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Advanced Synthesis & Catalysis

High-Valent Pentamethylcyclopentadienylcobalt(III) or -iridium(III)-Catalyzed C–H Annulation with Alkynes: Synthesis of Heterocyclic Quaternary Ammonium Salts

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Abstract: Nine types of diversely fused heterocyclic quaternary ammonium salts were constructed through an oxidative C–H annulation reaction. Both high-valent pentamethylcyclopentadienylcobalt(III) and pentamethylcyclopentadienyliridium(III) were found to be effective as catalyst for this reaction. Broad substrate scope and good functional group tolerance were observed.

Keywords: C–H activation; cobalt; heterocycles; iridium; oxidation

Heterocyclic quaternary ammonium salts are prevalent in functional molecules,[1] as represented by their wide occurrence in numerous natural products, displaying diverse bioactivities[2] (Figure 1). Conventional approaches for their synthesis suffer from the lack of generality, the necessity for pre-functionalization of the starting materials, and therefore the need of lengthy synthetic operations.[3]

Recently, in line with the increasing concerns of sustainable chemistry and green chemistry,[4] transition metal-catalyzed C–H activation reactions have matured as viable tools for atom- and step-economical organic syntheses.[5] In this regard, largely taking the advantage of high reactivities of noble transition metals, heterocycle syntheses through direct C–H annulations reaction are well developed.[6] This is appealing in the field of medicinal chemistry, wherein the rapid and straightforward assembly of a small molecule library with molecular complexity and diversity is crucial for lead discovery and optimization. Specifically, for the construction of heterocyclic quaternary ammonium salts, high-valent Cp*Rh(III)[7] is one of the major players with one exception of using Ru(II)[8] and Cp*Ir(III)[9] (Figure 2). To realize economically superior organic syntheses, there is a growing tendency of using earth-abundant and therefore less expensive first-row transition metals (for instance, iron, cobalt, nickel, and copper) in catalysis.[10] This is also appealing considering that new reactivities might be uncovered. Since the seminal works by Kanai,[11] high-valent Cp*Co(III) complexes have recently gained much attention as an effective catalyst for C–H activation reactions.[12] It is interesting to note that compared to its congener Cp*Rh(III), Cp*Co(III)

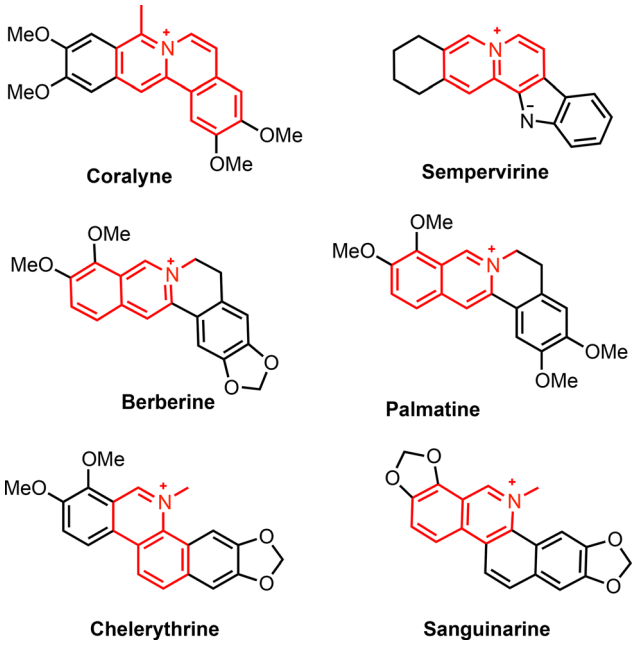


Figure 1. Representative bioactive heterocyclic quaternary ammonium salts in natural products.

