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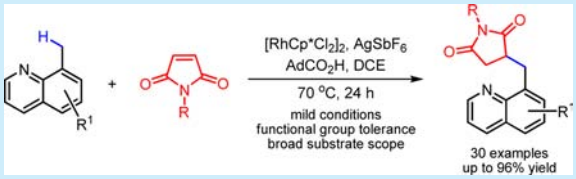
Rhodium(III)-Catalyzed C(sp^3)−H Alkylation of 8-Methylquinolines with Maleimides

Sangil Han, Jihye Park, Saegun Kim, Suk Hun Lee, Satyasheel Sharma, Neeraj Kumar Mishra, Young Hoon Jung, and In Su Kim*

School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

Supporting Information

ABSTRACT: The rhodium(III)-catalyzed cross-coupling reaction of 8-methylquinolines and maleimides is described. In contrast to the C(sp^2)−H functionalization, a first catalytic functionalization of sp^3 C−H bonds with maleimides is reported. This protocol provides a facile access to various succinimide scaffolds on 8-methylquinolines via a direct C−H cleavage approach.

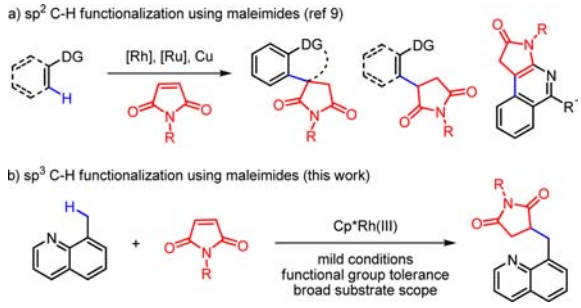


Transition-metal-catalyzed C−H bond activation and its subsequent functionalization have been an attractive topic in organic synthesis because of its remarkable potential for atom economy and environmental sustainability.[1] A variety of C(sp^2)−H functionalization has been already developed under metal catalysis in the past decade.[2] Recently, much attention has been moved toward the C(sp^3)−H functionalization events, which continue to be a challenging issue.[3] In this area, directing group assisted sp^3 C−H functionalization has been explored by use of amides, carboxylic acids, oximes, *N*-heterocycles, etc. In particular, 8-methylquinolines have been found as good substrates for sp^3 C−H functionalization due to its ability to form cyclometalated complexes.[4] Previously, palladium catalysts were intensively studied for the functionalization of 8-methylquinolines using various coupling partners.[5] Recently, other catalysts such as Rh(III), Ir(III), Ru(II), and Co(III) have been used for the sp^3 C−H activation of 8-methylquinolines.[6] For examples, the alkenylation reactions using 8-methylquinolines and internal alkynes were achieved for the formation of 8-allylquinolines under Rh(III) and Co(III) catalysis by Wang[6a] and Sundararaju,[6b] respectively. In addition, Chang and co-workers described the Ir(III)-catalyzed sp^3 C−H amidation on ketoximes and 8-methylquinolines with sulfonyl azides.[6c] Moreover, Rh(III), Ru(II), and Co(III) catalysts were also examined for the amination reactions using various aminating surrogates.[6d−l] Recently, the alkylation and alkenylation of 8-methyquinolines were also explored under rhodium catalysis.[6m−o]

Succinimides have been recognized as privileged structural cores found in a number of bioactive natural products, pharmaceuticals, and functional materials.[7] Furthermore, the reduced derivatives such as pyrrolidines and γ-lactams have been also found in a large number of pharmaceutically relevant molecules, thus making them one of the most important and promising compounds.[8]

With the advance of C−H functionalization, maleimides have been coupled with aromatic C(sp^2)−H bonds (Scheme 1).[9] For examples, Li[9a] and Zhu,[9b] respectively, demonstrated the

