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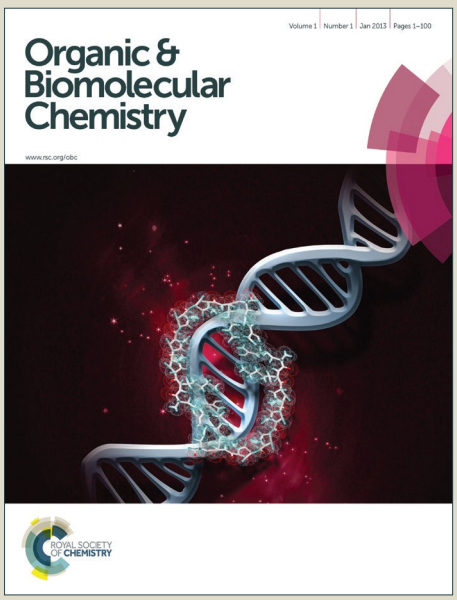

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ARTICLE

Synthesis of Substituted Benzo[*ij*]imidazo[2,1,5-*de*]quinolizine by Rhodium(III)-Catalyzed Multiple C–H Activation and Annulation†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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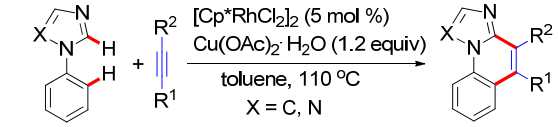
The cascade oxidative annulation reactions of aryl imidazoles with two molecules of alkynes via multiple C–H activation proceed efficiently in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ to give substituted benzo[*ij*]imidazo[2,1,5-*de*]quinolizine-based polyheteroaromatic compounds. This method is compatible with various functional groups, which are very useful for further synthetic transformations.

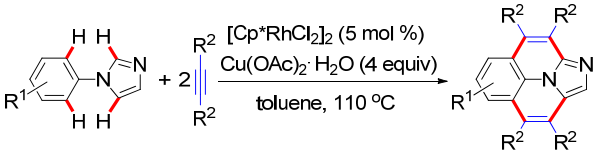
Introduction

Fused polycyclic heteroarene compounds have attracted significant interest owing to their potential utility in organic materials and pharmaceutical fields.[1] Therefore, the development of new protocols for efficient access to such extended π-systems is highly desirable. The transition-metal-catalyzed aromatic C–H bond activation has received increasing attention as a promising strategy for the synthesis of various conjugated polyheteroaromatic molecules owing to its high efficiency, atom economy, and functional group tolerance.[2] Recently, Rh(III)-catalyzed efficient syntheses of highly conjugated heterocyclic architectures *via* double/multiple C–H activation approach have received much attention.[3] Among these reactions, most of them were about introducing directing groups into the substrate to trigger *ortho* C–H bond activation and functionalization.[4] Only limited examples of double/multiple C–H bond activation without the coordination assistance coming from the directing group have been described in the construction of various conjugated polyheteroaromatic molecules through dehydrogenation and cyclization with internal alkynes.[5] Therefore, it is still highly desirable to apply this cyclization methodology to construct conjugated polyheteroaromatic molecules skeletons such as benzo[*ij*]imidazo[2,1,5-*de*]quinolizine derivatives through double/multiple C–H bond activation and annulations.

a) Previous work:
double C-H activation leading to aza-fused polycyclic quinolines



b) This work:
multiple C-H activation leading to aza-fused polycyclic quinolines



Scheme 1. Rhodium(III)-Catalyzed Annulations of Substituted Phenylimidazole with Alkynes

Quinoline moiety is an important structural unit present in various natural products and synthetic compounds that exhibit interesting biological[6] and optoelectronic properties.[7] In 2012, Chen[5a] reported the Rh(III)-catalyzed double C–H bond activation leading to complex aza-fused polycyclic quinolines (Scheme 1a). Being encouraged by such results and following our interest in Rh(III)-catalyzed C–H bond activation and heterocycle building,[4f,5i,8] herein we demonstrate an efficient Rh(III)-catalyzed reaction of *N*-aryl-substituted imidazoles with two molecules of alkynes to synthesize a variety of nicely decorated polycyclic heteroaromatic molecules containing benzo[*ij*]imidazo[2,1,5-*de*]quinolizine scaffolds (Scheme 1b).

Results and discussion

Initially, we investigated our studies by using phenylimidazole **1a** and diphenylacetylene **2a** as model substrates. As shown in Table 1, the desired product 3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine **3aa** was isolated in 88% yield by treating phenylimidazole **1a** (0.2 mmol) with diphenylacetylene **2a** (0.4 mmol) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (0.8 mmol) in toluene

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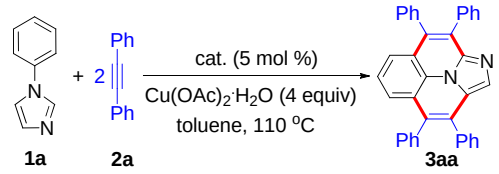
† Electronic Supplementary Information (ESI) available: CCDC 1433670. Experimental details, characterization and NMR spectra. See DOI: 10.1039/x0xx00000x.

