 (m, 2H) 1.08 (t, $J = 7.3$ Hz, 3H), 1.03 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.9$ (d, $J = 254.0$ Hz), 154.3 143.7 (d, $J = 6.0$ Hz), 137.1 (d, $J = 4.0$ Hz), 130.2 (d, $J = 9.0$ Hz), 127.9 (d, $J = 2.0$ Hz), 119.2 (d, $J = 5.0$ Hz), 117.9 (d, $J = 5.0$ Hz), 109.5 (d, $J = 19.0$ Hz), 37.6, 30.3, 24.2, 23.7, 14.8, 14.5; IR ($CDCl_3$): $\nu = 3078$, 3045, 2961,2931, 2872, 1633, 1580, 1454, 1415, 1389, 1089, 767 cm^{-1}; HR-MS (EI$^+$): $m/z = 231.1423$, calcd for $C_{15}H_{18}FN$ $[M]^+$: 231.1423.

3,4-Dipropylisoquinolin-6-amine (7h): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.83$ (s, 1H), 7.64 (d, $J = 8.6$ Hz, 1H), 6.92 (s, 1H), 6.88 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 2.90–2.81 (m, 4H), 2.12 (br s, 2H), 1.81–1.71 (m, 2H), 1.66–1.57 (m, 2H), 1.04 (t, $J = 7.3$ HZ, 3H), 1.01 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.7$, 148.9, 148.3, 137.9, 130.4, 126.6, 121.8, 118.0, 102.8, 36.7, 30.0, 23.8, 23.6, 14.7, 14.4; IR ($CDCl_3$): $\nu = 3328$, 3191, 3052, 2960, 2930, 2871, 1619, 1504, 1380, 1246, 1088, 1012, 725 cm^{-1}; HR-MS (EI$^+$): $m/z = 228.1626$, calcd. for $C_{15}H_{20}N_2$ $[M]^+$: 228.1626.

1-Methyl-3,4-dipropylisoquinoline (7i) [CAS No. 362061-46-9]: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.64 (t, J = 7.0 Hz, 1H), 7.48 (t, J = 7.9 Hz), 1H), 3.00–2.96 (m, 2H), 2.93–2.89 (m, 2H), 2.91 (s, 3H), 1.84–1.74 (m, 2H), 1.72–1.62 (m, 2H), 1.09 (t, J = 7.3 Hz, 3H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 151.9, 135.6, 129.6, 126.37, 126.31, 126.2, 125.4, 123.8, 37.7, 30.0, 24.4, 24.0, 22.6, 14.8, 14.6.

1-Cyclohexyl-3,4-dipropylisoquinoline (7j): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 3.50–3.45 (m, 1H), 2.97–2.88 (m, 4H), 1.94–1.77 (m, 9H), 1.70–1.61 (m, 2H), 1.55–1.46 (m, 2H), 1.42–1.35 (m, 1H), 1.08 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 151.7, 135.9, 128.9, 125.4, 125.2, 125.0, 124.7, 123.9, 41.6, 37.3, 32.8, 30.0, 27.1, 26.6, 24.2, 23.3, 12.9, 14.5; IR ($CDCl_3$): ν = 3071, 2958, 2929, 2870, 2853, 1615, 1565, 1504, 1449, 1377, 1323, 985, 761 cm^{-1}; HR-MS (FAB$^+$): m/z = 296.2383, calcd. for $C_{21}H_{29}N$ [M+H]$^+$: 296.2373.

1-Hexyl-3,4-dipropylisoquinoline (7k): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.65–7.61 (m, 1H), 7.50–7.46 (m, 1H), 3.23 (t, J = 7.9 Hz, 2H), 2.99–2.95 (m, 2H), 2.93–2.89 (m, 2H), 1.85–1.74 (m, 4H), 1.72–1.62 (m, 2H), 1.50–1.43 (m, 2H), 1.37–1.29 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 151.9, 135.9, 129.4, 126.16, 126.10, 125.4, 125.3, 123.9, 37.6, 35.9, 32.0, 30.5, 30.0, 29.8, 24.3, 24.0, 22.9, 14.9, 14.5, 14.3; IR ($CDCl_3$): ν = 3071, 2957, 2929, 2871, 1616, 1566, 1504, 1463, 1378, 1260,1028, 759 cm^{-1}; HR-MS (FAB$^+$): m/z = 298.2540, calcd. for $C_{21}H_{31}N$ [M+H]$^+$: 298.2529.