Scheme 1. C−H Functionalization Using Maleimides



Rh(III)-catalyzed tandem cyclization of aromatic C−H bonds with maleimides affording spirosuccinimides. In addition, the formation of spiro adducts was also described by Hirano and Miura via the Cu-mediated C−H transformation.[9c] Prabhu reported the Ru(II)-catalyzed sp^2 C−H alkylation reactions of acetophenones[9d] and *N*-benzoyl indoles[9e] with maleimides. In addition, Li et al. reported the Rh(III)-catalyzed annulation reaction between *N*-sulfinyl ketoimines and maleimides to give tricyclic pyrrolidone-fused isoquinolines.[9f] Recently, we disclosed the Rh(III)-catalyzed cross-coupling reactions of vinylic C(sp^2)−H bonds with maleimides to provide various succinimide scaffolds.[9g,h] In contrast to the C(sp^2)−H functionalization, there is no report on catalytic sp^3 C−H functionalization with maleimides. In continuation of our efforts toward the Rh(III)-catalyzed C−H functionalization using maleimides as coupling partners, we herein reported the first C(sp^3)−H activation of 8-methylquinolines and subsequent functionalization with maleimides to afford various succinimide derivatives.

Our investigation commenced by examining the coupling reaction of 8-methylquinoline (**1a**) and *N*-methyl maleimide (**2a**) under our previous reported conditions, as shown in entry 1 of Table 1.[9g,h] We were delighted to see the coupling between **1a**

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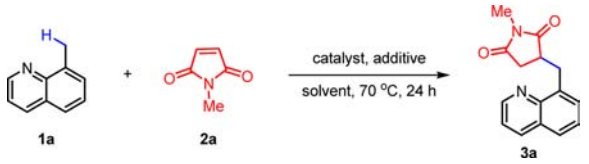
Table 1. Selected Optimization for Reaction Conditions[a]



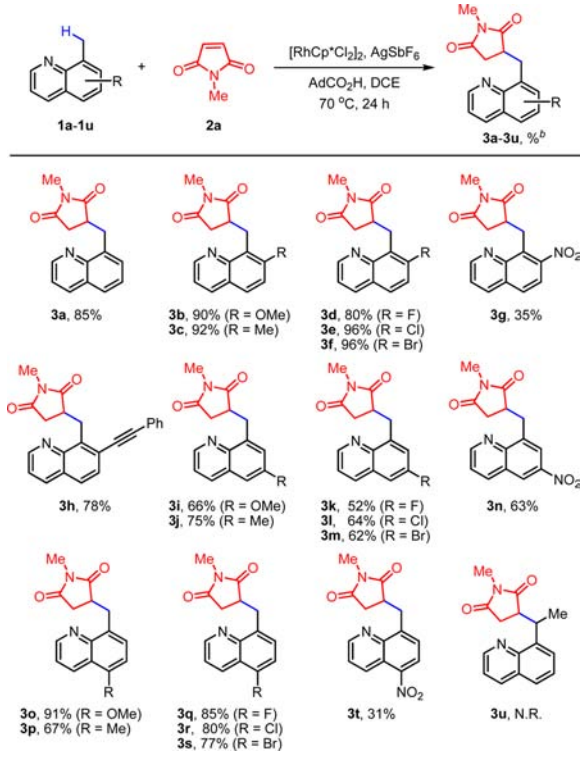
entry	catalyst	additive (mol %)	solvent	yield[b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	59
2		$AgSbF_6$ (10), AcOH (200)	DCE	N.R.
3		AcOH (200)	DCE	N.R.
4		DBU (200)	DCE	N.R.
5	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10)	DCE	13
6	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	20
7[c]	$[CoCp^*(CO)I_2]$	$AgSbF_6$ (20), AcOH (200)	DCE	N.R.
8	$[IrCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	N.R.
9	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	MeOH	25
10	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	THF	20
11	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	dioxane	30
12	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DMF	10
13	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (300)	DCE	67
14	$[RhCp^*Cl_2]_2$	$AgNTf_2$ (10), AcOH (300)	DCE	64
15	$[RhCp^*Cl_2]_2$	AgOTf (10), AcOH (300)	DCE	29
16	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (300)	DCE	78
17	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), $Cu(OAc)_2$ (300)	DCE	20
18	$[RhCp^*Cl_2]_2$	**$AgSbF_6$ (10), $AdCO_2H$ (300)**	**DCE**	**85**
19[d]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), $AdCO_2H$ (300)	DCE	54
20[e]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), $AdCO_2H$ (300)	DCE	16