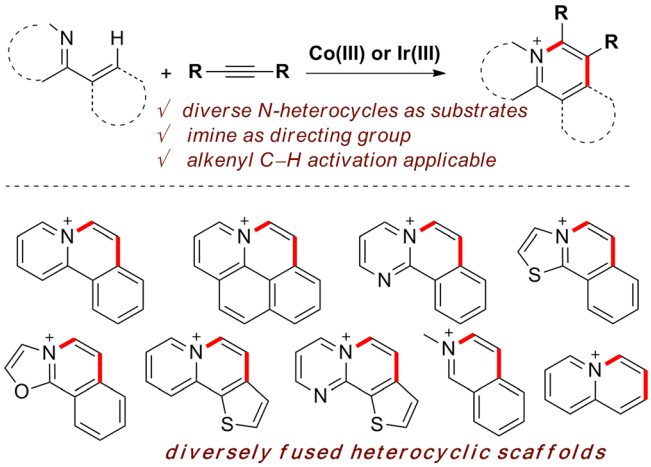


Figure 2. Synthesis of heterocyclic quaternary ammonium salts *via* direct C–H annulation.

seems to favor redox-neutral C–H addition reactions. Relatively fewer oxidative C–H functionalizations promoted by Cp*Co(III) are known in the literature.

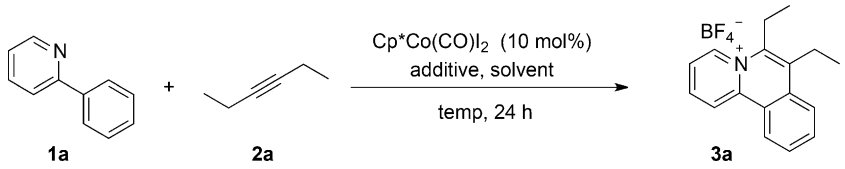
We have been interested in exploring the synthesis and modification of biologically active small molecules by using the C–H activation strategy.[13] In our effort to discover new heterocyclic scaffolds targeting G-quadruplex DNA,[14] a simple and effective method for the construction of heterocyclic quaternary ammonium salts with structural diversity is highly demanded.

Herein, we disclose our realization of a Cp*Co(III)-catalyzed oxidative C–H annulation of diverse N-heterocycles/imines with alkynes. A number of fused heterocyclic scaffolds were constructed in high efficiency. Importantly, the reaction is also amenable to alkenyl C–H activation. Additionally, we also explored the feasibility of using Cp*Ir(III)[15] as catalyst for this transformation, with good results being obtained. While preparing the manuscript, Cheng reported a similar work using Cp*Co(III) as catalyst under different reaction conditions.[16]

Initially, 2-phenylpyridine (**1a**) was reacted with hex-3-yne (**2a**) using $Cp^*Co(CO)I_2$ as catalyst. Delightfully, after extensive screening, we were able to obtain pyrido[2,1-*a*]isoquinolin-5-ium **3a** in 39% isolated yield under the reaction conditions of $Cp^*Co(CO)I_2$ (10 mol%), $AgBF_4$ (1.0 equiv.) and $Cu(OAc)_2$ (1.0 equiv.) in DCE at 60 °C for 24 h (Table 1, entry 1). A simple elevation of the temperature to 100 °C improved the yield to 86% (entries 2 and 3). Control experiments indicated that $Cp^*Co(CO)I_2$ is essential for the reaction (entry 4). The use of protic (MeOH) or polar (DMSO) solvents led to diminished yields (entries 5 and 6). The sole use of $AgBF_4$ as additive gave only 4% yield (entry 7).[16] Furthermore, the employment of different silver and copper salts as co-oxidant gave inferior results (entries 8–10).

