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FULL PAPER

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A Metal- and Azide-free Oxidative Coupling Reaction for the Synthesis of [1,2,3]Triazolo[1,5-a]quinolines and their Application to Construct C-C and C-P Bonds, 2-Cyclopropylquinolines and Imidazo[1,5-a]quinolines

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Abstract. An iodine-promoted one-pot cascade oxidative annulation reaction has been developed for the synthesis of [1,2,3]triazolo[1,5-a]quinolines from methyl azaarenes and *N*-tosylhydrazines. The reaction has a broad substrate scope and can be easily scaled up to gram-scale. 1,2,3-Triazoles are an important skeletal structure for the construction of C-C and C-P bonds, 2-cyclopropylquinolines and imidazo[1,5-a]quinolines, for which different synthetic applications were explored.

Keywords: Metal- and azide-free; [1,2,3]Triazolo[1,5-a]quinolines; Oxidative functionalization; Synthetic application.

Introduction

Triazole moieties have gained special attention as important five-membered heterocycles due to their widespread applications in chemistry, biology, and materials science.[1] More specifically, 1,2,3-triazole derivatives are utilized in chemical biology research and drug discovery.[2] In particular, fused 1,2,3-triazoles are important skeletal structures with a broad spectrum of biological properties, such as anti-carcinogenic, anti-photoaging, and anti-diabetic activity (Figue 1).[3]

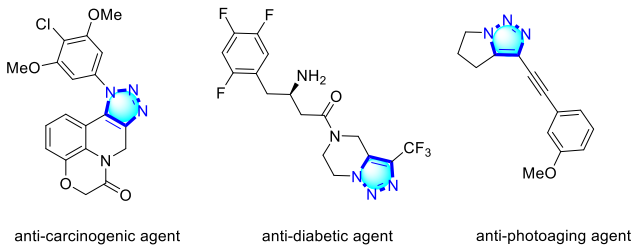

Figure 1. Some fused 1,2,3-triazole derivatives with biological activities.

The traditional method to synthesize 1,2,3-triazoles is through the 1,3-dipolar cycloaddition of azides and alkynes, also described as the Huisgen reaction.[4] However, the low efficiency and poor regioselectivity of this approach greatly limit its widespread application. The development of the copper(I)-catalyzed azide–alkyne cycloaddition reaction (CuAAC) to obtain disubstituted 1,2,3-triazoles has represented a remarkable advance in triazole synthesis, and it has become a premier example of "click chemistry" reaction.[5] Recently, stable and reactive *N*-tosylhydrazines reagents have been widely used in azide-free 1,2,3-triazoles synthesis. For example, Zhang and co-workers successfully constructed 1,2,3-triazoles from *N*-tosylhydrazines and amines through a copper-mediated reaction (Scheme 1a).[6] Moreover, a metal- and azide-free strategy for the synthesis of 1,2,3-triazoles has been reported by Wan's group, using molecular iodine as the only catalyst and offering a new perspective for the synthesis of fused 1,2,3-triazoles (Scheme 1b).[7]

Classical protocols for the synthesis of fused 1,2,3-triazoles mainly rely on the metal-catalyzed intramolecular 1,3-dipolar cycloaddition of azides with alkynes and the metal-catalyzed intramolecular C−C coupling reaction of triazoles with aryl halides (Scheme 1c).[8] In addition, novel methods for the synthesis of fused 1,2,3-triazoles have been reported to

