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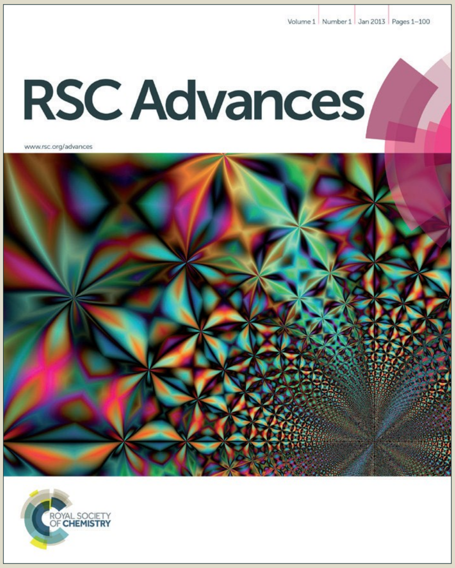

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ARTICLE

A Concise Synthesis of Quinolinium, and Biquinolinium Salts and Biquinolines from Benzylic Azides and Alkenes Promoted by Copper(II) Species

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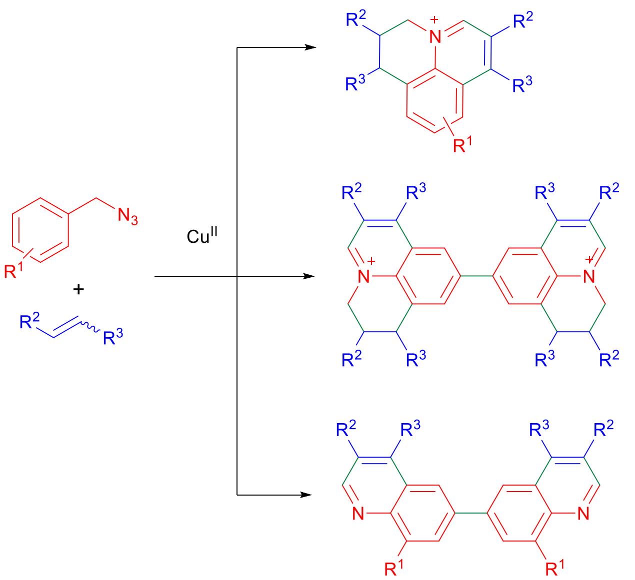
A novel copper-promoted multiple aza-[4 + 2] cycloaddition reaction of *N*-methyleneanilines in situ generated from benzylic azide and alkenes afforded quinolinium salts, biquinolinium salts, biquinolines or substituted quinolines depending on the substitution on the phenyl ring of benzylic azide. The reaction of *para* substituted benzylic azides and 2 equivalents of alkenes afforded the corresponding substituted quinolinium salts, while benzylic azides without a para substituent provided biquinolinium salts. The copper-promoted cycloaddition reaction also allows to get biquinoline products from *ortho*-substituted benzylic azides. These reactions work well with both terminal and internal alkenes. Unsymmetrical internal alkenes proceed with high regioselectivity. The reaction likely started by Lewis acidic Cu^{II}-assisted rearrangement of benzylic azide to *N*-methyleneaniline, followed by a [4 + 2] cycloaddition with alkene. Detailed mechanistic studies suggest that the biquinoline and biquinolinium salts are likely formed via radical processes.

Introduction

Lewis acid (LA) mediated aza-[4 + 2] cycloaddition reaction of 2-azadiene and electron rich alkenes is an important tool to construct nitrogen heterocycles.[1] In particular, the Povarov reaction (PR)[2] a [4 + 2] cycloaddition of N-arylimines and alkenes is a known effective method for the synthesis of tetrahydroquinolines (THQs), which can be easily transformed to quinolines by dehydrogenation.[3] Generally, Povarov reaction is performed using either a protic or Lewis acid as the catalyst and a *N*-arylimine as azadiene, and electron-rich alkenes, such as cyclic and acyclic enol ethers, enamides, enamines, and conjugated dienes as a dienophile.[4] Recently, arylmethyl azide was also shown to be a suitable substrate to undergo [4 + 2] annulation with alkene to afford THQs.[5] In addition to neutral nitrogen heterocycles, the synthesis of cationic N-heterocycles also received great attention owing to the various biological activities and materials applications.[6] In particular, applications of quinolinium salts in biological studies demands new synthetic methods for the synthesis of a wide range of substituted quinolinium salts.[7] A well-known method to these compounds involves the reaction of quinolines with alkyl halides.[8] However, the method is limited by the availability of substrates. Our continuing interest in the synthesis of N-heterocyclic salts has encouraged us to tackle this problem and to develop a straightforward route to the diversely substituted quinolinium salts.[9]

In this manuscript, we report a convenient method to access highly substituted quinolinium salts from benzyl azides and alkenes via a Cu^{II}-promoted double aza-[4 + 2] cycloaddition reactions (Scheme 1).



Scheme 1 Cu^{II}-Promoted multiple aza-[4 + 2] cycloaddition reactions.

Results and discussion

The reaction of 4-methylbenzyl azide (**1a**) and styrene (**2a**) in the presence of Cu(II) salt gave dihydro-1*H*-pyridoquinolinium salt

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†Electronic Supplementary Information (ESI) available: General experimental procedures, characterization details and ^1H and ^{13}C NMR spectra of new compounds. CCDC 1434531-1434533. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x.