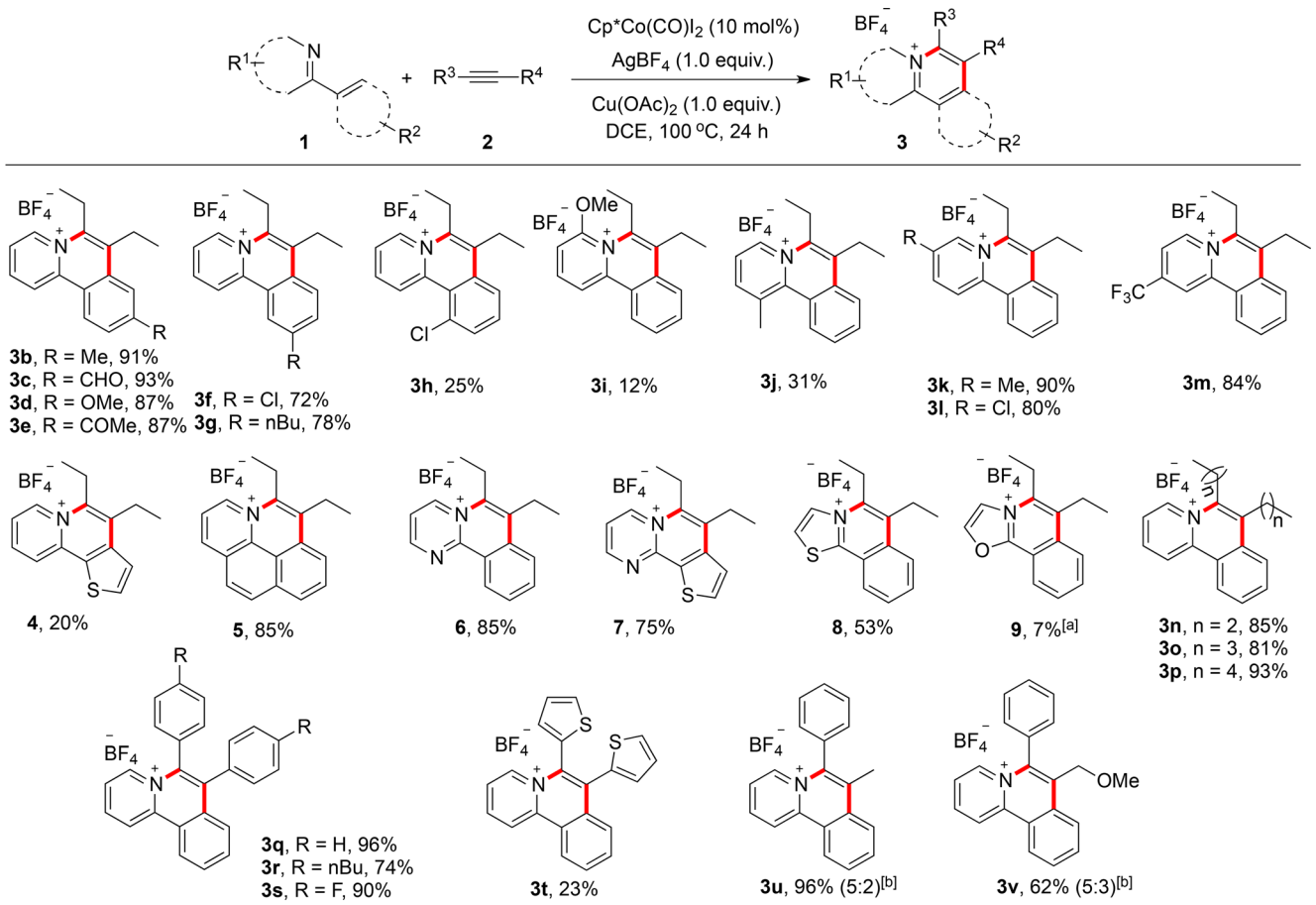
With the optimized reaction conditions in hand, the scope of this transformation was then extensively explored. In general, diverse heterocyclic quaternary ammonium salts were constructed in satisfactory to good yields (Scheme 1). 2-Phenylpyridines bearing different substituents regardless of the electronic properties underwent reaction smoothly (**3b–g**). The reaction took place at the less sterically hindered position when *meta*-substituted substrates were used (**3f** and **3g**). *ortho*-Substituents either on the aryl or pyri-

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Additive (equiv.)	Temperature [°C]	Yield[b]
1	DCE	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	60	39%
2	DCE	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	80	79%
3	DCE	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	100	86%
4	DCE	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	100	0[c]
5	MeOH	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	100	2%
6	DMSO	$AgBF_4$ (1.0), $Cu(OAc)_2$ (1.0)	100	13%
7	DCE	$AgBF_4$ (2.0)	100	4%
8	DCE	AgOAc (10%), $Cu(BF_4)_2{\cdot}6H_2O$ (2.0)	100	64%
9	DCE	AgOAc(1.0), $Cu(BF_4)_2{\cdot}6H_2O$ (1.0)	100	34%
10	DCE	$Cu(OAc)_2$ (1.0), $Cu(BF_4)_2{\cdot}6H_2O$ (1.0)	100	60%

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.9 mmol), $Cp^*Co(CO)I_2$ (0.03 mmol), additive, solvent (2.0 mL), 24 h.
[b] Isolated yields.
[c] Without catalyst.



