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Rhodium-Catalyzed Remote C-8 Alkylation of Quinolines with Activated and Unactivated Olefins: Mechanistic Study and Total Synthesis of EP4 Agonist

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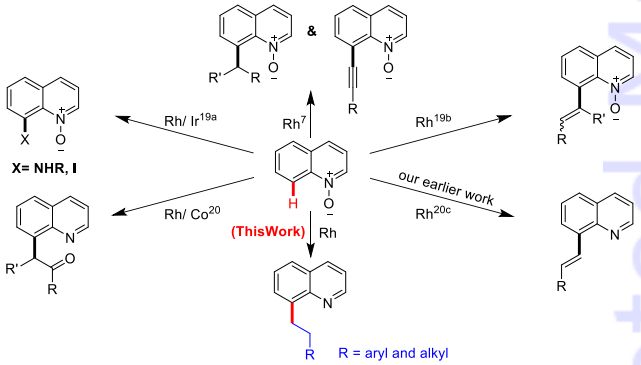
Abstract. Reported herein is a rhodium(III)-catalyzed regioselective distal C(sp2)-H bond alkylation of quinoline *N*-oxides using olefins as alkyl source and *N*-oxide as the traceless directing group. The reaction exhibits broad substrate scope with excellent selectivity for C-8 position and good yields of alkylated products. The usefulness of the developed catalytic protocol is established by synthesis of EP4 agonist. In mechanistic study, C-8 olefinated quinoline was identified as the reaction intermediate, which gets reduced to desired C-8 alkylated product in the presence of a rhodium(I) species (produced from rhodium(III) during reaction) and formic acid. Formic acid is produced from dimethylformamide in the presence of silver tetrafluoroborate.

Keywords: remote CH activation, rhodium, alkylation, quinoline *N*-oxide, olefin, EP4 agonist

The alkylation of arenes[1] and heteroarenes[2] with olefins *via* catalytic C-H bond activation represents an expedient method to elaborate these scaffolds in terms of atom-economy. [3] Olefins are considered ideal for alkylation due to their abundant availability, stability, and diversity.[4] Following the pioneer work of Murai et al. on carbonyl directed Ru-catalyzed alkylation of aromatic compounds with olefins,[1a] various methods have been reported for the alkylation of arenes and heteroarenes using transition metal catalysts.[5] Although the directing group assisted *ortho*-alkylation of *N*-heterocycles including quinolines has already been disclosed,[6] there is a single report for Rh-catalyzed C-8 alkylation of quinoline *N*-oxide.[7] Use of diazomalonate as an alkylating agent and requirement of additional step for the removal of directing group permit further development of alternate catalytic approach. Replacing diazomalonate with olefin as the alkylating source will be of utmost importance particularly in terms of atom-economy and availability.[8]

Quinoline moiety represents an important class of heterocycles extensively utilized in synthetic,[9] medicinal[10] and material chemistry.[11] Considering the significance of quinolines, various methods have been developed for their synthesis[12] and functionalization[13]. Recently, *N*-oxide as directing group has attracted great attention mainly for C-2 functionalization of quinoline *N*-oxide through transition metal catalyzed C-C,[6,14] C-N,[15] C-O,[16] C-S[17] and C-P[18] bond formation reactions. On the other hand, C-8 functionalization of quinolines is less studied, and in most of these developed catalytic methods, an additional step is required for the removal of directing group affecting the overall economy of the reaction (Scheme 1).[7,19] As a result, C-8 functionalization of quinoline with simultaneous removal of the directing group has been considered as an excellent step economic alternate (Scheme 1).[20]



Scheme 1. C-8 functionalization of quinoline.

In continuation of our efforts towards the development of an efficient catalytic method for the functionalization of quinolines, [20c,21] herein we disclose the first example of Rh-catalyzed remote (C-8) alkylation of quinoline by reacting quinoline *N*-oxide with olefins, where *N*-oxide act as a traceless directing group.