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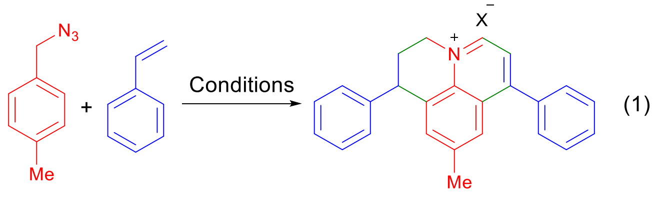
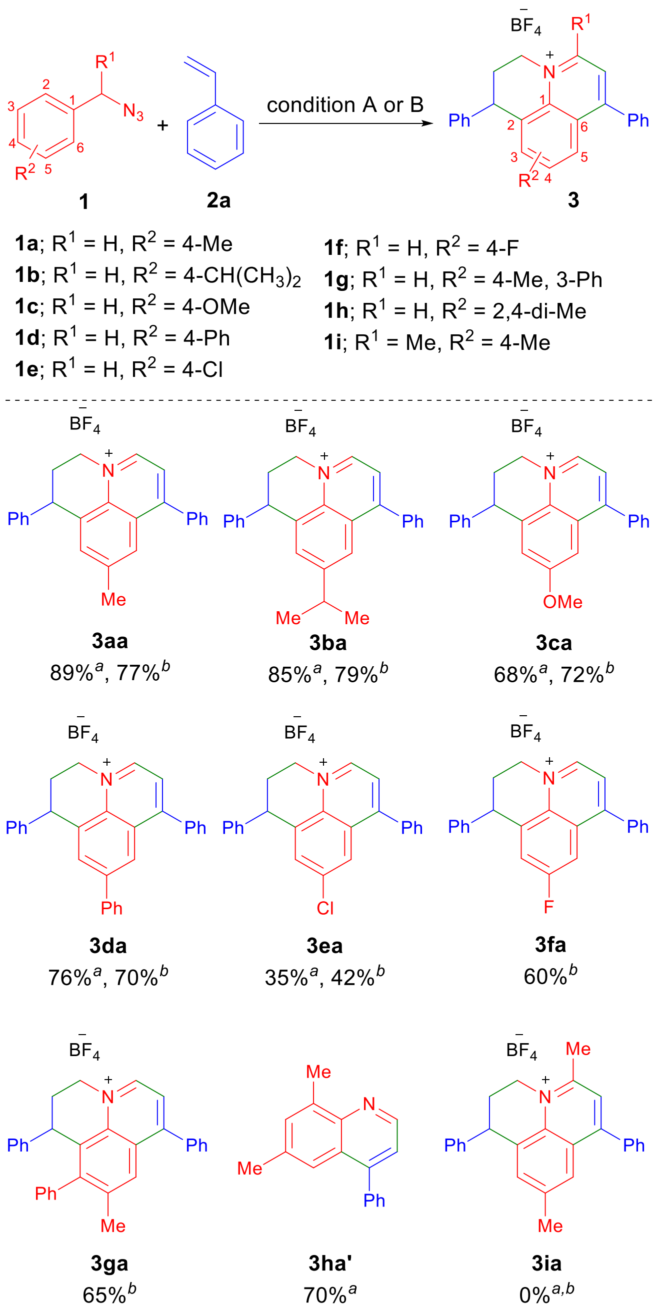
(**3aa**), which possesses an unusual fused tricyclic structure (eq 1) consisting of one *p*-toluidine, two styrene and two methylene units. In order to optimize the reaction, we performed a series of studies by varying the oxidant, solvent, the ratio of the substrates and the reaction temperature and time. After an extensive screening, we found that treatment of **1a** (0.64 mmol), **2a** (0.32 mmol), $CuSO_4$ (1.12 mmol), $NaBF_4$ (0.20 mmol), and H_2O (2.22 mmol) in CH_3NO_2 (3 mL) at 100 °C for 24 h gave the product **3aa** in 89% isolated yield and the reaction condition was denoted as condition A (see Supporting Information, Table S1 for the detailed optimization studies). In view of the excess amount of copper(II) salt used in condition A, we try to reduce the amount of copper salt by using various inorganic and organic oxidants along with catalytic amount of $CuSO_4$ in the reaction of **1a** and **2a** to give **3aa** (see Table S2). The results of this screening reveal that by using $(NH_4)_2S_2O_8$ as the oxidant, $CuSO_4$ can be reduced to a catalytic amount of 0.08 mmol, a decrease of 14 times compared to that of condition A. As a result, treatment of **1a** (0.64 mmol), **2a** (0.32 mmol), $CuSO_4$ (0.08 mmol), $(NH_4)_2S_2O_8$ (0.4 mmol), $NaBF_4$ (0.2 mmol), and H_2O (2.22 mmol) in $MeNO_2$ (3 mL) at 100 °C for 24 h afford **3aa** in 77% isolated yield. This optimized catalytic condition is referred as condition B. We also examined the effect of different metal salt on the product yield under reaction condition B; among the Fe^{III}-, Fe^{II}-, and In^{III}-salts tested, none of them is as active as $CuSO_4$.(Table S3).



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

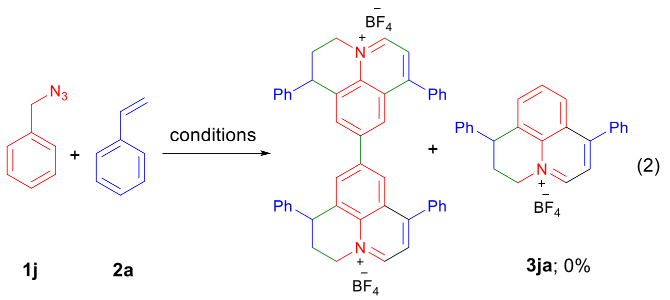
Next, we probe the scope of the copper promoted double aza-[4+2] cycloaddition reaction to form quinolinium salts. Various substituted benzyl azides (**1a-i**) were treated with styrene **2a** under both conditions A and B and their results are shown in Scheme 2. Thus, the reaction of *p*-iPr, *p*-OMe, *p*-Ph, *p*-Cl, *p*-F substituted benzyl azides (**1a-f**) with **2a** afforded the expected quinolinium salts **3ba-fa** in good yields. 3,4-Disubstituted benzyl azide **1g** was also effectively transformed into the respective quinolinium salt **3ga** in 65% yield. The reaction of *ortho* substituted benzyl azide **1h** gave a single [4 + 2] cycloaddition product, quinoline **3ha'**, presumably due to the presence of the *ortho* methyl group in **1h** that prevents a second [4 + 2] cycloaddition to give a quinolinium salt. Benzyl azide (**1i**) containing a methyl substituent at the benzylic position failed to undergo the expected [4 + 2] cycloaddition product (product **3ia**). Similarly, the benzylic azides containing strong electron withdrawing groups such as *p*-CF_3, *p*-NO_2, *p*-CN were ineffective under the reaction conditions.