[a] ^{1}H NMR yield .

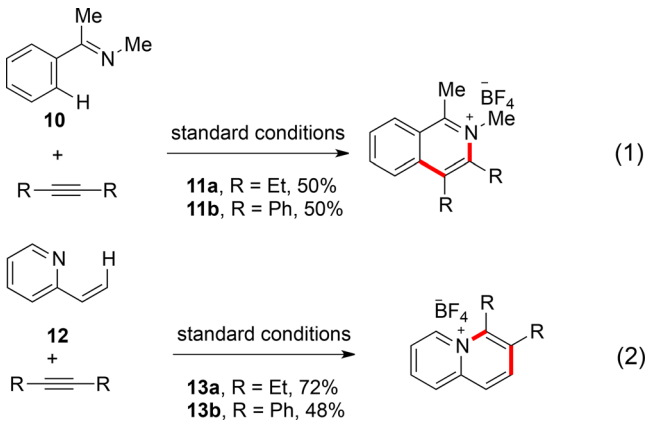
[b] The ratio of regioisomers was determined by ^{1}H NMR analysis and is given in the parentheses. The major isomer is shown.

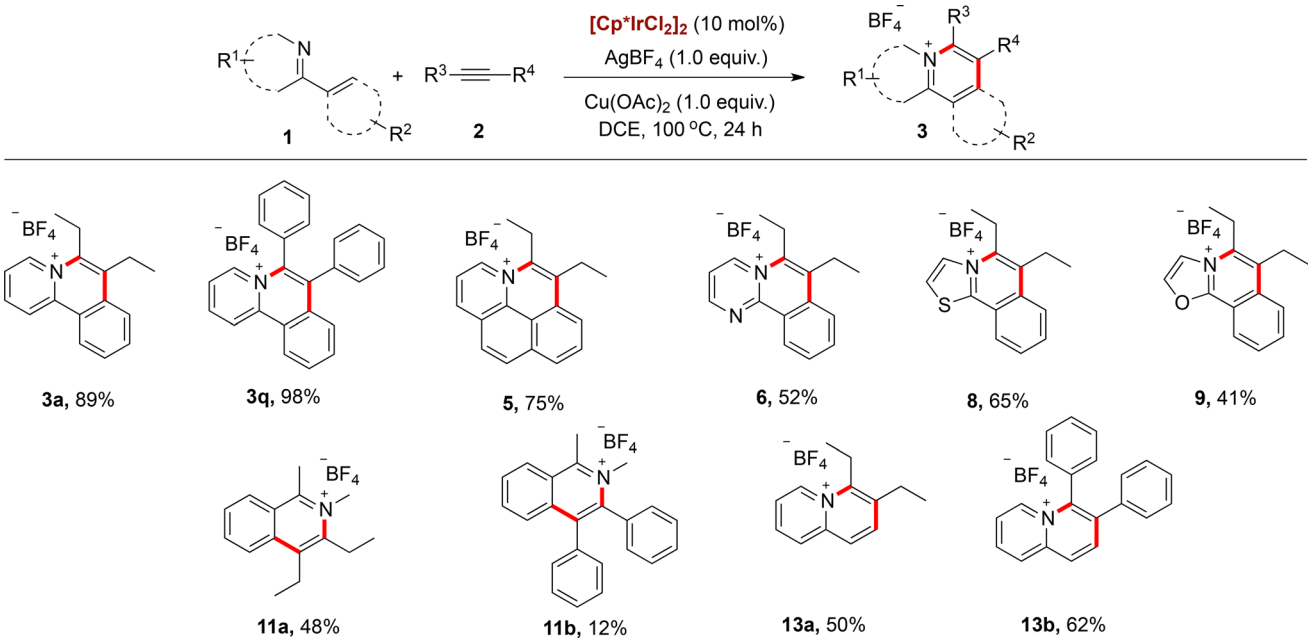
Scheme 1. Cp*Co(III)-catalyzed oxidative C–H annulation of N-heterocycles with alkynes.

dinyl rings deteriorated the reactivity due to steric reasons (**3h–j**). Importantly, it was found that other N-heterocycles such as pyrimidine (**6** and **7**) and thiazole (**8**) could also be applied as the directing groups, thus greatly enriching the structural diversity of the products. However, oxazole was found to be a less effective directing group (**9**). The reaction was also amendable to thienyl C–H activation, giving the corresponding tri-heterocycle fused compounds (**4** and **7**). Benzo[*h*]quinoline was also suitable for this transformation. In addition to dialkylalkynes, diarylalkynes were compatible with the current reaction conditions as well, giving the ammonium salts in good to excellent yields, although low efficiency for the reaction of dithienylacetylene was observed (**3q–t**). Two regioisomers were obtained when unsymmetrical alkynes were used (**3u** and **3v**).