During our previous work on remote alkenylation of quinoline,[20c] selectively C-8 alkylated product was observed in 40% NMR yield with a stoichiometric amount of $AgBF_4$ under standard reaction conditions.[22] With this observation, especially in terms of olefins as alkyl source, we thought to explore remote alkylation of *N*-oxide with olefins. The reaction of quinoline *N*-oxide (**2a**) with styrene (**1a**) was taken as a model reaction for optimization of different reaction parameters. Substrate **2a** was reacted with **1a** in the presence of $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (1 equiv), $Cu(OAc)_2$ (1 equiv) and AcOH (2 equiv) at 140°C in DMF as solvent for specified time (Table 1, entry 1). The alkylation occurred even in the absence of $Cu(OAc)_2$ or AcOH, albeit in low yield (Table 1, entry 5 &

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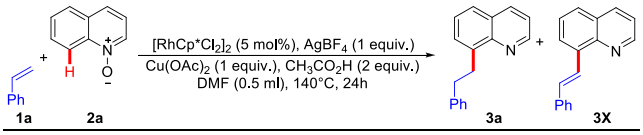
6). Use of 1 equiv. of $AgBF_4$ is critical for the reaction as lowering the amount to 0.5 equiv. gave only 33% yield of desired product along with 48% of olefinated side product (Table 1, entry 14).

Table 1. Optimization studies.[a]



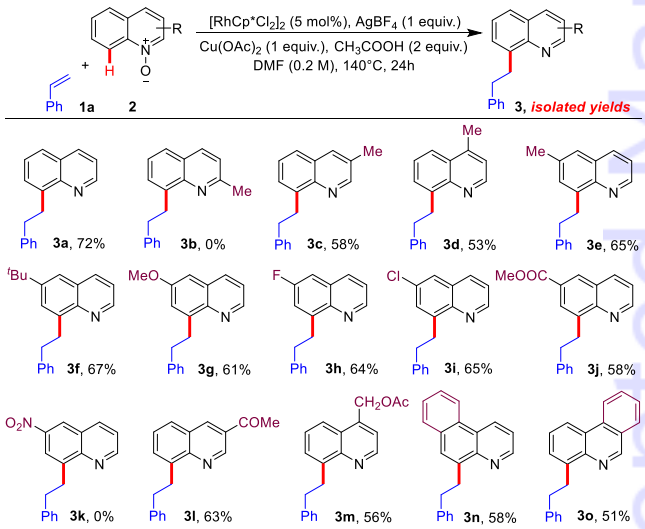
Entry	Catalyst (mol%)	Additives (equiv.)	Solvent	**3a** yield (%)[b]	**3b** yield (%)[b]
1	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	74 (**72**)[c]	n.d.
2	-	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	n.d.	n.d.
3	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgSbF_6$ (1) /CH_3CO_2H (2 equiv.)	DMF	10	42
4[d]	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	40	45
5[e]	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	22	n.d.
6	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1)	DMF	41	15
7[f]	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	n.d.	n.d.
8	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DCE	20	30
9[g]	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	40	25
10	$[RhCp^*Cl_2]_2$ (10 mol%)	$AgBF_4$ (1) /CH_3CO_2H (2 equiv.)	DMF	60	n.d.
11	$[RhCp^*Cl_2]_2$ (5 mol%)	HBF_4 (2) /CH_3CO_2H (2 equiv.)	DMF	56	n.d.
12	$[RhCp^*Cl_2]_2$ (5 mol%)	KBF_4 (2) /CH_3CO_2H (2 equiv.)	DMF	40	n.d.
13	$[RhCp^*Cl_2]_2$ (5 mol%)	$NaBF_4$ (2) /CH_3CO_2H (2 equiv.)	DMF	47	n.d.
14	$[RhCp^*Cl_2]_2$ (5 mol%)	$AgBF_4$ (0.5) /CH_3CO_2H (2 equiv.)	DMF	33	48

[a]reaction conditions: **2a** (0.10 mmol), **1a** (0.20 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (1 equiv.), $Cu(OAc)_2$ (1 equiv), acetic acid (2 equiv.), DMF (0.2 M), 140°C, 24 h. Quinoline and traces of another unidentified compounds were observed as by products in most of the reactions. [b]Yield based on NMR analysis of crude reaction mixture using tetrachloroethane as an internal standard. [c]Isolated yield in parentheses. [d] $Cu(OAc)_2.H_2O$ in place of $Cu(OAc)_2$ for 12 h. [e] without $Cu(OAc)_2$. [f] at 100 °C. [g] for 12h.