The copper-catalyzed synthesis of quinolinium salts from benzyl azides were effective with different alkenes (Scheme 3). Thus the reaction of 4-Me-, and 4-Br substituted styrenes afforded products **3ab** and **3ac** in good yields. In addition to vinyl arenes, simple alkyl alkene **2d** also effective in the double aza-cycloaddition reaction to give **3ad** in 61% yield. Treatment of *β*-methylstyrene (**2e**) with **1a** gave the expected quinolinium salt **3ae** in 69% yield. Interestingly, the reaction of allylbenzene (**2f**) with **1a** gave quinolinium salt **3af'** in 74% yield with elimination of a benzyl group at the quinoline ring. The structure of **3af'** was confirmed by X-ray structure analysis.[10] Similarly, *α*-methylstyrene (**2g**) reacted with **1a** to give **3ag'** with the elimination of a methyl group.

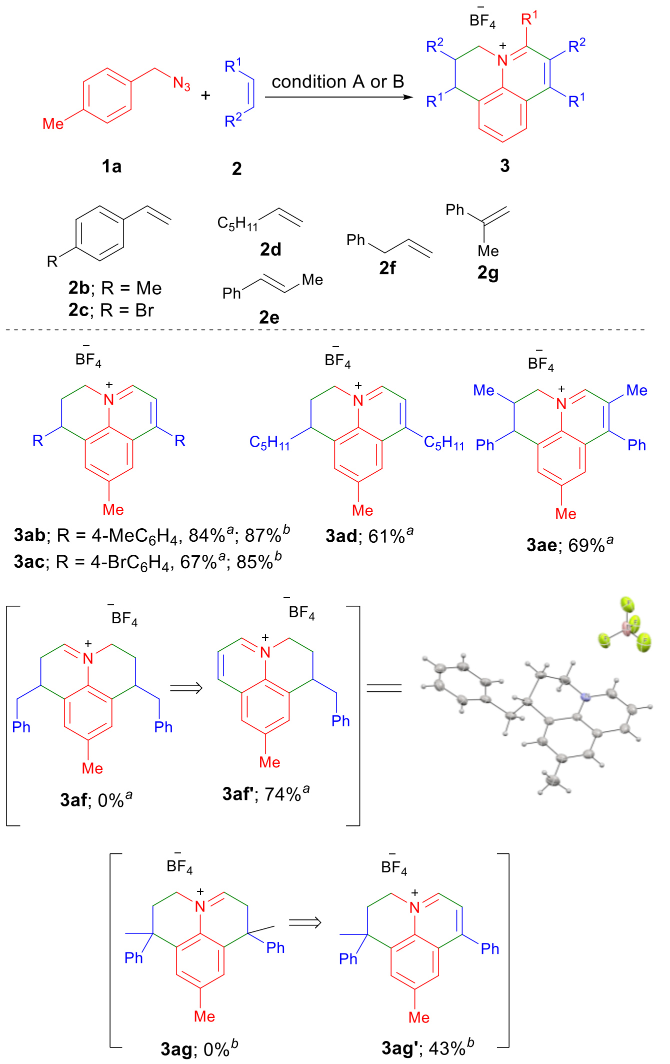


Scheme 2 Scope of benzyl azides in quinolinium salts formation. [a] Condition A: azide **1** (0.64 mmol), styrene **2a** (0.32 mmol), $CuSO_4$ (1.12 mmol), $NaBF_4$ (0.20 mmol), and H_2O (2.22 mmol) in $MeNO_2$ (3 mL) at 100 °C for 24 h. [b] Condition B: azide **1** (0.64 mmol), styrene **2a** (0.32 mmol), $CuSO_4$ (0.08 mmol), $NaBF_4$ (0.2 mmol), $(NH_4)_2S_2O_8$ (0.4 mmol), and H_2O (2.22 mmol) in $MeNO_2$ (3 mL) at 100 °C for 24 h. [c] Isolated yields are calculated based on **3a**, 0.16 mmol, as the upper limit (100%).