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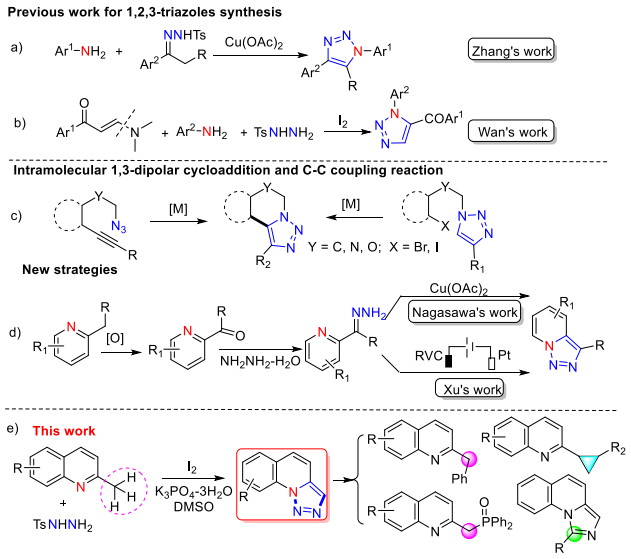
avoid the use of explosive and toxic organic materials such as sodium azides and azide derivatives.[9] In 2014, the Nagasawa group developed an efficient method for the preparation of [1,2,3]triazolo[1,5-a]pyridines through copper(II)-catalyzed oxidative N-N bond formation using 2-pyridine ketone hydrazones (Scheme 1d).[10] However, a metal catalyst is still unavoidable and the starting materials need to be firstly fabricated. Recently, the elegant electrochemical dehydrogenative cyclization of hydrazones of 2-acylpyridines for the synthesis of [1,2,3]triazolo[1,5-a]pyridines was reported by Xu's group (Scheme 1d).[11] This strategy was conducted under mild conditions without oxidation reagents and transition-metal catalysts.



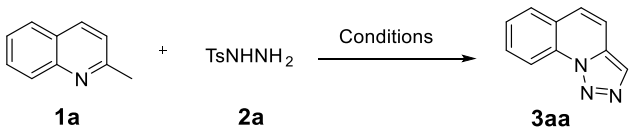
Scheme 1. Strategies for the synthesis of fused 1,2,3-triazoles.

1,2,3-Triazoles play an important role as key intermediates in organic synthesis.[12] They are regarded as "masked" diazo compounds and are widely utilized in cross-coupling reactions for C-C , C-X and C-P bonds formation.[13] Hence, it is essential to develop an effective method for the synthesis of fused 1,2,3-triazoles under metal- and azide-free conditions from simple substrates. Inspired by the preceding works,[14] we hypothesized that I_2 might oxidize the sp^3 C-H bond of 2-methyl-azaheteroarenes, which followed by annulation with *N*-tosylhydrazines, would deliver fused 1,2,3-triazoles. The key steps involve molecular iodine as the activator for the tandem formation of the C-N bond followed by a formal [3+2] cycloaddition to afford the desired fused 1,2,3-triazoles (Scheme 1e).

Results and Discussion

According to the description above, 2-methyl quinoline (**1a**) and $TsNHNH_2$ (**2a**) were used as the model substrates for the optimization of the conditions (Table 1). The desired product **3aa** was obtained with a 50% yield in the presence of I_2 (1.5 equiv.) and K_2CO_3 (2.0 equiv.) at 100°C in DMSO under air (Table 1, entry 1). Next, a series of bases were screened for this reaction, such as Cs_2CO_3, Na_2CO_3, $NaHCO_3$, NaOH, and K_3PO_4-$3H_2O$ (Table 1, entries 2-6). It was found that K_3PO_4-$3H_2O$ was the most effective additive and increased the product yield to 62% (Table 1, entry 6). The yield was as high as 75% when the dose of I_2 was increased to 150–300 mol % (Table 1, entries 7–9). Further optimization of the reaction temperature revealed that 110°C was optimal for the reaction (Table 1, entries 10-13). After optimization of the dosage of K_3PO_4-$3H_2O$ (Table 1, entries 14-16), the desired product (**3aa**) was obtained in an 83% yield using 3.0 equivalents of K_3PO_4-$3H_2O$ (Table 1, entry 14).

Table 1. Optimization Studies for the Preparation of **3aa**[a].