Use of $AgSbF_6$ and other silver salts in place of $AgBF_4$ did not prove beneficial (Table 1, entry 3).[22] Although, lower yield of the desired product was observed when HBF_4, KBF_4, and $NaBF_4$ were used in place of $AgBF_4$, selectivity was complete (Table 1, entry 11, 12 & 13).[22] Either no reaction or low yield of desired product was observed at a temperature below 140°C (Table 1, entry 7). From the screening of various acids and bases, acetic acid (2 equiv) was found as an additive of choice.[22] Moreover, different organic solvents including DCE (Table 1, entry 8), toluene, 1,4-dioxane etc. were also investigated and DMF was found to be the best solvent for the current reaction.[22] The closed vessel proved to be critical for successful reaction as in open vessel under reflux condition only traces of products were observed.

Having these optimized reaction conditions in hand, substrate scope was explored with respect to substituted quinoline *N*-oxides and styrenes (Table 2 & 3). Various quinolines reacted smoothly, thus giving the product in moderate to good yields (Table 2). Quinoline *N*-oxide with electron donating substituents such as -Me, -OMe and -^{t}Bu at different position afforded C-8 alkylated product in moderate to good yields (entry **3c-g**). Unfortunately, desired product was not observed in the case of 2-methyl quinoline *N*-oxide, which might be due to steric effect (entry **3b**). Halogen substituents such as -fluoro and -chloro on quinoline *N*-oxide were well tolerated providing further opportunity for functionalization (entry **3h-i**). Although, labile electron withdrawing functional group such as ester and acetyl were well endured, 6-NO_2 quinoline *N*-oxide failed to provide the desired product (entry **3j-l**). Quinoline *N*-oxide bearing protected alcohol underwent alkylation in moderate yield without any deprotection (entry **3m**). Polycondensed heteroarenes such as benzo(f)quinoline *N*-oxide and phenanthridine *N*-oxide also reacted smoothly giving corresponding alkylated products with excellent regioselectivity in 58% and 51% isolated yields, respectively (entry **3n-o**).

Table 2. Scope with quinoline *N*-oxides.[a]

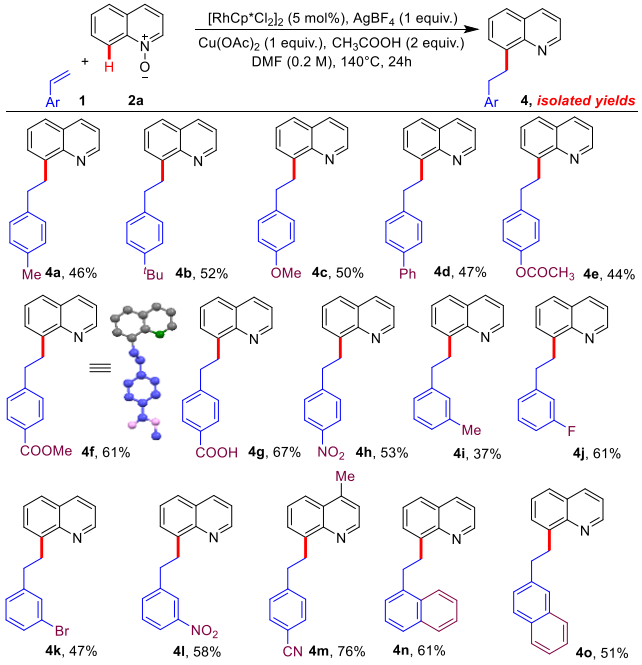


[a]reaction conditions: **1a** (0.20 mmol), **2** (0.10 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (1 equiv.), $Cu(OAc)_2$ (1 equiv), acetic acid (2 equiv.), DMF (0.2 M), 140 °C, 24 h.