(2.0 mL) at 110 °C for 12 h (Table 1, entry 1). The structure of compound **3aa** was confirmed by its ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS). Other solvents were tested in the reaction, and toluene proved to be the solvent of choice (Table 1, entries 2–6). Moreover, no expected product was detected when $[RuCl_2(p\text{-cymene})]_2$ was used as a catalyst (Table 1, entries 7–8). Pleasingly, when the amount of **2a** was increased slightly, the reaction yield was increased to 93% (Table 1, entry 11). The yield had a tiny reduction when the amount of $Cu(OAc)_2{\cdot}H_2O$ was reduced (Table 1, entry 12). Based on the above results, we determined the best reaction condition as *N*-phenylimidazole (**1a**) (0.2 mmol) and diphenylacetylene (**2a**) (0.44 mmol) in the presence of $[Cp^*RhCl_2]_2$ (5 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (0.8 mmol) in toluene (2.0 mL) at 110 °C under argon for 12 h (Table 1, entry 11).

Table 1. Optimization of the reaction conditions[a]



1a **2a** **3aa**

Entry	Cat. (5 mol%)	Solvent	Yields [%][b]
1	$[Cp^*RhCl_2]_2$	toluene	88%
2	$[Cp^*RhCl_2]_2$	MeOH	Trace
3	$[Cp^*RhCl_2]_2$	CH_3CN	Trace
4	$[Cp^*RhCl_2]_2$	1,4-dioxane	80%
5	$[Cp^*RhCl_2]_2$	*o*-xylene	73%
6	$[Cp^*RhCl_2]_2$	THF	72%
7	$[RuCl_2(p\text{-cymene})]_2$	toluene	N.D.
8	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	N.D.
9	-	toluene	N.D.
10[c]	$[Cp^*RhCl_2]_2$	toluene	N.D.
11[d]	**$[Cp^*RhCl_2]_2$**	**toluene**	**93%**
12[d,e]	$[Cp^*RhCl_2]_2$	toluene	86%

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.8 mmol), solvent (2.0 mL), 110 °C, Ar atmosphere, 12 h. [b]Isolated yield. [c]No $Cu(OAc)_2{\cdot}H_2O$. [d]**2a** (0.44 mmol). [e]$Cu(OAc)_2{\cdot}H_2O$ (0.6 mmol). N.D. = Not detected.

With the optimal reaction conditions established, various substituted phenylimidazole **1a–k** were treated with diphenylacetylene (**2a**) to give the corresponding products **3** in moderate to good yields (Table 2). The structure of **3ea** was confirmed by its ^{1}H and ^{13}C NMR spectra, HRMS, and single-crystal X-ray diffraction analysis (Figure 1). Various functional groups commonly encountered in organic synthesis were tolerated well, such as halide (products **3ba–da**). Additionally, 4-methyl, 4-*tert*-butyl substituted and electron-rich substrates reacted nicely with **2a** to give the corresponding products **3ea–ha** in good yields (70–94%). In contrast, 4-nitro phenylimidazole **1i** provided **3ia** only in 5% yield. However, the electron-withdrawing substrates **1j** and **1k** gave the corresponding **3ja** and **3ka** in high yields respectively.

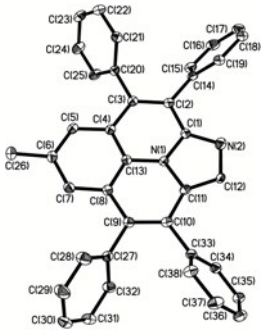
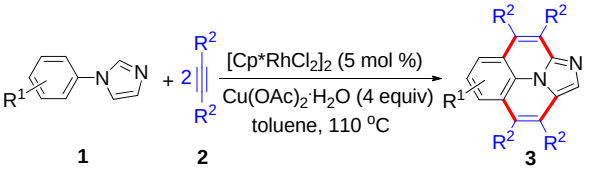


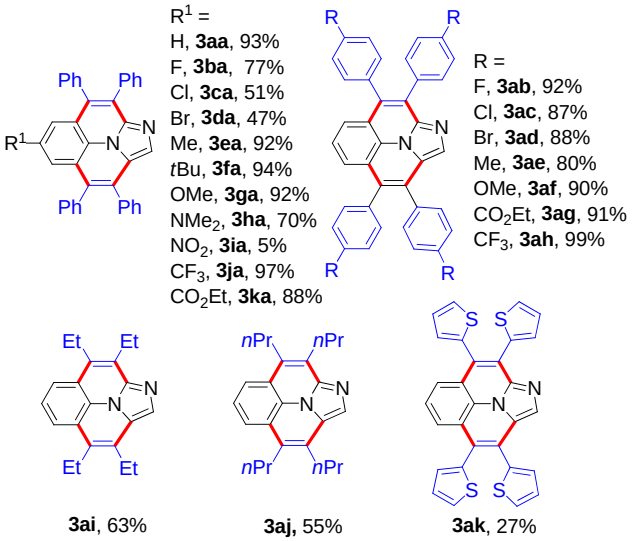
Figure 1. Molecular structure of **3ea**.