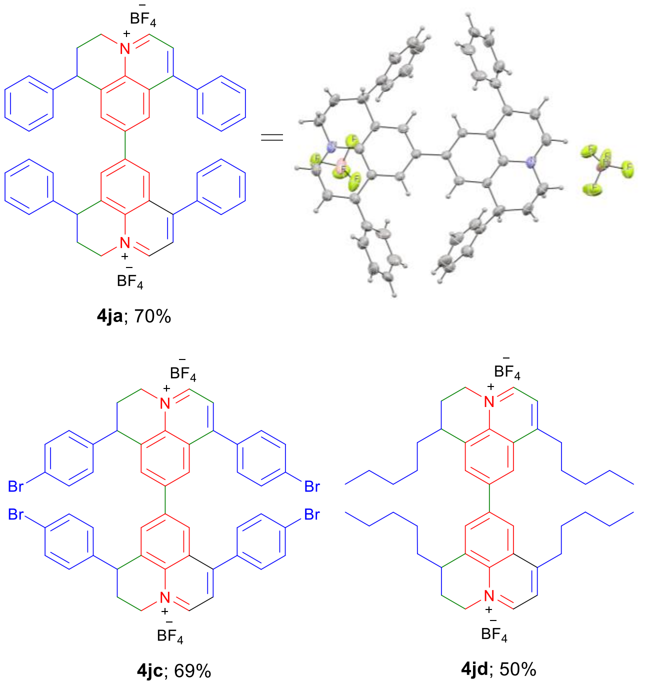
Interestingly, treatment of benzyl azide (**1j**) with **2a** under conditions A and B gave the biquinolinium salt product **4ja** in 5% yield (eq 2) instead of **3ja**. The structure of **4ja** was unambiguously confirmed by X-ray structure analysis.[10] To improve the yield of **4ja**, we conducted a series of optimization studies and found that treatment of **1j** (0.64 mmol), **2a** (0.32 mmol), and Cu(BF$_4$)$_2$·6H$_2$O (0.80 mmol) in CH$_3$NO$_2$ at 100 °C for 24 h offered **4ja** in 70% isolated yield (see Table S4). With the optimized conditions in hand, we tested the reaction of different alkenes with **2a** (Scheme 4). 4-Bromostyrene (**2c**) effectively underwent multiple cycloadditions to give **4jc** in 69% yield. Luckily, hept-1-ene (**2d**) also gave biquinolinium cation in 50% yield. However, the reaction of other alkenes **2f-g** with benzyl azide (**1j**) resulted in inseparable complex mixtures. Interestingly, the reaction of *ortho* substituted benzylic azide such as 2-methylbenzyl azide (**1k**) and styrene (**2a**) afforded 6,6'-biquinolinyl derivative **5ka** in 80% yield (Scheme 5). The structure was confirmed by its ^{1}H and ^{13}C NMR, HRMS, and single crystal X-ray analysis.[10] Similarly, 2-bromobenzylic azide **(1l)** gave product **5la** in 20% yield. Other vinylic substrates **2c** and **2d** reacted effectively with **1k** to give products **5kc** and **5kd** in 74 and 53% yields, respectively. The reaction also proceeded smoothly with β-methyl styrene (**2e**) giving **5ke** in 54% yield. On the other hand, the use of allylbenzene (**2f**) as olefin substrate for the reaction with **1k**, afforded product **5kf'** instead of **5kf** in 66% yield. The benzyl group in **2f** was cleaved during this copper-promoted reaction, similar to the reaction of **1a** with **2f** to give product **3af'** (Scheme 3).



4ja; 5% (2)

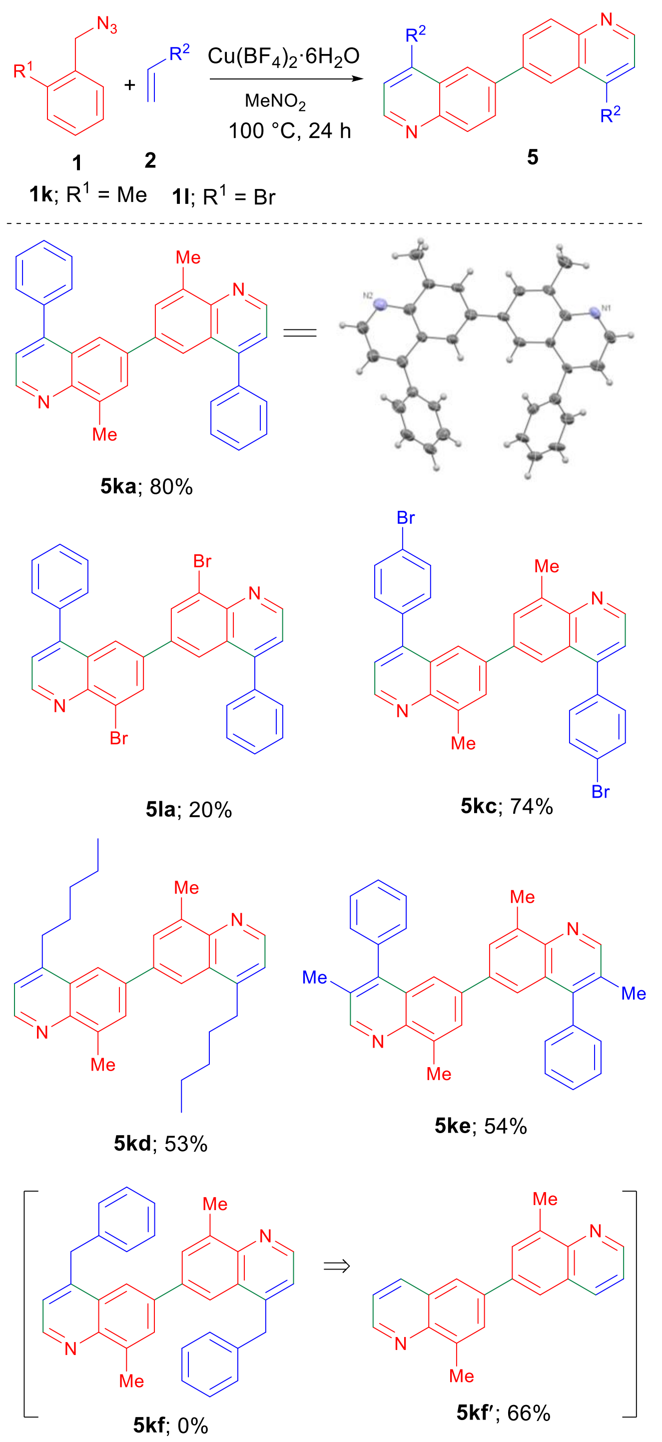


Scheme 3 Scope of alkenes in the quinolinium salts formation. ^{a} Condition B: azide **1a** (0.64 mmol), alkene **2** (0.32 mmol), CuSO$_4$ (0.08 mmol), NaBF$_4$ (0.2 mmol), (NH$_4$)$_2$S$_2$O$_8$ (0.4 mmol), and H$_2$O (2.22 mmol) in MeNO$_2$ (3 mL) at 100 °C for 24 h. ^{b} Condition A: azide **1a** (0.64 mmol), alkene **2** (0.32 mmol), CuSO$_4$ (1.12 mmol), NaBF$_4$ (0.2 mmol) and H$_2$O (2.22 mmol) in MeNO$_2$ (3 mL) at 100 °C for 24 h. ^{c} Isolated yields are given based on **2a** (0.16 mmol) as the limiting reagent.