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (2.5 mol %), additive (quantity noted), solvent (1 mL) under air at 70 °C for 24 h in pressure tubes. [b]Isolated percent yield by flash column chromatography. [c]10 mol % of Co(III) catalyst was used. [d]The reaction was carried out at 100 °C. [e]The reaction was carried out at room temperature.

and **2a** in the combination of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ in the presence of AcOH in DCE at 70 °C providing the desired product **3a** in 59% yield (Table 1, entry 1). Control experiments revealed that cationic rhodium catalyst and acid additive is highly crucial for this coupling reaction (Table 1, entries 2–5). Other catalysts such as Ru(II), Co(III), and Ir(III) were found to be ineffective in this transformation (Table 1, entries 6–8). Further screening of solvents showed that DCE is an optimal solvent for the formation of our desired product **3a** (Table 1, entries 9–12). In addition, increasing the amount of AcOH provided the increased formation of **3a** in 67% yield (Table 1, entry 13). The exchange of silver additives to $AgNTf_2$ and AgOTf to generate cationic rhodium complexes gave 64% and 29% yields of **3a**, respectively (Table 1, entries 14 and 15). Interestingly, we were pleased to find that 1-adamantane carboxylic acid ($AdCO_2H$) was found to be the best additive to give our desired product **3a** in 85% yield (Table 1, entries 16–18). Finally, it should be noted that the reaction temperature is quite important to undergo the coupling reaction in high yield, as shown in entries 19 and 20.

With the optimized reaction conditions in hand, the substrate scope and limitation of 8-methylquinolines were examined, as shown in Scheme 2. The coupling of *N*-methyl maleimide (**2a**)

Scheme 2. Scope of 8-Methylquinolines[a]



[a]Reaction conditions: **1a–1u** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $AdCO_2H$ (300 mol %), DCE (1 mL) under air at 70 °C for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography.

and 8-methylquinolines **1b–1f** with electron-donating and halogen groups at the C7-position was found to be good substrates in the alkylation reaction on $C(sp^3)$–H bonds to afford the corresponding products **3b–3f** in high yields, whereas NO_2-substituted 8-methylquinoline **1g** was found to be less reactive under the present reaction conditions. Particularly noteworthy was the tolerance of the reaction conditions to the bromo and chloro moieties, providing a versatile synthetic manipulation for further functionalization of the products. We were delighted to observe that the alkyne substituent at the C7-position was also compatible to furnish our desired product **3h** in 78% yield. In addition, C6-substituted compounds **1i–1n** with electron-rich and -deficient groups also afforded our desired products **3i–3n** in moderate to good yields. In the case of C5-substituted 8-methylquinolines **1o–1t**, we observed the very similar reactivity like those found in C7-substituted 8-methylquinolines. These results suggest that this transformation is highly dependent on the electronic nature on aromatic ring. When more sterically congested 8-ethylquinoline **1u** was subjected under the optimal reaction conditions, no formation of product was detected. This outcome can also explain the