The scope of styrenes as the alkylating source was subsequently studied in reaction with **2a** (Table 3). The reaction of quinoline *N*-oxide (**2a**) with various electron donating and withdrawing 4-substituted styrene's e.g. 4-Me, 4-^{t}Bu, 4-OMe, 4-Ph, 4-OCOMe, 4-CO_2Me, 4-CO_2H, and 4-NO_2, afforded C-8 alkylated products with excellent regioselectivity in moderate to good yields (entry **4a-h**). Product **4f** was ambiguously characterized with X-ray.[23] It is worth full to mention here that product **4g** synthesized here is an intermediate in the synthesis of Ep4 agonist.[24] Functional groups such as -Me, -F, -Br and –NO_2 at *meta* position of styrene were also well tolerated (entry **4i-l**). The reaction of 4-methylquinoline *N*-oxide with 4-cyano styrene proceeded smoothly under present reaction condition providing the desired product in 76% yield

(entry **4m**). Substrates such as 1- and 2-vinylnaphthalene provided the desired product in 61% and 51% yields, respectively (entry **4n-o**).

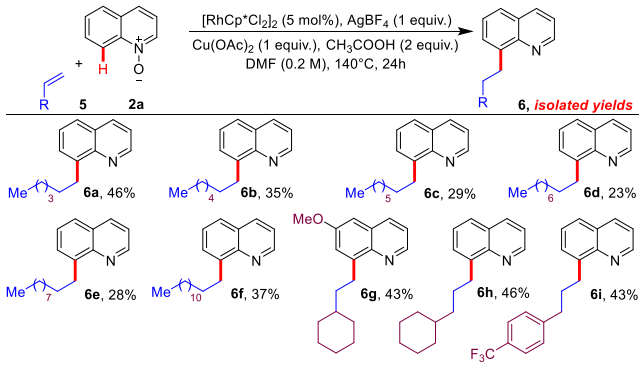
Table 3. Scope with styrenes.



[a]reaction conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (1 equiv.), $Cu(OAc)_2$ (1 equiv), acetic acid (2 equiv.), DMF (0.2 M), 140 °C, 24 h.

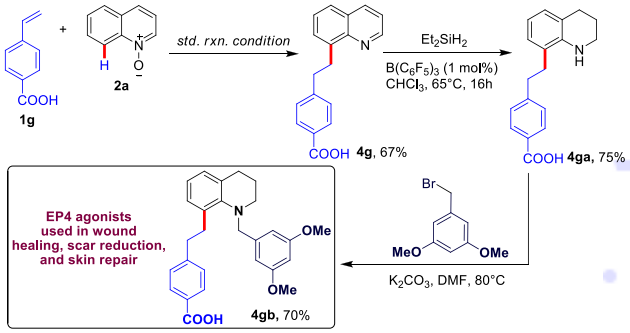
In continuation with these successful results using styrenes, aliphatic olefins were further explored as alkylating reagents (Table 4). Aliphatic olefins are considered as challenging substrates due to their unreactive nature.[8,25] Long chain olefin such as 1-hexene, 1-heptene, 1-octene, 1-nonene, 1-decene, and 1-tridecene were well compatible under current reaction conditions (entries **6e-f**). The reaction of vinyl- and allylcyclohexane with **2a** provided the desired product in moderate yields (entries **6g-h**). Aliphatic olefin such as 1-allyl-4-(trifluoromethyl)benzene also found compatible under current reaction conditions (entry **6i**).

Table 4. Scope with quinoline *N*-oxides and aliphatic olefins.[a]



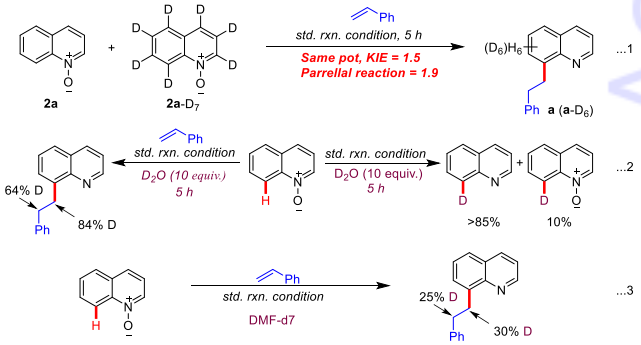
[a]reaction conditions: **5** (0.20 mmol), **2a** (0.10 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (1 equiv.), $Cu(OAc)_2$ (1 equiv), acetic acid (2 equiv.), DMF (0.2 M), 140 °C, 24 h. Isolated yield in parenthesis.