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

Entry	I_2 (equiv.)	Temp. (°C)	Base (equiv.)	Yield (%)[b]
1	1.5	100	K_2CO_3 (2.0)	50
2	1.5	100	Cs_2CO_3 (2.0)	54
3	1.5	100	Na_2CO_3 (2.0)	48
4	1.5	100	NaOH (2.0)	43
5	1.5	100	$NaHCO_3$ (2.0)	54
6	1.5	100	K_3PO_4-$3H_2O$ (2.0)	62
7	2.0	100	K_3PO_4-$3H_2O$ (2.0)	69
8	2.5	100	K_3PO_4-$3H_2O$ (2.0)	75 (73)[c]
9	3.0	100	K_3PO_4-$3H_2O$ (2.0)	72
10	2.5	80	K_3PO_4-$3H_2O$ (2.0)	54
11	2.5	90	K_3PO_4-$3H_2O$ (2.0)	63
12	2.5	110	K_3PO_4-$3H_2O$ (2.0)	78
13	2.5	120	K_3PO_4-$3H_2O$ (2.0)	75
14	2.5	110	K_3PO_4-$3H_2O$ (3.0)	83
15	2.5	110	K_3PO_4-$3H_2O$ (4.0)	79
16	2.5	110	K_3PO_4-$3H_2O$ (5.0)	78

[a] Reaction conditions: 2-methyl quinoline **1a** (0.3 mmol) and I_2 were heated in DMSO (3 mL) for 4-6 h, followed by $TsNHNH_2$ (0.36 mmol) and additive were added for another 5 h. [b] Isolated yields. [c] K_3PO_4 was used.

A series of 2-methyl quinoline derivatives were examined to assess the generality of this method and to evaluate the electronic influence of the aromatic ring substituents. As shown in Scheme 2, while the quinoline rings bearing electron-donating groups (e.g., 7-Me, 6,8-Me_2, 5-OMe, 7-OMe 7-OEt), the corresponding products **3ba-3fa** were obtained in moderate to good yields (54-78%). The electron-withdrawing groups, such as F, Cl, Br, CO_2Me, CO_2Et, and $CO_2CH(CH_3)_2$, could slightly increase the reactivity (73-80%, **3ga-3na**). Furthermore, the 4-phenyl substituted substrate (**1o**) also reacted with $TsNHNH_2$ (**2**) to give satisfying results (68%, **3oa**). Moreover, two heteroatom containing substrates, 2-methylquinoxaline (**1p**) and 2-methyl-1,8-

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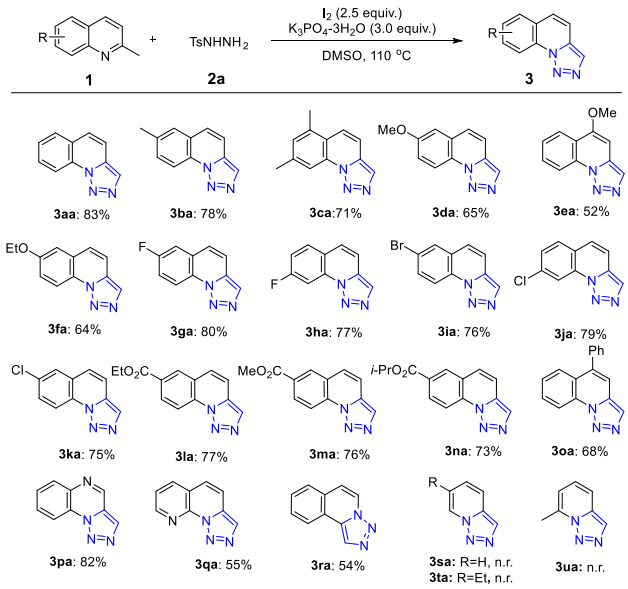
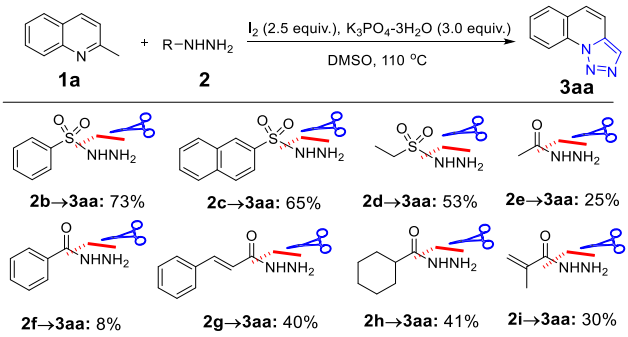
naphthyridine (**1q**) reacted with $TsNHNH_2$ (**2**) to generate the desired products **3pa** and **3qa** in 82% and 55% yields, respectively. Last, 1-methylisoquinoline **1r** gave the corresponding products **3ra** in 54% yield. However, 2-methyl pyridine (**2s**), 2-methyl-4-ethyl pyridine (**2t**), and 2,6-dimethyl pyridine (**2u**) were not suitable for the reaction, probably due to the difficulty of methyl pyridines to generate the intermediate pyridine-2-carbaldehyde.