To further extend the scope, imine **10** was reacted with both dialkylalkyne and diarylalkyne [Eq. (1)]. Gratifyingly, under the identical reaction conditions, 1,2-isoquinolinium salts (**11a** and **11b**) were formed in satisfactory yields. In addition, the oxidative annulation of alkenyl C–H bond with alkynes was also explored. The reactions of 2-vinylpyridine took place smoothly, giving the corresponding quinolizin-5-ium salts in good efficiency [**13a** and **13b**, Eq. (2)].

Cp*Ir(III), the congener of Cp*Co(III) and Cp*Rh(III), was relatively less studied in C–H annulation reactions.[15] We were intrigued whether this



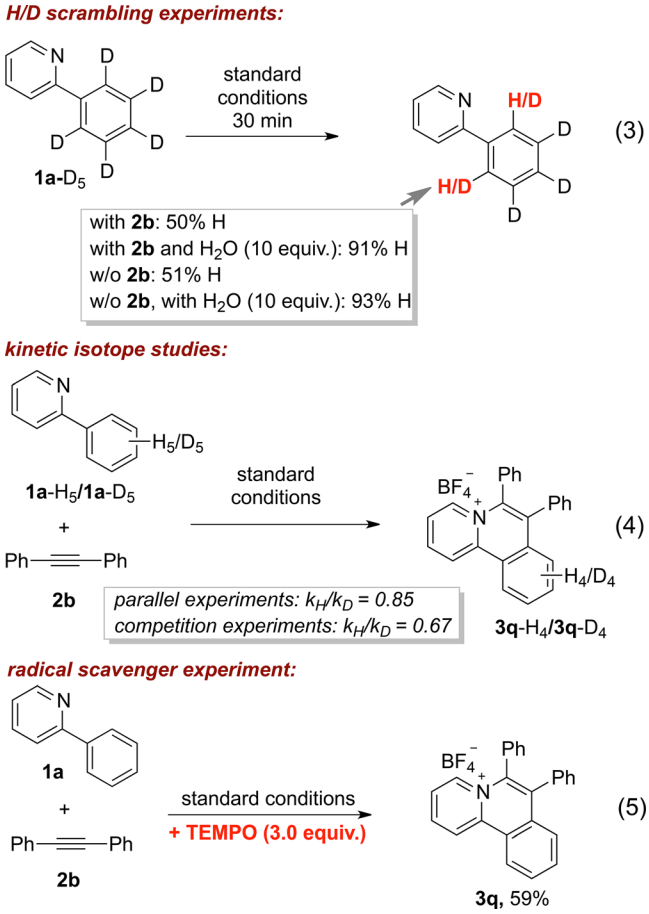


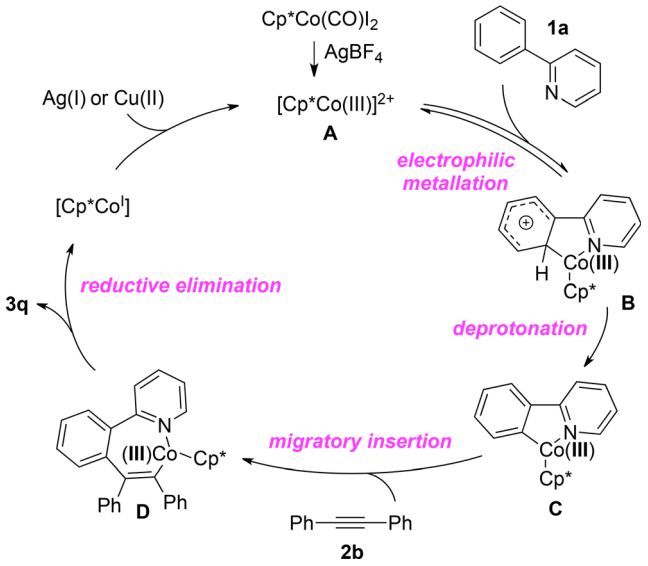
Scheme 2. Cp*Ir(III)-catalyzed oxidative C–H annulation of N-heterocycles with alkynes.