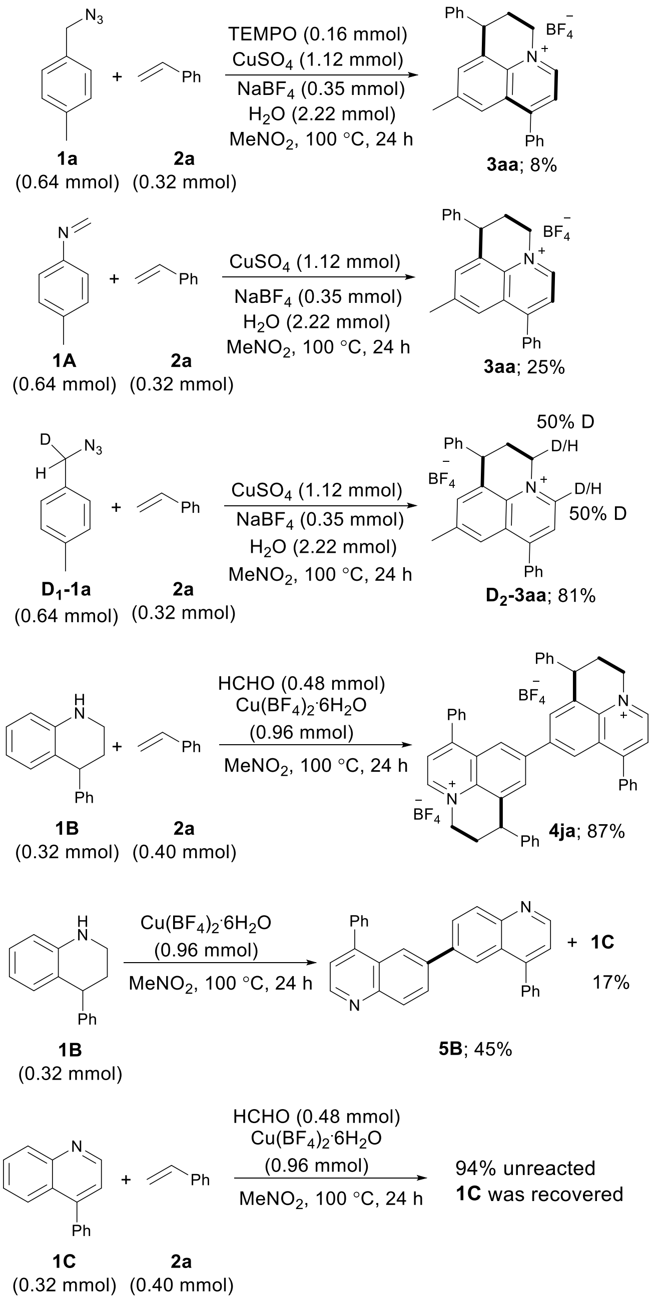


Scheme 4 Scope of alkenes in the synthesis of biquinolinium salts. ^{a} Reaction conditions: benzylic azide **1** (0.64 mmol), alkene **2** (0.32 mmol), and Cu(BF$_4$)$_2$·6H$_2$O (0.80 mmol) in MeNO$_2$ (3 mL) at 100 °C for 24 h. ^{b} Isolated yields calculated based on alkene (0.16 mmol) as the limit.

To understand the mechanism of this multiple aza-[4 + 2] cycloaddition reaction, several controlled experiments were performed as shown in Scheme 6. The reaction of **1a** and **2a** under reaction condition A, but with an extra addition of 1 equivalent of radical scavenger 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), is blocked nearly completely affording **3aa** in less than 10% yield. Next, we used pre-formed 4-methyl-*N*-methyleneaniline (**1A**) with **2a** under the reaction conditions to give **3aa** in 25% yield. The result indicates that *N*-aryl imine is a possible intermediate in situ formed from benzylic azides under the reaction conditions. Furthermore, we conducted the reaction of **D1-1a** with **2a** and the product **D$_2$-3aa** showed 50% deuterium incorporation at the two adjacent carbons connected to the quinoline nitrogen atom. The result suggests that both *N*-carbons of **3aa** are from the CH$_2$ group of **1a**. In addition, two molecules of **1a** are required for the formation of a molecule of **3aa**. Next, we treated 4-phenyl-1,2,3,4-tetrahydroquinoline (**1B**) with formaldehyde and styrene (**2a**) in the presence of Cu^{II}-salt to give product **4ja** in 87% yield. Similarly, treatment of **1B** in the presence of Cu(BF$_4$)$_2$·6H$_2$O gave 6,6'-biquinoline derivative **5B** in 45% yield along with 17% 4-phenylquinoline (**1C**). Finally, we treated **1C** with styrene and formaldehyde under the reaction conditions and neither dimer product (Schemes 4 and 5) nor quinolinium product (Schemes 2 and 3) was observed.



Scheme 5 Synthesis of substituted biquinolines. ^{a} Reaction conditions: benzylic azide **1** (0.64 mmol), alkene **2** (0.32 mmol), and Cu(BF$_4$)$_2$·6H$_2$O (0.80 mmol) in MeNO$_2$ (3 mL) at 100 °C for 24 h. ^{b} Isolated yields calculated based on alkene (0.16 mmol) as limiting reagent.



Scheme 6 Mechanistic studies.