Scheme 2. Substrate scope of substituted 2-methyl quinolines and derivatives. Reaction conditions: **1** (0.3 mmol), I_2 (0.75 mmol) in DMSO (3 mL) at 110 °C for 4-6 h, then **2a** (0.36 mmol) and K_3PO_4-$3H_2O$ (0.9 mmol) were added and stirred at 110 °C until the disappearance of **2a** (monitored by TLC). Isolated yields provided. N.r. = no reaction.

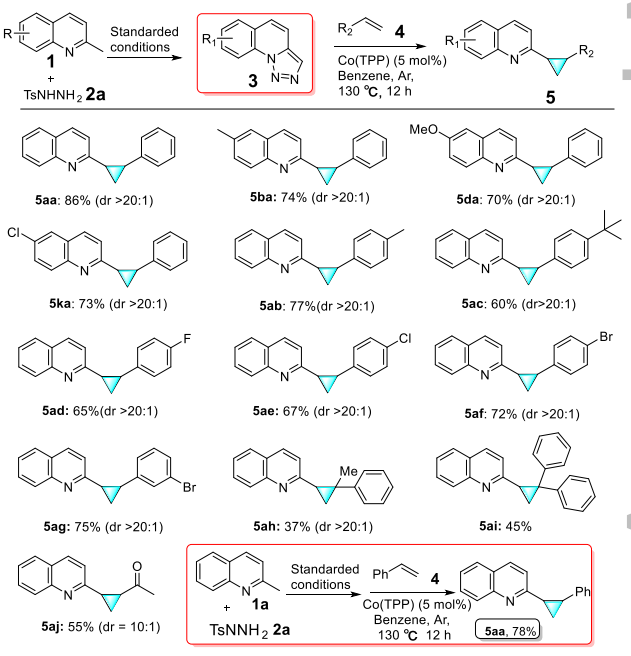
Next, a series of acylhydrazine derivatives were examined (Scheme 3). It was found that various sulfonylhydrazide and acylhydrazine substrates were all suitable for the reaction to afford the same product **3aa**. Aromatic sulfonylhydrazides, such as benzenesulfonohydrazide **2b** and naphthalene-2-sulfonohydrazide **2c**, successfully reacted with 2-methyl quinoline to deliver the product in a good yield. Aliphatic ethanesulfonohydrazide **2d** could only afford the product in a moderate yield. Additionally, aromatic, aliphatic, or conjugated acylhydrazines substrates **2e-2i** only gave the end product in a low yield.