Aside from **2a**, other symmetrical alkynes were also tested for the present reaction (Table 2). Gratifyingly, substituted diphenylacetylenes both with electron-rich or electron-deficient groups could give high yields (80–99%). For dialkylacetylenes, 3-hexyne **2i** and 4-octyne **2j** afforded moderate yields of **3ai** (63%) and **3aj** (55%), respectively. Interestingly, di(2-thienyl)acetylene **2k** also reacted smoothly with **1a** to give the annulated product **3ak** in 27% yield. On the other hand, unsymmetrical alkynes such as 1-phenyl-1-butyne produced four regioisomeric products caused by poor regioselectivity which would not allow separation. In the cases of **3ca**, **3da**, **3ai**, **3aj**, and **3ak**, the yields are slight lower (51%, 47%, 63%, 55%, and 27%), and the corresponding by-products incorporated only one molecule of alkyne were also isolated in 17%, 19%, 25%, and 22% yields, respectively.

Table 2. Reaction of substituted phenylimidazole **1** with alkynes **2**[a,b]



1 **2** **3**



3ai, 63% **3aj**, 55% **3ak**, 27%

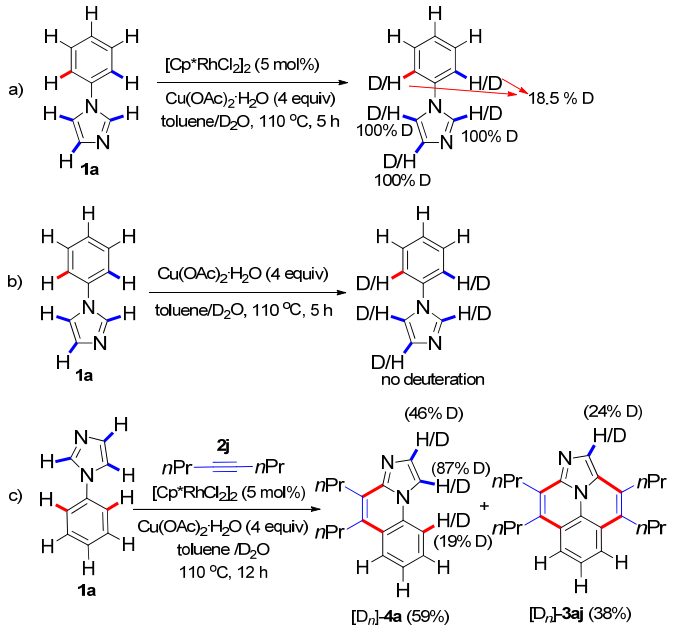
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.44 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.8 mmol), toluene (2.0 mL), 110 °C, Ar atmosphere, 12 h. [b]Isolated yield.

To further demonstrate the efficiency and practicality of this cascade reaction, a scale-up reaction was performed. Thus,

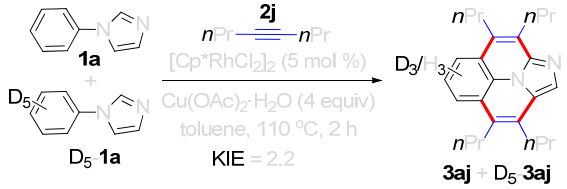
gram-scale synthesis of **3aa** was achieved in 83% yield (1.242 g) with 24 h.

To gain more insight into the mechanism of this reaction, H/D exchange reactions were examined (Scheme 2). When the reaction was performed in the absence of **2** (Scheme 2a and b), 18.5% deuteration at the *ortho*-H position on the phenyl ring and 100% deuteration at all the imidazole ring positions were found. No deuterium was observed at the phenyl ring or imdazole ring when repeating the reaction but without the Rh-catalyst. This indicates that Rh-catalyst plays a key role in the directed C–H activation of **1a**. In the presence of **2j**, deuteration at the imidazole C–H bonds of the product was detected (Scheme 2c). These results indicate that imidazole C–H and phenyl ring C–H activations are reversible. The lower yield (38%) of [D$_n$]-**3aj** than that for the non-deuterated product **3aj** (55%) indicated the addition of water might have some deleterious effect in the reaction.

Moreover, we tested the kinetic isotope effect (KIE) experiments shown in the Scheme 3. The KIE was found to be k_H/k_D= 2.2, indicating that the cleavage of the phenyl ring C–H bond was probably involved in the rate-determining step.

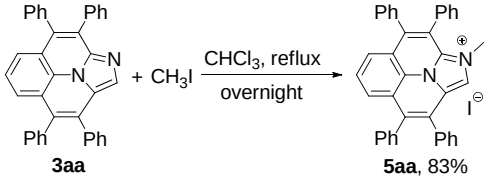


Scheme 2. H/D exchange experiments



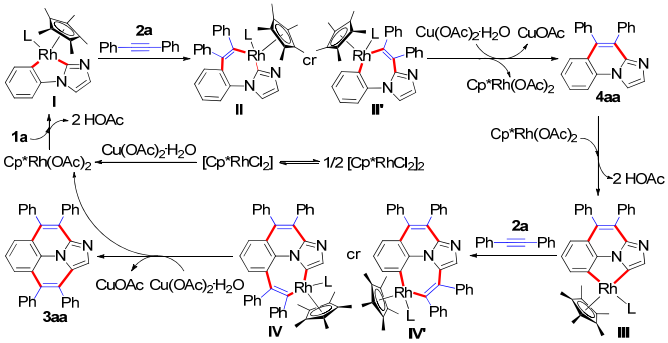
Scheme 3. KIE experiment

To afford the structurally diverse compounds, we tried to treat **3aa** with iodomethane to produce benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium salts **5aa** which exhibits intense fluorescence (Scheme 4).[5f,i]