1-Phenyl-3,4-dipropylisoquinoline (7l) [CAS No.387862-67-1]: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, J = 8.5 Hz, 2.8 Hz, 2H), 7.68–7.64 (m, 3H), 7.53–7.40 (m, 4H), 3.10–3.00 (m, 4H), 1.91–1.82 (m, 2H), 1.80–1.71 (m, 2H), 1.15 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 258.3, 152.4, 140.4, 136.3, 130.2, 129.6, 128.4, 128.38, 128.30, 127.3, 125.5, 125.4, 123.5, 37.6, 30.2, 24.3, 23.9, 14.9, 14.5.

1-(But-1-en-1-yl)-1-propyl-1*H*-isoindole (8): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7.33 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.71 (d, J = 15.5 Hz, 1H), 5.63–5.56 (m, 1H), 3.91 (s, 3H), 2.05–1.95 (m, 3H), 1.84–1.77 (m, 1H), 1.14–1.04 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H), 0.88–0.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.28, 158.24, 154.5, 131.4, 130.5, 129.4, 127.8, 115.2, 109.2, 84.1, 55.6, 40.6, 25.8, 17.2, 14.5, 13.7; IR ($CDCl_3$): ν = 3087, 3006, 2959, 2934, 2911, 2872, 1702, 1612, 1547, 1269, 1029, 970, 788 cm^{-1}; HR-MS (FAB$^+$): m/z = 243.1626, calcd. for $C_{16}H_{21}NO$ [M]$^+$: 243.1623.

8-(Oct-4-en-4-yl)-3,4-dipropylisoquinoline (9a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.60–7.56 (m, 1H), 7.24 (d, J = 7.0 Hz, 1H), 5.48 (t, J = 7.3 Hz, 1H), 3.02–2.98 (m, 2H), 2.95–2.91 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 2.27 (q, J = 7.3 Hz, 2H), 1.86–1.77 (m, 2H), 1.74–1.64 (m, 2H), 1.54–1.45 (m, 2H), 1.35–1.25 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 149.0, 144.5, 138.2, 135.9, 132.8, 129.5, 128.1, 125.8, 125.4, 121.6, 37.5, 35.1, 30.6, 30.3, 24.3, 23.7, 23.2, 21.9, 14.9, 14.6, 14.3, 14.2; IR ($CDCl_3$): ν = 3069, 2959, 2931, 2872, 1771, 1715, 1605, 1575, 1463, 1378, 1259, 1125, 897, 802, 718 cm^{-1}; HR-MS (EI$^+$): m/z = 323.2610, calcd. for $C_{23}H_{33}N$ [M]$^+$: 323.2613.

1-Methyl-8-(oct-4-en-4-yl)-3,4-dipropylisoquinoline (9b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, J = 8.6 Hz, 0.9 Hz, 1H), 7.52–7.48 (m, 1H), 7.16 (dd, J = 6.8 Hz, 0.9 Hz, 1H), 5.51 (t, J = 7.1 Hz, 1H), 2.99–2.88 (m, 4H), 2.96 (s, 3H), 2.75–2.67 (m, 1H), 2.32–2.15 (m, 2H), 2.11–2.04 (m, 1H), 1.85–1.75 (m, 2H), 1.73–1.64 (m, 2H), 1.59–1.46 (m, 2H), 1.38–1.20 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.1, 144.19, 144.13, 137.1, 129.7, 128.5, 128.4, 126.1, 124.8, 122.7, 37.6, 36.4, 30.6, 30.4, 27.2, 24.3, 23.9, 22.8, 21.6, 14.8, 14.6, 14.3; IR ($CDCl_3$): ν = 3071, 2960, 2872, 2732, 1699, 1597, 1462, 1377, 1089, 807 cm^{-1}; HR-MS (FAB$^+$): m/z = 338.2856, calcd. for $C_{24}H_{35}N$ [M+H]$^+$: 338.2842.