Considering the unique reactivity of 1,2,3-triazole moieties for various efficient synthetic transformations,[15] the potential application of the [1,2,3]triazolo[1,5-a]quinolines was investigated. First, a concise route for the formal synthesis of 2-cyclopropylquinoline derivatives via the Cobalt(II) tetraphenylporphyrin (Co(TPP)) catalyzed cyclization of 1,2,3-triazoles with alkenes is provided in Scheme 4. A series of 2-cyclopropylquinoline derivatives, in



Scheme 3. Substrate scope of substituted sulfonylhydrazide derivatives. Reaction conditions: **1a** (0.3 mmol), I_2 (0.75 mmol) in DMSO (3 mL) at 110 °C for 4-6 h, then **2** (0.36 mmol) and K_3PO_4-$3H_2O$ (0.9 mmol) were added and, stirred at 110 °C until the disappearance of **2** (monitored by TLC). Isolated yields provided.

which aromatic rings are substituted with diverse groups, were synthesized using Co(II)-based metalloradical activation for cyclopropanation. Notably, the di-substituted olefin substrates were also compatible with the reaction (**5ah-5ai**). Following the success of the formation of 2-cyclopropylquinolines from [1,2,3]triazolo[1,5-a]quinolines and alkene, the possibility of performing a one-pot transformation of methyl azaarenes, alkene, and *N*-tosylhydrazine was explored. Specifically, the 2-(2-phenylcyclopropyl)quinoline (**5aa**) could be obtained in good yield via a one-pot tandem method.



Scheme 4. Synthesis of 2-cyclopropylquinoline derivatives. Reaction conditions: 3 (0.2 mmol), Co(TPP) (5 mol%) and 4 (0.4 mmol) in benzene (2 mL) at 130 °C under argon atmosphere for 12h. Isolated yields provided. dr = diastereomeric ratio.

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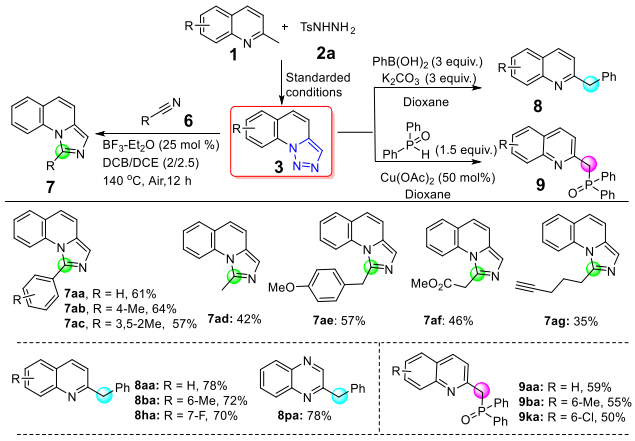
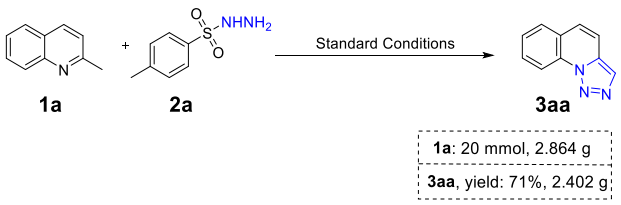
To further explore the application of 1,2,3-triazolo[1,5-a]quinolines, the construction of imidazoquinoline through denitrogenative transannulation of quinolinetriazoles with nitriles using $BF_3{\cdot}Et_2O$ as catalyst was analyzed (Scheme 5). Different acyclic and aromatic 1-substituted imidazo[1,5-a]quinolines were obtained from the corresponding alkyl and aryl substituted nitriles in high yields (**7aa-7ag**). In addition, quinolinetriazoles can be utilized as robust building blocks to access α-secondary quinoline via a denitrogenative C−C or C-P cross-coupling reaction. The reaction of 1,2,3-triazolo[1,5-a]quinolines (**3**) with phenylboronic acid could smoothly produce the 2-benzylquinoline derivatives (**8**) in good yields (70-78%). Moreover, 1,2,3-triazolo[1,5-a]quinolines (**3**) were successfully applied to the synthesis of 2-picolylphosphoryl derivatives (**9**) through a copper-catalyzed denitrogenative C-P coupling reaction with diphenylphosphine oxide. These results demonstrated that quinolinetriazole could be applied for structural modification by the incorporation of quinoline units.