Scheme 4. Alkylation of **3aa**

Based on the above experimental results and the relating references,[5] a possible mechanism is proposed for the present catalytic reaction (Scheme 5). The first step is likely to be a C–H bond activation process thus affording the five-membered cyclometalated intermediate **I** by elimination of two molecules of HOAc. Then an alkyne coordinates following by inserting the coordinated alkyne into the Rh–C bond to give the seven-membered rhodacycle **II** or **II'**. Then, **II** or **II'** reacts with $Cu(OAc)_2{\cdot}H_2O$ to give **4aa** and regenerates the rhodium(III) species. Compound **4aa** continuously proceeded C–H bond activation affording the cyclometalated intermediate **III**. Similar to **I**, the alkyne coordinates and inserts to generate **IV** or **IV'**. Subsequent reductive elimination from **IV** or **IV'** affords the annulation product **3aa** and the regenerated rhodium(III) species continues the catalytic cycle.



Scheme 5. Proposed mechanistic pathway of the annulation reaction

Conclusions

In conclusion, we have successfully developed a new method for efficient synthesis of substituted benzo[*ij*]imidazo[2,1,5-*de*]quinolizine with conjugated π-systems *via* rhodium(III)-catalyzed cascade oxidative annulation reaction of *N*-aryl-substituted imidazoles with alkynes. This protocol is compatible with various functional groups such as fluoro, chloro, alkoxy, and ester, which are very useful for further synthetic transformations. Further applications of this approach in the construction of organic optoelectronic materials and a detailed mechanistic investigation are in progress in our laboratory.

Experimental

General Information

All the reactions were carried out under argon atmosphere using standard Schlenk technique. ^{1}H NMR (400 MHz), ^{19}F (376 M Hz), and ^{13}C NMR (100 MHz) were recorded on a NMR spectrometer with DMSO-d_6 and $CDCl_3$ as solvent. Chemical

shifts of ^{1}H, ^{19}F and ^{13}C NMR spectra are reported in parts per million (ppm). The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.00 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.43 ppm). All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). Column chromatography was performed on silica gel 200–300 mesh or alumina 200–300 mesh. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm). High-resolution mass spectrometry (HRMS) was done on a FTICR-mass spectrometer. $[Cp^*RhCl_2]_2$[9] and *N*-arylimidazoles[10] were prepared following the literature procedures. Unless otherwise noted below, all other compounds have been reported in the literature or are commercially available without any further purification.

General Procedure for Rh(III)-Catalyzed Oxidative Annulation Reactions of *N*-arylimidazoles with Alkynes

A mixture of substituted arylimidazole **1** (0.2 mmol, 1.0 equiv), alkyne **2** (0.44 mmol, 2.2 equiv), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.01 mmol, 5 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (160.0 mg, 0.8 mmol, 4.0 equiv) were weighted in a Schlenk tube equipped with a stir bar. Dry toluene (2.0 mL) was added and the mixture was stirred at 110 °C for 12 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. After that purification by column chromatography on silica gel or alumina column with dichloromethane/petroleum ether or ethyl acetate/petroleum ether.

3,4,8,9-Tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3aa): Yellow-green solid (92.4 mg, 93%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1H), 7.36 (d, *J* = 6.9 Hz, 2H), 7.34 (s, 1H), 7.33 – 7.26 (m, 8H), 7.21 – 7.19 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 136.6, 136.5, 136.4, 135.9, 134.6, 132.2, 130.7, 130.6, 130.5, 130.4, 129.8, 128.8, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 126.5, 126.4, 125.6, 125.2, 124.9, 121.9, 121.3. HRMS (ESI) calcd for $C_{37}H_{25}N_2$ $[M+H]^+$ 497.2018, found 497.2014.

6-Fluoro-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ba): Yellow-green solid (79.6 mg, 77%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.44 – 7.26 (m, 19H), 7.24 (s, 1H), 7.13 (d, *J* = 10.3 Hz, 1H), 7.07 (d, *J* = 10.2 Hz, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.61 (s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9 ($J_{C\text{-}F}$ = 241.0 Hz), 138.9, 136.4, 136.1, 135.8, 134.9, 134.8, 131.2, 131.1, 130.7, 130.5, 130.4, 130.3, 129.7, 128.7, 128.6, 128.3 ($J_{C\text{-}F}$ = 10.0 Hz), 128.2, 127.9, 127.6, 127.4, 126.7 ($J_{C\text{-}F}$ = 9.7 Hz), 126.2, 107.6 ($J_{C\text{-}F}$ = 23.6 Hz). HRMS (ESI) calcd for $C_{37}H_{24}FN_2$ $[M+H]^+$ 515.1924, found 515.1921.

6-Chloro-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ca): Yellow-green solid (54.0 mg, 51%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (s, 1H), 7.40 – 7.22 (m, 22H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 136.2, 136.0, 135.7, 134.7, 134.6, 131.1, 130.9, 130.8, 130.7, 130.5, 130.4, 130.3, 129.8, 129.0, 128.8, 128.7, 128.2, 127.9, 127.7, 126.4, 126.3, 120.7, 120.2. HRMS (ESI) calcd for $C_{37}H_{24}ClN_2$ $[M+H]^+$ 531.1628, found 531.1628.