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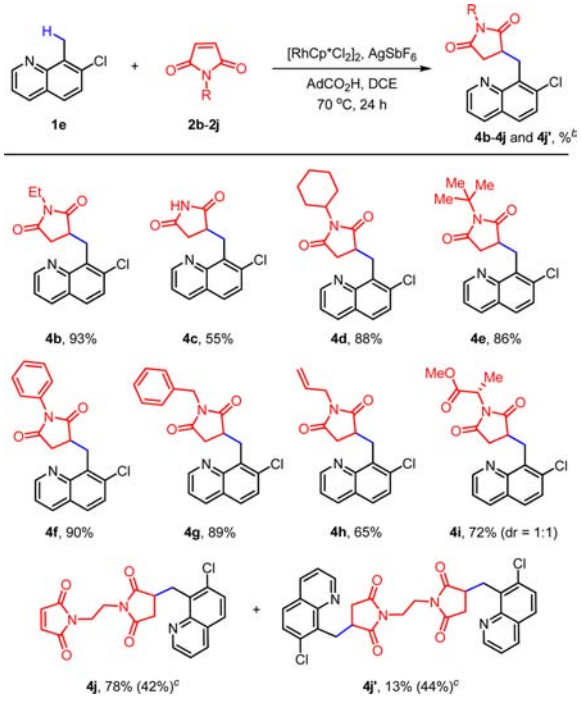
monoalkylation reaction of 8-methylquinolines without a second sp^3 C−H functionalization on products.

To further evaluate the scope of this coupling reaction, various maleimides **2b**−**2j** were subjected to react with 7-chloro-8-methylquinoline (**1e**) under the optimal reaction conditions (Scheme 3). *N*-Alkyl and *N*-aryl as well as unprotected

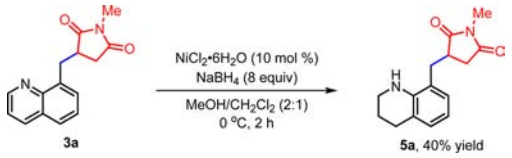
Scheme 3. Scope of Maleimides[a]



[a]Reaction conditions: **1e** (0.2 mmol), **2b**−**2j** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $AdCO_2H$ (300 mol %), DCE (1 mL) under air at 70 °C for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]**1e** (0.5 mmol), **2j** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $AdCO_2H$ (300 mol %).

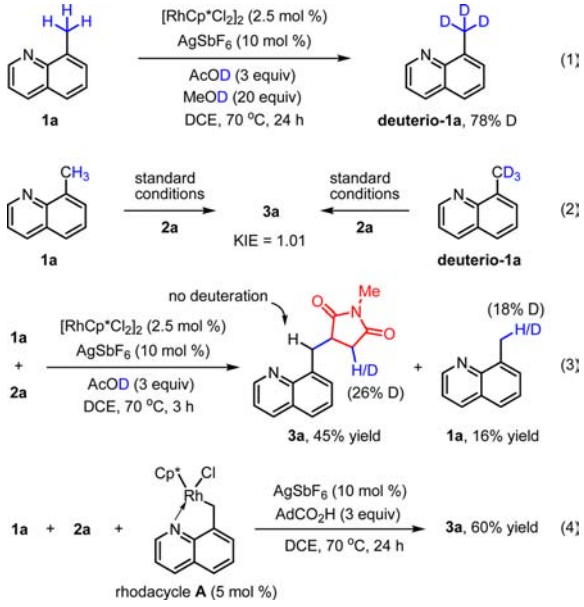
maleimides **2b**−**2g** smoothly participated in the C−H alkylation reaction to deliver our desired products **4b**−**4g** in moderate to high yields. Gratifyingly, *N*-allyl maleimide (**2h**) also displayed good reactivity to give **4h** in 65% yield. Notably, we found that maleimide **2i** derived from L-alanine was also found to be tolerable with complete chemoselectivity providing **4i** in 72% yield with a 1:1 diastereomeric ratio. In addition, this reaction displayed good monoselectivity for the coupling of **2j** with **1e** under the optimized reaction conditions to afford **4j** (78%) and **4j′** (13%). On reversing the limiting reagent, we found an increase in the formation of bis-alkylated product **4j′** in 44% yield. Meanwhile, we have also screened the coupling between 8-methylquinoline (**1a**) and other olefins, such as acrylates, quinones, maleates, and maleic anhydride. In addition, other widely used substrates for the C(sp^3)−H functionalization were also investigated for the coupling with maleimides. However, all the above reactions did not deliver any coupling products under the optimized reaction conditions (see Supporting Information for details). To highlight the synthetic utility of succinimide-containing quinolines, the selective reduction of quinoline ring of alkylated product **3a** was performed using $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ to give tetrahydroquinoline derivative **5a** in 40% yield (Scheme 4).[10]