1-Cyclohexyl-8-(oct-4-en-4-yl)-3,4-dipropylisoquinoline (9c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.11 (dd, J = 6.8 Hz, 0.7 Hz, 1H), 5.52 (t, J = 7.0 Hz, 1H), 3.86–3.81 (m, 1H), 2.96–2.82 (m, 4H), 2.71–2.64 (m, 1H), 2.25 (q, J = 7.3 Hz, 2H), 2.18–2.08 (m, 2H), 1.90–1.81 (m, 4H), 1.70–1.62 (m, 4H), 1.60–1.47 (m, 3H), 1.42–1.18 (m, 6H), 1.09 (t, J = 7.3 Hz, 3H), 1.02 (td, J = 7.3 Hz, 1.0 Hz, 6H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 151.0, 144.5, 143.2, 137.3, 128.6, 128.1, 127.8, 125.2, 123.1, 122.9, 42.9, 37.2, 35.9, 34.7, 31.9, 30.8, 30.5, 27.3, 27.2, 26.6, 24.1, 23.1, 23.0, 21.7, 15.0, 14.6, 14.49, 14.47; IR ($CDCl_3$): ν = 3075, 2958, 2927, 2870, 2851, 1597, 1557, 1450, 1378, 1225, 982, 891, 771 cm^{-1}; HR-MS (EI$^+$): m/z = 405.3389, calcd. for $C_{29}H_{43}N$ [M]$^+$: 405.3396.

1-Hexyl-8-(oct-4-en-4-yl)-3,4-dipropylisoquinoline (9d): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.4 Hz, 1H), 7.50–7.46 (m, 1H), 7.13 (d, J = 6.7 Hz, 1H), 5.60 (t, J = 7.0 Hz, 1H), 3.60–3.53 (m, 1H), 3.01–2.81 (m, 5H), 2.71–2.64 (m, 1H), 2.23 (q, J = 7.5 Hz, 2H), 2.11–2.04 (m, 1H), 1.86–1.77 (m, 2H), 1.73–1.63 (m, 2H), 1.57–1.47 (m, 4H), 1.25–1.15 (m, 8H), 1.09 (t, J = 7.2 Hz, 3H), 1.05–1.00 (m, 6H), 0.85–0.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 151.2, 144.2, 143.7, 137.3, 128.8, 128.7, 128.2, 125.7, 123.8, 122.9, 38.2, 37.5, 36.3, 32.2, 31.4, 30.8, 30.5, 29.7, 24.3, 23.7, 23.0, 22.9, 21.7, 14.9, 14.6, 14.4, 14.33, 14.31; IR ($CDCl_3$): ν = 3068, 2959, 2932, 2872, 1710, 1463, 1378, 1179, 1089, 772 cm^{-1}; HR-MS (FAB$^+$): m/z = 408.3622, calcd. for $C_{29}H_{45}N$ [M+H]$^+$: 408.3625.

8-(Oct-4-en-4-yl)-1-phenyl-3,4-dipropylisoquinoline (9e): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.6 Hz, 1H), 7.60–7.57 (m, 2H), 7.40–7.28 (m, 5H), 5.29 (t, J = 7.2 Hz, 1H), 3.07–3.03 (m, 2H), 3.01–2.89 (m, 2H), 1.84–1.60 (m, 8H), 1.27–1.05 (m, 2H), 1.12 (t, J = 7.3 Hz, 3H), 1.03–0.92 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H), 0.63 (t, J = 7.3 Hz, 3H), 0.56 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 152.1, 144.7, 140.7, 138.4, 135.8, 131.8, 130.4, 129.7, 129.5, 128.9, 128.1, 127.1, 126.5, 126.2, 125.0, 123.1, 37.6, 33.0, 30.3, 30.2, 24.4, 24.1, 22.7, 21.8, 14.8, 14.5, 14.1, 13.8; IR ($CDCl_3$): ν = 3067, 2960, 2872, 1690, 1614, 1557,1461, 1381, 1086, 761 cm^{-1}; HR-MS (EI+): m/z = 399.2923, calcd. for $C_{29}H_{37}N$ [M]$^+$: 399.2926