6-Bromo-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3da): Yellow-green solid (53.9 mg, 47%). M.p. 299-301 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (s, 1H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.44 – 7.27 (m, 20H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 136.2, 135.9, 135.7, 134.7, 134.5, 131.1, 130.7, 130.5, 130.4, 129.7, 129.3, 128.8, 128.7, 128.2, 127.9, 127.7, 126.7, 126.3, 123.6, 123.0, 118.9. HRMS (ESI) calcd for $C_{37}H_{24}BrN_2$ $[M+H]^+$ 575.1123, found 575.1118.

6-Methyl-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ea): Yellow-green solid (94.2 mg, 92%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 7.34 (m, 19H), 7.24 (d, *J* = 5.9 Hz, 2H), 7.16 (s, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 137.0, 136.8, 136.3, 135.2, 134.5, 131.5, 130.7, 130.6, 130.0, 129.9, 129.3, 129.1, 128.6, 128.5, 128.1, 127.9, 127.6, 127.4, 127.3, 126.6, 126.3, 125.1, 121.8, 121.6, 22.3. HRMS (ESI) calcd for $C_{38}H_{27}N_2$ $[M+H]^+$ 511.2174, found 511.2173.

6-(*tert*-Butyl)-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3fa): Yellow-green solid (104.1 mg, 94%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 4.3 Hz, 2H), 7.44 – 7.29 (m, 19H), 1.24 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.7, 139.1, 136.9, 136.7, 136.3, 135.6, 135.3, 131.8, 130.7, 130.6, 130.5, 129.8, 129.7, 129.1, 128.9, 128.5, 128.4, 128.1, 127.8, 127.6, 127.4, 126.5, 126.3, 125.9, 124.6, 118.4, 118.3, 35.2, 31.5. HRMS (ESI) calcd for $C_{41}H_{33}N_2$ $[M+H]^+$ 553.2644, found 553.2648.

6-Methoxy-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ga): Yellow-green solid (97.1 mg, 92%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.43 – 7.27 (m, 19H), 7.24 (s, 1H), 6.94 (dd, *J* = 7.7, 2.3 Hz, 2H), 3.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 138.8, 136.9, 136.6, 136.1, 135.1, 134.9, 131.2, 130.7, 130.5, 130.4, 129.8, 129.7, 128.6, 128.5, 128.1, 127.8, 127.6, 127.4, 127.1, 126.3, 126.2, 126.0, 107.5, 105.8, 55.5. HRMS (ESI) calcd for $C_{38}H_{27}N_2O$ $[M+H]^+$ 527.2123, found 527.2122.

6-(Dimethylamino)-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ha): Brown solid (75.1 mg, 70%). M.p. >300°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1H), 7.46 – 7.29 (m, 20H), 6.78 (d, *J* = 6.9 Hz, 2H), 2.80 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 138.6, 137.3, 137.0, 136.5, 135.5, 134.9, 131.3, 130.8, 130.7, 130.6, 130.1, 129.9, 129.4, 128.5, 128.4, 128.0, 127.8, 127.5, 127.3, 126.6, 126.0, 125.9, 124.4, 106.6, 105.5, 41.0. HRMS (ESI) calcd for $C_{39}H_{30}N_3$ $[M+H]^+$ 540.2440, found 540.2435.

6-Nitro-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ia): Brown solid (5.3 mg, 5%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (s, 1H), 8.22 (s, 1H), 7.89 (s, 1H), 7.47 – 7.26 (m, 20H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.9, 139.7, 135.8, 135.6, 135.4, 135.3, 134.2, 132.8, 132.1, 131.7, 131.3, 130.6, 130.5, 130.4, 129.7, 129.1, 129.0, 128.6, 128.4, 128.3, 128.2, 128.1, 127.4, 126.7, 125.5, 116.6, 115.1. HRMS (ESI) calcd for $C_{37}H_{24}N_3O_2$ $[M+H]^+$ 542.1869, found 542.1874.

3,4,8,9-Tetraphenyl-6-(trifluoromethyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ja):

Yellow-green solid (109.5 mg, 97%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H), 7.72 (s, 1H), 7.61 (s, 1H), 7.45 – 7.26 (m, 20H). ^{19}F NMR ($CDCl_3$, 376 MHz,) δ -61.02 (s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 136.0, 135.8, 135.6, 135.4, 134.6, 131.7, 131.4 ($J_{C\text{-}F}$ = 12.2 Hz), 130.7, 130.6, 130.5, 130.4, 129.7, 128.8, 128.7, 128.2, 127.9, 127.8, 127.7, 127.1, 127.0, 126.8, 126.6, 125.5, 125.2, 117.5 ($J_{C\text{-}F}$ = 122.9 Hz). HRMS (ESI) calcd for $C_{38}H_{24}F_3N_2$ $[M+H]^+$ 565.1892, found 565.1892.