Scheme 4. Reduction of Quinoline Moiety



To gain mechanistic insight into this reaction, reversibility and kinetic isotope effect (KIE) experiments were performed, as shown in eqs 1 and 2 of Scheme 5. When AcOD and MeOD were

Scheme 5. Mechanistic Investigation



added to the reaction mixtures, remarkable H/D exchange in recovered **deuterio-1a** was observed, which is indicative of the reversible rhodation−proto(deuterio)derhodation process. Next, KIE experiments resulted in a k_H/k_D value of 1.01, thus suggesting that C−H cleavage might not be involved in the rate-determining step.[11] When **1a** and **2a** was subjected to the standard conditions using AcOD, 26% deuterium incorporation on the C4-position of succinimide ring was observed, suggesting that the reaction of rhodacycle **A** with maleimides is much faster than the protonation of **A** (Scheme 5, eq 3). In addition, when a stoichiometric amount of rhodacycle **A** reacted with **2a**, no deuteration of benzylic C−H bonds of **3a** was detected, suggesting that the catalytic cycle might be irreversible. Finally, rhodacycle **A** was found to be an active species in the reaction (Scheme 5, eq 4).

Based on above-mentioned mechanistic investigation, a proposed reaction pathway is outlined in Scheme 6. A cationic Rh(III) catalyst can coordinate to a nitrogen atom of 8-methylquinoline (**1a**), which subsequently activates an sp^3 C−H bond to generate the rhodacycle intermediate **A**. Coordination of **2a** and migratory insertion deliver a seven-membered rhodacycle species **C**.[12] Finally, protonation by $AdCO_2H$ can take place to furnish our desired product **3a**, and the active Rh(III) species can recycle in the catalytic system. It should be mentioned that *β*-H elimination products were not detected due to the absence of a *syn*-planar *β*-H atom with respect to the Rh atom.

In conclusion, we described the first rhodium(III)-catalyzed direct sp^3 C−H alkylation reaction of 8-methylquinolines with

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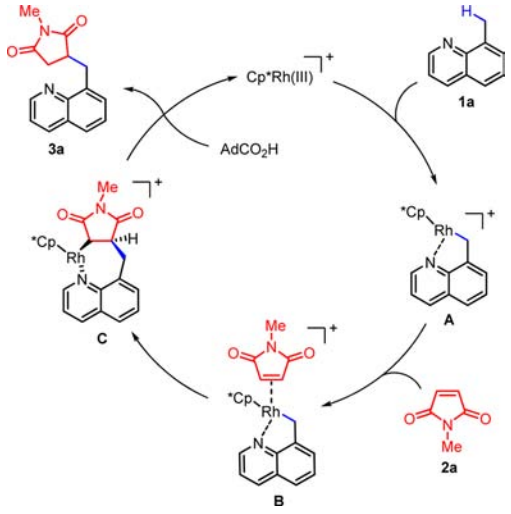
Scheme 6. Proposed Reaction Mechanism



maleimides. This protocol has been applied to a wide range of substrates and typically proceeds with excellent levels of chemoselectivity as well as with high functional group tolerance. Further biological evaluation of synthetic succinimide derivatives of 8-methylquinolines is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02295.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds; unsuccessful results for sp^3 C−H fuctionalization with various olefins (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: insukim@skku.edu.

Notes

The authors declare no competing financial interest.

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