Typical Procedure for Preparing Isoquinolinium Salt 18a by Reaction of Secondary Benzylamine 19a and Alkyne 3a in the Presence of 4b/6/HBF_4 (Table 3)

To a 1 mL pressure vial was added *N*-methylbenzylamine (**19a**, 60.6 mg, 0.5 mmol), diphenylacetylene (**3a**, 106.9 mg, 0.6 mmol), $[Cp^*RhCl_2]_2$ (**4b**, 3.7 mg, 0.00625 mmol), $Cu(OAc)_2 \cdot H_2O$ (**6**, 200 mg, 1.0 mmol), 48% of HBF_4 soluion in H_2O (67 μL, 0.5 mmol) and methanol (500 μL). The mixture was stirred at 100 °C for 4 h. After cooling and dilution with CH_2Cl_2, the mixture was filtered through a celite pad. The filtrate was concentrated under vacuum and the residue was carefully washed with ethyl acetate and hexane to give 2-methyl-3,4-diphenylisoquinolinium tetrafluoroborate (**18a**) as a white solid; yield: 178.2 mg (93%).

2-Methyl-3,4-diphenylisoquinolinium tetrafluoroborate (18a) [CAS No. 114943-84-9]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.05$ (s, 1H), 8.60 (d, $J = 8.0$ Hz, 1H), 7.96 (t, $J = 7.9$ Hz, 1H), 7.88 (t, $J = 7.5$ Hz, 1H), 7.63 (d, $J = 8.2$ Hz, 1H), 7.34–7.26 (m, 8H), 7.16–7.13 (m, 2H), 4.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.8$, 144.4, 139.1, 138.1, 137.0, 133.4, 131.6, 131.3, 131.0, 130.3, 130.2, 129.1, 128.8, 128.6, 127.6, 126.4, 48.6; ^{11}B NMR (96 MHz, $CDCl_3$): $\delta = -0.91$; ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -152.13$, -152.18.

2-Methyl-3,4-dipropylisoquinolinium tetrafluoroborate (18b) [CAS No. 1356496-71-3]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (s, 1H), 8.41 (d, $J = 8.1$ Hz, 1H), 8.10–8.03 (m, 2H), 7.77 (t, $J = 7.3$ Hz, 1H), 4.52 (s, 3H), 3.09 (q, $J = 7.8$ Hz, 4H), 1.73–1.66 (m, 4H), 1.14 (q, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.5$, 145.3, 137.6, 136.96, 136.93, 131.8, 130.2, 126.8, 123.6, 46.8, 13.1, 30.7, 24.1, 22.6, 14.7, 14.4.

2,4-Dimethyl-3-phenylisoquinolinium tetrafluoroborate (18c) [CAS No. 1356496-74-6]: ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 9.80$ (s, 1H), 8.53 (d, $J = 8.2$ Hz, 1H), 8.28–8.20 (m, 2H), 8.02–7.99 (m, 1H), 7.68–7.67 (m, 3H), 7.41–7.39 (m, 2H), 4.13 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 150.1$, 144.2, 138.1, 137.6, 134.5, 131.8, 131.7, 131.4, 131.2, 130.2, 129.5, 127.1, 124.6, 48.7, 16.3.

2,3,4-Triphenylisoquinolinium tetrafluoroborate (18d) [CAS No. 1356496-80-4]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.72$ (s, 1H), 8.57 (d, $J = 8.2$ Hz, 1H), 8.03 (t, $J = 8.0$ Hz, 1H), 7.91 (t, $J = 7.7$ Hz, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.52–7.50 (m, 2H), 7.36–7.28 (m, 8H), 7.11–7.01 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.7$, 144.6, 142.3, 139.5, 139.0, 137.9, 133.5, 132.0, 131.47, 131.10, 130.6, 130.5, 129.6, 129.3, 128.8, 128.6, 128.0, 127.1, 127.0, 126.7.