6-(Ethoxycarbonyl)-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ka): Yellow-green solid (100.0 mg, 88%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 1.0 Hz, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 7.46 – 7.27 (m, 20H), 4.29 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 139.7, 136.2, 136.0, 135.9, 135.8, 134.8, 132.6, 131.8, 130.7, 130.6, 130.5, 130.0, 129.8, 128.7, 128.6, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 126.7, 126.6, 126.4, 124.9, 123.1, 121.6, 61.2, 14.1. HRMS (ESI) calcd for $C_{40}H_{29}N_2O_2$ $[M+H]^+$ 569.2229, found 569.2230.

3,4,8,9-Tetrakis(4-fluorophenyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ab): Yellow-green solid (104.9 mg, 92%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.50 – 7.40 (m, 2H), 7.39 – 7.27 (m, 5H), 7.25 – 7.18 (m, 4H), 7.09 (td, J = 8.4, 4.6 Hz, 4H), 7.02 (t, J = 8.5 Hz, 4H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.11 (s), -113.60 (s), -113.64 (s), -113.81 (s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1 ($J_{C\text{-}F}$ = 247.6 Hz), 139.2, 134.8, 132.5, 132.4, 132.4, 132.3, 132.2, 131.8, 131.5, 131.4, 131.0, 130.7, 130.6, 129.4, 128.7, 126.7, 126.5, 126.3, 125.1, 124.9, 121.7, 120.9, 115.9 ($J_{C\text{-}F}$ = 21.4 Hz), 115.4 ($J_{C\text{-}F}$ = 32.3 Hz). HRMS (ESI) calcd for $C_{37}H_{21}F_4N_2$ $[M+H]^+$ 569.1641, found 569.1643.

3,4,8,9-Tetrakis(4-chlorophenyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ac): Yellow-green solid (110.7 mg, 87%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 7.42 – 7.28 (m, 6H), 7.25 (dd, J = 9.6, 6.5 Hz, 6H), 7.21 – 7.16 (m, 3H), 7.12 (t, J = 8.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 134.9, 134.7, 134.6, 134.1, 134.0, 133.9, 133.8, 133.7, 133.0, 132.0, 131.9, 131.8, 131.1, 130.9, 130.7, 129.2, 129.1, 128.8, 128.5, 128.4, 126.8, 126.2, 126.1, 125.0, 124.8, 121.8, 121.1. HRMS (ESI) calcd for $C_{37}H_{21}Cl_4N_2$ $[M+H]^+$ 633.0459, found 633.0447.

3,4,8,9-Tetrakis(4-bromophenyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ad): Yellow-green solid (143.4 mg, 88%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.54 (s, 4H), 7.45 (t, J = 10.4 Hz, 6H), 7.33 (d, J = 7.0 Hz, 1H), 7.26 (s, 2H), 7.20 (d, J = 7.4 Hz, 2H), 7.13 (t, J = 8.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 135.3, 135.1, 134.6, 134.5, 133.5, 132.3, 132.2, 132.1, 131.8, 131.5, 131.4, 130.8, 130.7, 130.5, 129.1, 128.9, 128.4, 126.9, 126.2, 126.0, 125.0, 124.7, 122.3, 122.1, 122.0, 121.8, 121.1. HRMS (ESI) calcd for $C_{37}H_{21}Br_4N_2$ $[M+H]^+$ 808.8438, found 808.8427.

3,4,8,9-Tetra-*p*-tolylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ae): Yellow-green solid (88.1 mg, 80%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 7.36 – 7.26 (m, 2H), 7.26 – 7.20 (m, 3H), 7.17 (d, J = 8.7 Hz, 3H), 7.12 – 7.05 (m, 7H), 7.05 – 6.98 (m, 4H), 2.30 (s, 6H), 2.25 (d, J = 9.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 137.2, 137.0, 136.9, 136.8, 135.1, 134.0, 133.8, 133.4, 132.3, 131.4, 130.6, 130.5, 130.4, 129.7, 129.3, 129.2, 128.8, 128.6, 126.6, 125.3, 124.4, 121.4, 120.6, 21.31. HRMS (ESI) calcd for $C_{41}H_{33}N_2$ $[M+H]^+$ 553.2644, found 553.2635.

3,4,8,9-Tetrakis(4-methoxyphenyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3af): Brown solid (110.5 mg, 90%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.44 – 7.31 (m, 5H), 7.23 (s, 2H), 7.15 (t, J = 9.3 Hz, 4H), 6.91 – 6.86 (m, 4H), 6.81 (t, J = 7.2 Hz, 4H), 3.81 (s, 6H), 3.78 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 158.6, 139.5, 134.7, 132.0, 131.8, 131.7, 131.0, 130.9, 130.4, 129.5, 129.3, 129.0, 128.9, 128.6, 127.6, 126.7, 126.6, 126.5, 125.4, 124.4, 121.2, 120.4, 114.0, 113.9, 113.5, 113.4, 55.1. HRMS (ESI) calcd for $C_{41}H_{33}N_2O_4$ $[M+H]^+$ 617.2440, found 617.2442.