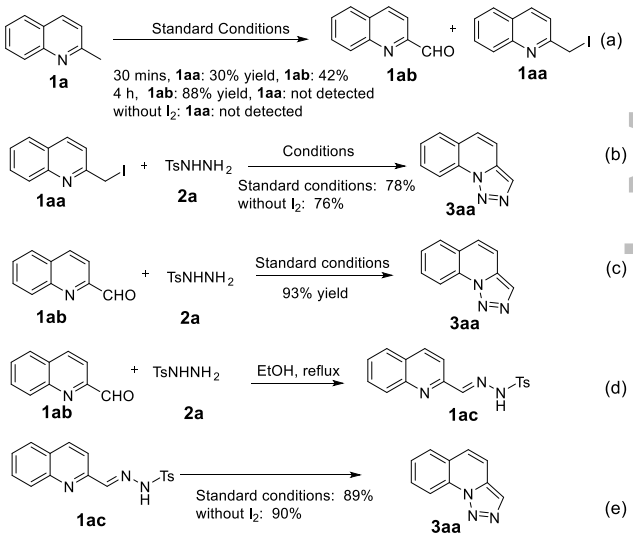
Scheme 5. Transformations of [1,2,3]triazolo[1,5-a]quinolines. Isolated yields provided.

In order to show the potential application of this synthetic route, the reaction was performed on a gram scale with 20 mmol of starting material **1a** (2.864 g), giving the desired product **3aa** (2.402 g) in a 71% yield (Scheme 6). This promising result presents the possibility for large-scale applications.



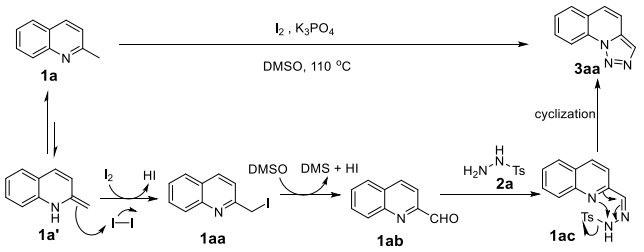
Scheme 6. Scale-up of the reaction.

To gain further insight into the reaction mechanism, control experiments were performed as illustrated in Scheme 7. It was found that 2-methylquinoline (**1a**) was converted into quinoline-2-carbaldehyde (**1ab**) in an 88 % yield in the presence of I_2 and DMSO at 110 °C for 4 h, whereas this conversion could not proceed without I_2 (Scheme 7a). 2-(Iodomethyl)quinoline (**1aa**) was detected in a 30% yield as the transformation proceeded for 30 min, while quinolin-2-carboxaldehyde (**1ab**) was detected in a 42% yield. Furthermore, 2-(iodomethyl) quinoline (**1aa**) reacted with $TsNHNH_2$ (**2**) to obtain the product (**3aa**) in good yield with or without I_2 (Scheme 7b). The reaction of quinolin-2-carboxaldehyde (**1ab**) with $TsNHNH_2$ (**2**) also proceeded smoothly with an excellent yield (Scheme 7c). These results demonstrate that quinoline-2-carbaldehyde (**1ab**) and 2-(iodomethyl)quinoline (**1aa**) may be key intermediates in the transformation. Subsequently, the reaction between quinolin-2-carboxaldehyde (**1ab**) and $TsNHNH_2$ (**2**) in EtOH with reflux was examined to dismiss the possibility of the transformation from **1ab** to **3aa** (Scheme 7d). The reaction could afford product **1ac**, which could further transform into product **3aa** under standard conditions or without I_2 (Scheme 7e). These results indicated that **1ac** also played an important role in the reaction as the potential intermediate.



Scheme 7. Control Experiments.

Based on the results and previous literature reports, a plausible mechanism was proposed as shown in Scheme 8 (with **3aa** as an example). Initially, 2-methylpyridine (**1a**) undergoes an iodination reaction with I_2 to afford the intermediate 2-(iodomethyl)quinoline (**1aa**). Subsequently, 2-(iodomethyl)quinoline (**1aa**) is oxidized by DMSO to generate quinoline-2-carbaldehyde (**1ab**) via a Kornblum oxidation. Next, the condensation reaction between quinoline-2-carbaldehyde (**1ab**) and $TsNHNH_2$ (**2**) leads to the intermediate **1ac**, which is responsible for the annulation and oxidation process that results in product **3aa**.