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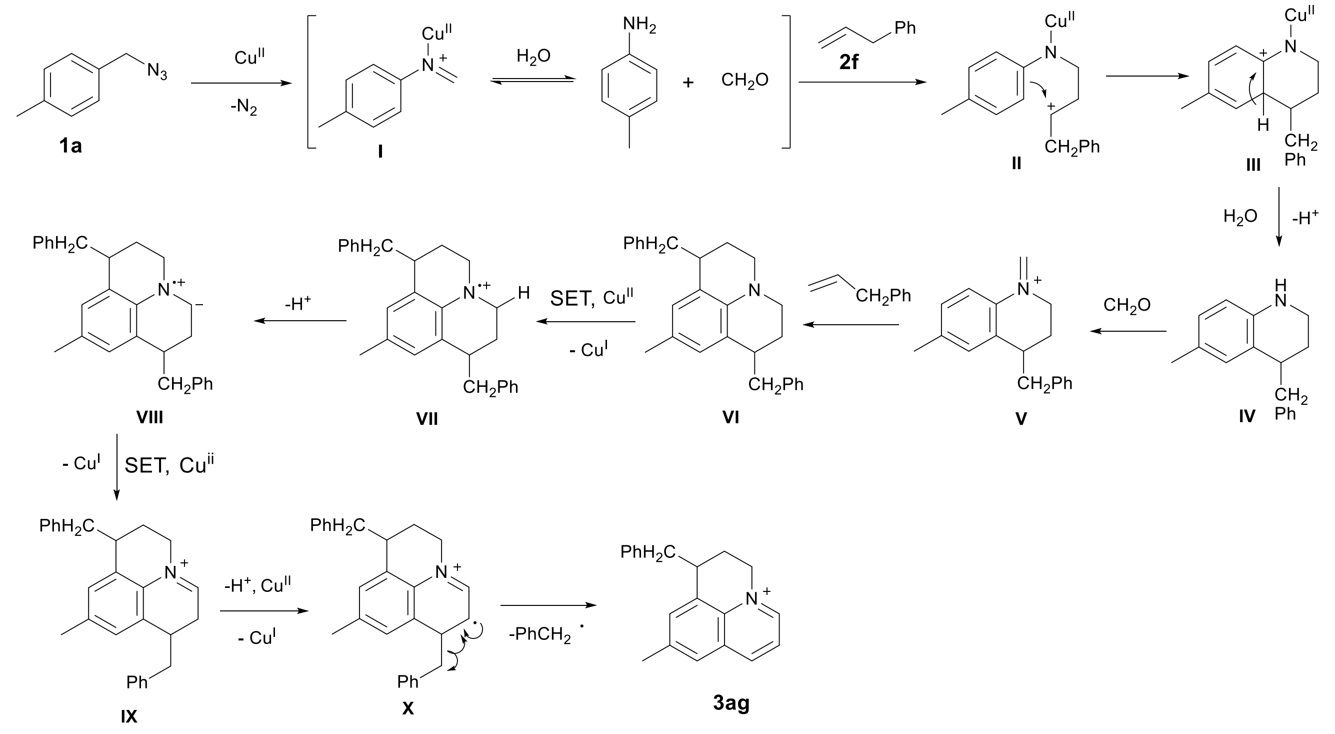
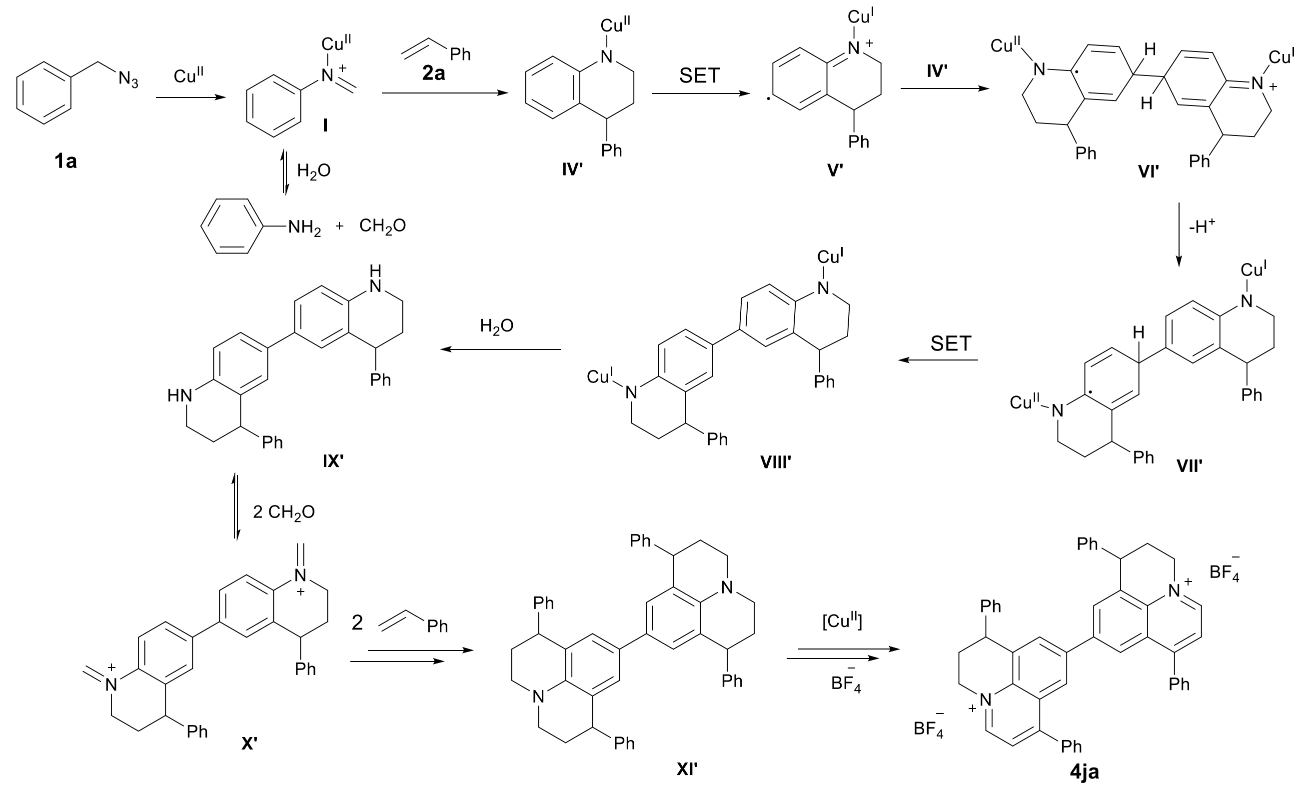
Based on the mechanistic studies and known literature a plausible mechanism for the multiple aza-[4 + 2] cycloaddition reaction using 4-methyl benzyl azide (**1a**) and allylbenzene (**2f**) is proposed as shown in Scheme 7. It is expected that