Tetraethyl 4,4',4'',4'''-(benzo[*ij*]imidazo[2,1,5-*de*]quinolizine-3,4,8,9-tetrayl)tetrabenzoate (3ag): Brown solid (142.2 mg, 92%). M.p. 256-258 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 7.8, 3.2 Hz, 4H), 7.98 (d, J = 8.1 Hz, 4H), 7.71 (s, 1H), 7.47 (d, J = 8.0 Hz, 3H), 7.42 (t, J = 6.1 Hz, 3H), 7.35 (t, J = 7.7 Hz, 5H), 4.38 (tt, J = 14.2, 7.1 Hz, 8H), 1.44 – 1.35 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 166.0, 165.9, 141.1, 140.9, 140.2, 139.2, 138.8, 134.8, 131.2, 130.8, 130.7, 130.6, 130.5, 130.1, 130.0, 129.9, 129.7, 129.6, 129.4, 129.3, 128.7, 127.1, 126.0, 125.7, 125.0, 124.5, 121.8, 121.1, 61.1, 60.9, 14.2. HRMS (ESI) calcd for $C_{49}H_{41}N_2O_8$ $[M+H]^+$ 785.2863, found 785.2854.

3,4,8,9-Tetrakis(4-(trifluoromethyl)phenyl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ah): Brown solid (152.3 mg, 99%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H), 7.71 – 7.65 (m, 4H), 7.61 (d, J = 7.9 Hz, 4H), 7.55 – 7.49 (m, 3H), 7.46 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 8.3 Hz, 5H), 7.33 (d, J = 7.8 Hz, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz,) δ -62.64 (s), -62.70 (s), -62.76 (s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 139.8, 139.1, 138.9, 138.1, 134.6, 131.1, 131.0, 130.9, 130.6, 130.5, 130.4, 130.3, 130.1, 130.0, 129.2, 128.8, 128.5, 127.9, 127.3, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7, 125.6, 125.57, 125.31, 125.27, 125.2, 125.20, 125.15, 124.6, 122.6, 122.5, 122.4, 122.1, 121.4, 119.8, 68.1, 38.7, 30.3, 29.7, 28.9, 23.7, 22.7, 14.0, 10.9. HRMS (ESI) calcd for $C_{41}H_{21}F_{12}N_2$ $[M+H]^+$ 769.1513, found 769.1519.

3,4,8,9-Tetraethylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ai): Yellowish solid (38.1 mg, 63%). M.p. 142-144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 6.8 Hz, 2H), 7.98 – 7.89 (m, 2H), 3.46 (dd, J = 13.6, 6.5 Hz, 2H), 3.21 (dd, J = 14.7, 7.3 Hz, 2H), 3.04 (dd, J = 14.6, 7.2 Hz, 2H), 2.99 – 2.91 (m, 2H), 1.48 (t, J = 6.8 Hz, 3H), 1.40 – 1.30 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 133.8, 129.6, 129.5, 129.1, 129.0, 125.7, 125.3, 124.4, 124.1, 122.6, 118.0, 117.3, 22.4, 21.1, 21.0, 20.6, 14.7, 14.6, 13.6, 13.3. HRMS (ESI) calcd for $C_{21}H_{25}N_2$ $[M+H]^+$ 305.2018, found 305.2012.

3,4,8,9-Tetrapropylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3aj): Yellowish solid (39.6 mg, 55%). M.p. 142-144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H), 7.74 (dd, J = 6.3, 2.7 Hz, 1H), 7.65 (dd, J = 8.8, 5.3 Hz, 2H), 3.24 – 3.18 (m, 2H), 3.07 – 3.00 (m, 2H), 2.93 (dd, J = 15.9, 10.0 Hz, 4H), 1.89 – 1.76 (m, 4H), 1.71 (m, 4H), 1.16 – 1.09 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 132.8, 129.5, 128.7, 128.1, 127.9, 126.0, 125.6, 124.4, 124.3, 122.7, 118.2, 117.4, 31.4, 30.3, 30.0, 29.8, 23.5, 23.4,

22.3, 21.9, 14.5. HRMS (ESI) calcd for $C_{25}H_{33}N_2$ $[M+H]^+$ 361.2644, found 361.2643.

3,4,8,9-Tetra(thiophen-2-yl)benzo[*ij*]imidazo[2,1,5-*de*]quinolizine (3ak): Brown solid (28.5 mg, 27%). M.p. >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (s, 1H), 7.76 (s, 1H), 7.59 – 7.46 (m, 5H), 7.40 (t, J = 5.8 Hz, 2H), 7.34 (s, 1H), 7.24 – 7.19 (m, 1H), 7.17 (s, 2H), 7.13 (s, 1H), 7.08 (d, J = 4.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) 138.6, 137.3, 137.0, 136.8, 135.5, 131.0, 129.7, 129.6, 128.8, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 126.7, 126.5, 126.3, 126.0, 125.6, 125.5, 125.1, 124.9, 124.8, 122.3, 121.5. HRMS (ESI) calcd for $C_{29}H_{17}N_2S_2$ $[M+H]^+$ 521.0275, found 521.0276.

Gram-Scale Synthesis of 3aa

A mixture of phenylimidazole **1a** (432.6 mg, 3.0 mmol), diphenylacetylene **2a** (1.1760 g, 6.6 mmol), $[Cp^*RhCl_2]_2$ (92.70 mg, 0.15 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (2.3960 g, 12.0 mmol) were weighted in a Schlenk tube equipped with a stir bar. Dry toluene (30 mL) was added and the mixture was stirred at 110 °C for 24 h under Ar atmosphere. Afterwards, it was diluted with CH_2Cl_2 and transferred to a round bottom flask. Alumina was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by column chromatography on alumina, affording **3aa** (1.2420 g) as a yellow-green solid in 83% yield.