complex could also promote the same reaction. To our delight, by simply switching the catalyst to $[Cp^*IrCl_2]_2$, the oxidative annulation of diverse heterocyclic substrates gave comparable results to the Cp*Co(III)-catalyzed version (Scheme 2). Furthermore, imine and 2-vinylpyridine underwent the reaction smoothly as well under the current catalytic system. It is noteworthy that the reaction was also amenable to an oxazole substrate, providing another type of heterocyclic scaffold in reasonable yield (**9**).

To better understand the mechanism, several experiments were conducted. A swift H/D scramble was observed regardless of the presence or absence of a coupling partner [Eq. (3)]. The incorporated proton is supposed to come from the moisture of solvent. This speculation is consistent with a more pronounced H/D scramble when 10 equivalents of H_2O were added. Interestingly, inverse equilibrium isotope effect values of 0.85 and 0.67 were measured for parallel and competition experiments, respectively [Eq. (4)]. These results implicate rehybridization of the C–H bond from sp^2 to sp^3 in the C–H bond activation step.[17] It should be noted that these observations are in sharp contrast to Cheng's observations.[16] In addition, the use of the radical scavenger TEMPO in the reaction did not hamper the reactivity, which is indicative that a radical mechanism is not involved in the reaction [Eq. (5)].[18]

A plausible mechanism for the Cp*Co(III)-catalyzed oxidative annulation reaction is outlined in Scheme 3. Initially, the halogen abstraction and ligand exchanges yield the reactive cationic catalyst $[Cp^*Co(III)]^{2+}$ (**A**). Thereafter, coordination of the nitrogen atom of the N-heterocycle is followed by a C–H bond cleavage to form a cyclocobaltated spe-





Scheme 3. Proposed mechanism.

cies **C**. Based on our mechanistic studies, the C–H activation step might proceed *via* an electrophilic metallation mechanism rather than the concerted metallation-deprotonation (CMD) or single electron transfer mechanism,[18] and is reversible. Subsequently, a migratory insertion of alkyne gives a seven-membered ring intermediate **D**. Upon reductive elimination, the heterocyclic quaternary ammonium salt is formed. The reduced Cp*Co(I) species is regenerated by the oxidation of copper or silver salt.

In summary, we have successfully developed a Cp*Co(III)-catalyzed C–H annulation reaction with alkynes towards the syntheses of heterocyclic quaternary ammonium salts. Diverse N-heterocycles and imines were found to be efficient directing groups for this transformation. In addition, alkenyl C–H activation was also realized, greatly extending the reaction scope. Importantly, we identified that the Cp*Ir(III) complex was also effective for this transformation. The evaluation of the biological activity of these products toward G-quadruplex DNA is currently underway in our laboratories. Given the simplicity of this reaction and the importance of heterocyclic quaternary ammonium salts as functional molecules, we anticipate this reaction may find applications.

Experimental Section

General Procedure

To a 10-mL sealed tube were added the corresponding substrate (0.3 mmol), alkyne (0.9 mmol, 3.0 equiv.), $Cp^*Co(CO)I_2$ or $[Cp^*IrCl_2]_2$ (0.03 mmol), $AgBF_4$ (0.3 mmol), $Cu(OAc)_2$ (0.3 mmol) and DCE (2.0 mL). The resulting reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to room temperature, the reaction mixture was then subjected to flash column chromatography on silica gel using EtOAc/petroleum ether (1:1), and then DCM/MeOH (20:1) as the eluent to give the products.

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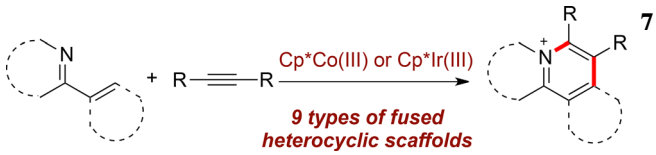

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