Scheme 7 Plausible Reaction Mechanism for the Synthesis of Quinolinium Cations.



Scheme 8 Possible Reaction Mechanism for the Formation of Biquinolinium Cations.

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4-methyl-*N*-methyleneaniline (**I**) is formed in situ from benzylic azide.[5,11] A dual [4 + 2] cycloaddition of in situ formed imine intermediate with alkene **2f** affords julolidine derivative **VI**.[4,12,13] Copper-mediated multiple single electron transfer (SET) oxidation process offers the final quinolinium cation. During the aromatization process of julolidine **VI**, a benzyl group instead of a hydrogen is eliminated. The cationic product **3ag** is stabilized by the non-nucleophilic anion BF_4.[6,14] The presence of H_2O is important for the present reaction. Because the cascade reaction involves a second aza-[4 + 2] cycloaddtion of imine cation **V** with alkene, the formation of this imine cation needs one molecule of HCHO, which is generated from the reaction of *N*-methyleneaniline **I** with H_2O.

A possible pathway for the formation of 6,6'-biquinolinium cation is depicted in Scheme 8. It follows similar steps shown in Scheme 7 up to the formation of 1,2,3,4-tetrahydro quinoline derivative **IV'**. Then oxidative dimerization of **IV'** to give dimer **IX'** likely proceeds via a series of Cu^{II} induced SET processes, nucleophilic addition, deprotonation and protonation.[15] Further condensation of **IX'** with formaldehyde released from the Cu^{II}-catalyzed decomposition of benzyl azide give di-iminium ions **X'**. Again, aza-cycloaddition reaction with **2a** offers **XI'**. Cu^{II}-oxidation via a SET process in the presence of stabilizing BF_4 anion provides the final product **4ja**. While the ortho substituted benzylic azides gave 6,6'-biquinoline product **5** (Scheme 5) from intermediate **IX'** through Cu^{II}-oxidation (Scheme 7).

The new quinolinium and biquinolinium salts exhibit strong photoluminescence properties. A preliminary studies were performed using **3aa** and **4ja** to understand the fluorescence properties in solution. As shown in Figure 1, the quinolinium salts **3aa** and **4ja** showed blue emissions. In addition, the fluorescence intensity of these compounds is very high prompting us to determine their fluorescence quantum yields (Φ_f) using 9,10-diphenylanthracene as the reference.[16] Surprisingly, Φ_f of >99% for **3aa** and 80% for **4ja** were observed in dichloromethane solution. It is worth to mention that this type of fluorescent molecules highly useful in nonlinear optical (NLO) applications, fluorescent stains for biological studies, particle size analysis and chemosensors.[7,17] Moreover, these compounds also can be potential candidates as dopants for efficient solution-process organic light emitting diodes (OLEDs).[18]

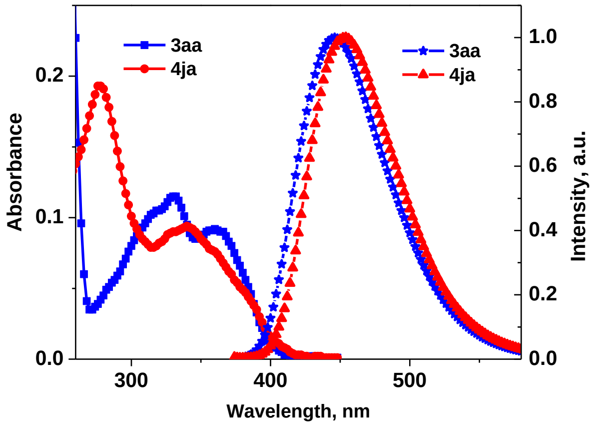

Figure 1. The absorption and emission spectra of compounds **3aa** and **4ja** at a concentration of 1×10^{-5} m in CH_2Cl_2.

Conclusions

In summary, we have successfully demonstrated a copper promoted multiple aza-[4 + 2] cycloaddition reactions between benzylic azides and alkenes. Three different types of products including quinolinium cations, biquinolinium cations, and biquinolines are formed from *para*-substituted, unsubstituted, and ortho-substituted benzylic azides, respectively. A wide range of functional groups on the benzylic azides can be tolerated. Moreover, high regioselectivity can be achieved with unsymmetrical alkenes. The reaction mechanism involves a Lewis acidic copper promoted rearrangement of benzylic azide to *N*-arylimine, followed by aza-[4 + 2] cycloaddition with alkene to provide 1,2,3,4-tetrahydroquinoline product, which further undergoes condensation with formaldehyde followed by another [4 + 2] cycloaddition with alkene to give the julolidine derivative. The mechanistic studies suggest that the oxidation of 1,2,3,4-tetrahydroquinoline to aromatic quinoline moiety goes through a copper mediated SET process. However, further detailed mechanistic studies are needed to elucidate the exact reaction mechanism, which is ongoing in our laboratory.