Deuterium Exchange Experiment

a) A mixture of phenylimidazole **1a** (28.8 mg, 0.2 mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.01 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (160.0 mg, 0.8 mmol) were weighted in a Schlenk tube equipped with a stir bar. Dry toluene (1.8 mL) and D_2O (0.2 mL) were added and the mixture was stirred at 110 °C for 5 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. The mixed products were purified by flash column chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/2-1/1).

b) A mixture of phenylimidazole **1a** (28.8 mg, 0.2 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (160.0 mg, 0.8 mmol) were weighted in a Schlenk tube equipped with a stir bar. Dry toluene (1.8 mL) and D_2O (0.2 mL) were added and the mixture was stirred at 110 °C for 5 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. The mixed products were purified by flash column chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/2-1/1).

c) A mixture of phenylimidazole **1a** (28.8 mg, 0.2 mmol), 4-Octyne **2j** (48.5 mg, 0.44mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.01 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (160.0 mg, 0.8 mmol) were weighted in a Schlenk tube equipped with a stir bar. Dry toluene (1.8 mL) and H_2O (0.2 mL) were added and the mixture was stirred at 110 °C for 12 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. The mixed products were purified by flash column chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/8).

Preparation of D_5-Iodobenzene

The D_5-iodobenzene was prepared by following a similar procedure for the synthesis of iodobenzene according to the published procedure.[11] A mixture of D_6-benzene (0.46 mL, 5 mmol), AgOTf (1.284 g, 5 mmol), and iodine (1.27 g, 5 mmol) in dry CH_2Cl_2 (20 mL) was stirred for 15 min at room temperature in dark condition. Then the reaction mixture was passed through a short Celite pad and washed with CH_2Cl_2. The combined filtrates were washed with dilute NH_4OH solution, dilute Na_2SO_3, and water, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting residue was utilized directly for further reaction purpose.

Preparation of *N*-(D_5-phenyl)imidazole (D_5-1a)[10]

A mixture of CuI (53.8 mg, 0.28 mmol), Cs_2CO_3 (1.84 g, 5.6 mmol), imidazole (269.4 mg, 3.9 mmol), and d_5-iodobenzene (591 mg, 2.8 mmol) in DMF (60 mL) was stirred for 30 min at room temperature under Ar, and then heated at 120 °C for 40 h. After cooling to room temperature, the mixture was diluted with ethyl acetate, filtered through a pad of silica gel, and washed with water. Then the organic phase was dried over anhydrous Na_2SO_4 and the filtrate was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluent: EtOAc/petroleum = 1/1) to provide the desired product (209 mg, 50%).

General Procedure for the KIE Experiments

a) Competition Experiment between 1a and [D_5]-1a

A mixture of **1a** (14.4 mg, 0.1 mmol), D_5-**1a** (14.9 mg, 0.1 mmol), 4-Octyne (48.5 mg, 0.44 mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.01 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (160.0 mg, 0.8 mmol) were weighed in a Schlenk tube equipped with a stir bar. Dry toluene (2.0 mL) was added and the mixture was stirred at 110 °C for 2 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. The purification was performed by column chromatography on silica gel (eluent: EtOAc/petroleum = 1/8) to give the mixed products **3aa/**[D_4]-**3aa**.

b) Independent Experiment Using the Deuterated and the Protonated Substrates

A mixture of **1a** (14.4 mg, 0.1 mmol) or D_5-**1a** (14.9 mg, 0.1 mmol), 4-Octyne (24.2 mg, 0.22 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (80.0 mg, 0.4 mmol) were weighed in a Schlenk tube equipped with a stir bar. Dry toluene (1.0 mL) was added and the mixture was stirred at 110 °C for 1 h under Ar atmosphere. Afterward, the two independent reaction mixtures were poured into a same round flask. The solvent was evaporated under reduced pressure, and the residue was absorbed to a small amount of alumina. The purification was performed by column chromatography on silica gel (eluent: EtOAc/petroleum = 1/8) to give the mixed products **3aa/**[D_4]-**3aa**.

Alkylation of 3aa

A mixture of 3,4,8,9-Tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizine **3aa** (248.3 mg, 0.5 mmol) and iodomethane (99.4 mg, 0.7 mmol) in $CHCl_3$ (5.0 mL) under Ar atmosphere was refluxed overnight in a round-bottom flask equipped with

a condenser. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was absorbed onto small amounts of alumina. Purification by flash column chromatography on alumina first with CH_2Cl_2 as eluent gave **3aa** (40.7 mg, 16%), then with MeOH/CH_2Cl_2 = 1/20 as eluent afforded **5aa**[5i] (265.8 mg, 83%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.53 (s, 2H), 7.41 (s, 3H), 7.29 (s, 3H), 7.25 – 7.08 (m, 15H), 3.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 136.2, 134.3, 133.7, 133.3, 132.0, 131.1, 130.9, 129.8, 129.5, 129.3, 129.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.5, 126.2, 125.2, 125.1, 124.7, 124.4, 124.1, 120.7, 38.9.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Nos 21372122 and 21421062) for financial support.

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