Scheme 8. Plausible mechanism.

Conclusion

A novel and efficient molecular iodine-mediated coupling cyclization reaction for the synthesis of [1,2,3]triazolo[1,5-a]quinolines from methyl azaarenes and *N*-tosylhydrazines was developed. This method features meta- and azide-free conditions and has a broad substrate scope and high functional group tolerance. The protocol provides easy access to diversely functionalized [1,2,3]triazolo[1,5-a]quinoline derivatives and easy scale-up. Moreover, several synthetic applications of this methodology were explored to construct C-C and C-P bonds, 2-cyclopropylquinolines and imidazo[1,5-a]quinolines. Future research directions include the exploration of the further application of the reaction.

Experimental Section

General procedure for the preparation of [1,2,3]triazolo[1,5-a]quinolines Compounds (3): A 25 mL pressure vial was charged with 2-methylquinoline (**1**) (1.0 equiv.) and I_2 (2.5 equiv.) in DMSO (3.0 mL). The vial was sealed and the resulting mixture was stirred at 110 °C for 4-6 h under an air atmosphere, after disappearance of the reactant (monitored by TLC), then $TsNHNH_2$ (**2a**) (1.2 equiv.) and K_3PO_4-$3H_2O$ (3.0 equiv.) were added at 110 °C for another 5 h. After the reaction completed, and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **3**.

General procedure for the preparation of 2-cyclopropylquinoline Compounds (5): A 2-neck 25 mL pressure vial was charged with [1,2,3]triazolo[1,5-a]quinolines (**3**) (1.0 equiv.), Co(TPP) (5 mol%), styrenes (**4**) (2.0 equiv.), and benzene (2.0 mL) under an argon atmosphere. The vial was sealed and the resulting mixture was stirred at 130 °C for 12 h. After the reaction completed (monitored by TLC), benzene was removed under reduced pressure and chromatographic separation with silica gel to yield the corresponding product **5**.

General procedure for the preparation of 1-substitutedimidazo[1,5-a]quinoline Compounds (7): A 2-neck 25 mL pressure vial was charged with [1,2,3]triazolo[1,5-a]quinolines (**3**) (1.0 equiv.), nitriles (**6**) (2 equiv.), $BF_3{\cdot}Et_2O$ (25 mol%), dichlorobenzene (DCB) (0.2 mL) and dichloroethane (DCE) (0.25 mL). The vial was sealed and the resulting mixture was stirred at 140 °C for 12 h under an air atmosphere. After the reaction completed (monitored by TLC), solvent was removed under reduced pressure and then added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The combined organic phase was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **7**.

General procedure for the preparation of 2-benzylquinoline Compounds (8): A 2-neck 25 mL pressure vial was charged with [1,2,3]triazolo[1,5-a]quinolines (**3**) (1.0 equiv.), phenylboronic acid (3 equiv.), K_2CO_3 (3 equiv.) and dioxane (1.5 mL). The vial was sealed and the resulting mixture was stirred at 150 °C for 24 h under an argon atmosphere. After the reaction completed (monitored by TLC), solvent was removed under reduced pressure and then added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The combined organic phase was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **8**.

General procedure for the preparation of 2-picolylphosphoryl Compounds (9): A 2-neck 25 mL pressure vial was charged with [1,2,3]triazolo[1,5-a]quinolines (**3**) (1.0 equiv.), diphenylphosphine oxide (1.5 equiv.), $Cu(OAc)_2$ (50 mol %) and dioxane (1.5 mL). The vial was sealed and the resulting mixture was stirred at 100 °C for 24 h under an argon atmosphere. After the reaction completed (monitored by TLC), solvent was removed under reduced pressure and then added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The combined organic phase was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **9**.

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FULL PAPER

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