Experimental section

General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere on a dual-manifold Schlenk line and in oven-dried glassware. All reagents were purchased commercially and used without further purification. Reagent grade nitromethane was used as such from Alfa Aesar without further purification. NMR spectra (^1H and ^{13}C) were measured on a Bruker Avance III 400 MHz spectrometer. High resolution (HR) mass data were measured with a JEOL JMS-700 spectrometer. Infrared spectra were recorded on a HORIBA FT-IR 720 using KBr plates. UV-visible absorption and Fluorescence spectra were measured using Hitachi U-3300

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spectrophotometer and Hitachi F-7000 spectrophotometer, respectively.

General procedure for the synthesis of substituted benzylic azides[5b]

Substituted benzyl bromide (1.0 equiv) and sodium azide (1.5 equiv) were dissolved in DMF (2.0 mL/mmol) and stirred at room temperature for overnight. At the end of the reaction, the mixture was diluted with water and extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$ and concentrated in vacuo and the crude product was purified by a silica gel column (*n*-hexane/EtOAc, 90:10) to afford the substituted benzyl azide.

General procedure for the synthesis of quinolinium salts 3

***Condition A**:* A sealed tube that contained $CuSO_4$ (178 mg, 1.12 mmol) and $NaBF_4$ (24 mg, 0.2 mmol) was evacuated and purged with nitrogen gas three times. $MeNO_2$ (2.0 mL) was then added to the tube, and the suspension was stirred for 2 min at ambient temperature. Then, para-substituted benzylic azide **1** (0.64 mmol), alkene **2** (0.32 mmol), H_2O (40 μL, 2.22 mmol), and additional $MeNO_2$ (1 mL) were added to the system via syringe sequentially. The reaction was stirred at 100°C for 24 h. At the end of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a Celite pad, and washed three times with CH_2Cl_2 (3 × 20 mL). The combined filtrate was concentrated in vacuo and the mixture was purified by a silica gel column using DCM/MeOH (95:5) as eluent to afford the desired pure product **3**.

***Condition B**:* A sealed tube that contained $CuSO_4$ (13 mg, 0.080 mmol), $NaBF_4$ (24 mg, 0.20 mmol) and $(NH_4)_2S_2O_8$ (92 mg, 0.40 mmol) was evacuated and purged with nitrogen gas three times. $MeNO_2$ (2.0 mL) was then added to the tube, and the suspension was stirred for 2 min at ambient temperature. Then, para-substituted benzylic azide **1** (0.64 mmol), alkene **2** (0.32 mmol), H_2O (40 μL, 2.22 mmol) and additional $MeNO_2$ (1 mL) were added to the system via syringe sequentially. The reaction was stirred at 100°C for 24 h. At the end of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a Celite pad, and washed three times with CH_2Cl_2 (3 × 20 mL). The combined filtrate was concentrated in vacuo and the mixture was purified by a silica gel column using DCM/MeOH (95:5) as eluent to afford the desired pure product **3**.

General procedure for the synthesis of biquinolinium salts 4

A sealed tube containing $Cu(BF_4)_2 \cdot 6H_2O$ (276 mg, 0.80 mmol) was dissolved in $MeNO_2$ (2 mL) under nitrogen gas. Then, unsubstituted benzylic azide **1** (0.64 mmol), alkene **2** (0.32 mmol) and additional $MeNO_2$ (1 mL) were added to the system via syringe sequentially. The reaction was allowed to stir at 100 °C for 24 h. When the reaction was completed, the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a Celite pad and washed several times with CH_2Cl_2 (50 mL). The combined filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel column using DCM/MeOH (95:5) as eluent to afford the desired pure product **4**.

General procedure for the synthesis of substituted biquinolines 5

A sealed tube containing $Cu(BF_4)_2.6H_2O$ (276 mg, 0.80 mmol) was dissolved in $MeNO_2$ (2 mL) under nitrogen gas. Then, ortho-substituted benzyl azide **1** (0.64 mmol), alkene **2** (0.32 mmol) and additional $MeNO_2$ (1 mL) were added to the system via syringe sequentially. The reaction was allowed to stir at 100 °C for 24 h. When the reaction was completed, the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a Celite pad and washed several times with CH_2Cl_2 (50 mL). The combined filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel column using *n*-hexane/ethyl acetate (95:5) as eluent to afford the desired pure product **5**.

Acknowledgements

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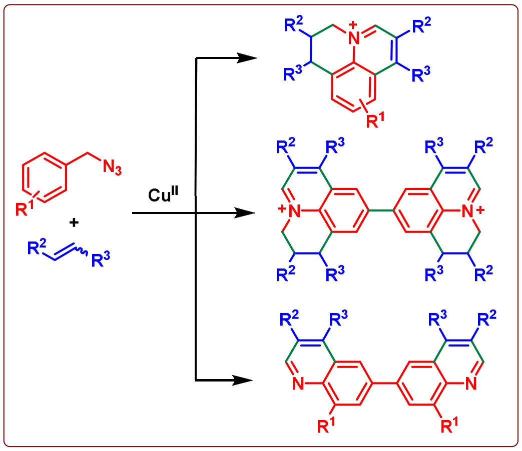
Graphical Abstract:

A Concise Synthesis of Quinolinium, and Biquinolinium Salts and Biquinolines from Benzylic Azides and Alkenes Promoted by Copper(II) Species

Wei-Chen Chen, Parthasarathy Gandeepan, Chia-Hung Tsai, Ching-Zong Luo, Pachaiyappan Rajamalli and Chien-Hong Cheng*



A copper promoted multiple aza-[4 + 2] cycloaddition reactions between benzylic azides and alkenes are described. Four different products including quinolinium and biquinolinium cations, and biquinolines and quinolines can be formed depending on the substituents on the benzylic azides.