2-(4-Methoxyphenyl)-3,4-diphenylisoquinolinium tetrafluoroborate (18e) [CAS No. 1356496-82-6]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.65$ (s, 1H), 8.50 (d, $J = 8.1$ Hz, 1H), 7.97 (t, $J = 7.5$ Hz, 1H), 7.85 (t, $J = 7.5$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.36 (d, $J = 8.8$ Hz, 2H), 7.26–7.21 (m, 7H), 7.04–6.96 (m, 5H), 6.73 (d, $J = 8.8$ Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.3$, 150.7, 144.6, 139.1, 138.6, 137.4, 135.0, 133.3, 131.6, 131.2, 131.1, 131.0, 130.2, 128.9, 128.5, 128.3, 127.9, 127.8, 126.9, 126.3, 114.3, 55.4.

2-Benzyl-3,4-diphenylisoquinolinium tetrafluoroborate (18f) [CAS No. 114943-82-7]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.03$ (s, 1H), 8.57 (d, $J = 8.2$ Hz, 1H), 7.93 (t, $J = 7.3$ Hz, 1H), 7.82 (t, $J = 7.7$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.25–7.13 (m, 9H), 7.07–7.04 (m, 4H), 6.85 (d, $J = 7.0$ Hz, 2H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.9$, 144.3, 139.8, 138.2, 137.5, 133.2, 133.0, 131.7, 131.2, 130.8, 130.7, 130.2, 130.0, 129.26, 129.20, 128.7, 128.6, 128.6, 128.5, 127.4, 126.3, 63.6.

General Procedure for the Preparation of Dihydroisoquinolinium Salt by the Reaction of Tertiary Benzylamines in the Presence of 4b/6/KPF_6 (Table 3)

To a 1 mL pressure vial was added *N*,*N*-dimethylbenzylamine (**19a**, 67.6 mg. 0.5 mmol), 3-hexyne (**3d**, 49.2 mg, 0.6 mmol), $[Cp^*RhCl_2]_2$ (**4b**, 3.7 mg, 0.00625 mmol), $Cu(OAc)_2 \cdot H_2O$ (**6**, 200 mg, 1.0 mmol), KPF_6 (110.4 mg, 0.6 mmol) and methanol (700 μL). The reaction mixture was stirred at 100 °C in a preheated oil-bath for 8 h. After cooling the vessel to room temperature the mixture was diluted with CH_2Cl_2. The reaction mixture was filtered through a celite pad and the celite pad was washed with CH_2Cl_2. The combined filtrate was concentrated under vacuum and the residue was diluted with a small amount of CH_2Cl_2 again. Addition of Et_2O led to precipitation of 3,4-diethyl-2,2-dimethyl-1,2-dihydroisoquinolin-2-ium hexafluorophosphate (**20a**) as an off-white solid; yield: 125.3 mg (69%).

3,4-Diethyl-2,2-dimethyl-1,2-dihydroisoquinolin-2-ium hexafluorophosphate (20a) [CAS No. 151655-55-5]: ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.56$–7.41 (m, 4H), 4.60 (s, 2H), 3.23 (s, 6H), 2.66 (q, $J = 7.5$ Hz, 4H), 1.34 (t, $J = 7.5$ Hz, 3H), 1.18 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 141.1$, 134.8, 130.9, 130.6, 129.4, 128.2, 126.1, 124.8, 66.7, 51.4, 22.3, 20.4, 14.8, 13.8; anal. calcd. for $C_{15}H_{22}F_6NP$: C 49.86, H 6.14, N 3.88; found: C 49.45, H 6.18, N 4.07.

3,4-Diethyl-2-methylisoquinolin-2-ium hexafluorophosphate (18g): ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 9.43$ (s, 1H), 8.34 (d, $J = 8.2$ Hz, 1H), 8.23 (d, $J = 8.6$ Hz, 1H), 8.16 (t, $J = 7.2$ Hz, 1H), 7.92 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 149.9$, 146.6, 139.2, 138.1, 137.7, 131.6, 131.0, 127.1, 124.2, 47.2, 23.0, 22.2, 15.0, 13.3; IR ($CDCl_3$): $\nu =$ 3087, 2988, 2942, 2881, 1635,1452, 1392, 1281,1184, 1119, 925, 836, 557 cm^{-1}; HR-MS (FAB^+): $m/z = 200.1437$, calcd. for $C_{14}H_{18}N$ $[M-PF_6^-]^+$: 200.1439.

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