To demonstrate the utility of the current catalytic method, synthesis of an EP4 agonist, used for the treatment of wound healing and skin repair, was carried out (Scheme 2).[24] Product **4g** was treated with diethyl silane in the presence of borane catalyst giving 4-2(2-(1,2,3,4-tetrahydroquinoline-8-yl)ethyl)benzoic acid.[26] Finally, tetrahydroquinoline product was reacted with 3,5-dimethoxybenzyl bromide in the presence of K_2CO_3 to get 4-(2-(1-(3,5-dimethoxybenyl)-1,2,3,4-tetrahydroquinoline-8-yl)ethyl)benzoic acid, which acts as an EP4 agonist.[24]



Scheme 2. Synthetic application.

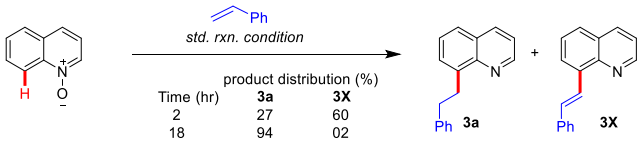
Preliminary mechanistic experiments were carried out to get first sight of the reaction pathway. In a competition experiment of **2a** and deuterated quinoline *N*-oxide (d_7-**2a**) with **1a** under standard reaction condition for 5h, kinetic isotopic effect (KIE) of $K_H/K_D \approx 1.5$ was observed (Scheme 3, equation 1). In the case of two parallel reactions, KIE of $K_H/K_D \approx 1.9$ was calculated (Scheme 3, equation 1) representing that C-H bond cleavage may be the rate limiting step.[27] The difference in the KIE effect may be due to the exchange of deuterium with a proton in the competition reaction. Further, treatment of **2a** without **1a** under standard reaction condition in the presence of D_2O led to the recovery of quinoline with >85% incorporation of deuterium at C-8 position which suggests that the first step of carbometallation might be reversible (Scheme 3, equation 2). Deuterium incorporation was observed at *α*- and *β*–position on the alkyl chain in the final product when the standard reaction was carried out in the presence of D_2O (Scheme 3, equation 2). This experiment indicated the occurrence of linear/branch process for olefin insertion, where the linear process is favored in the forward direction. When standard reaction was carried out in the presence of d7-DMF deuteration was observed at α- and *β*–position of alkyl chain indicating that DMF is involved in the reduction of alkenylated intermediated (Scheme 3, equation 3).[22]



Scheme 3. Deuterium labeling experiments.

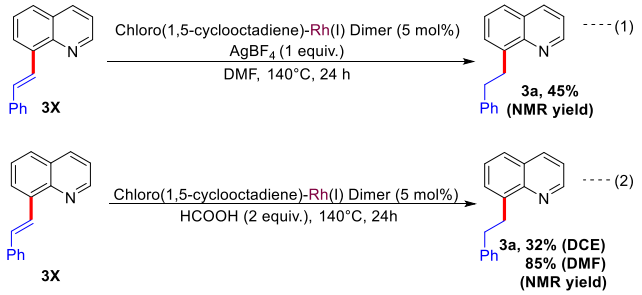
Further, to get an idea of intermediate, standard reaction was analyzed at a different time interval (Scheme 4).

Initially, at 2h, alkenylated product (**3X**) was detected in a major amount (60%) compared to alkylated product (27%). After 18h, alkylated product (94%) was observed as the only major product whereas **3X** was found in traces.[22] This experiment indicated that it might be possible that alkenylated product is getting reduced to the final product during the reaction. To confirm this, **3X** was reacted under standard reaction conditions which provided only 10% alkylated product. These experiments indicated that **3X** might not be the only intermediate in the course of the current reaction.



Scheme 4. Intermediate study.

Further, use of Rh(I) instead of Rh(III) provide 45% yield of **3a** from **3X** which indicate the role of Rh (I) species in the reduction reaction (Scheme 5, equation 1). Here silver salt ($AgBF_4$) must be involved in the conversion of DMF to Me_2NH and formic acid.[28] Intermediate **3X** can undergo a reduction in the presence of Rh(I) and HCOOH generated from DMF to provide final product and Rh(I) species.[29] To confirm this, reduction of **3X** to **3a** was carried out in the presence of Rh (I) and HCOOH using DCE as solvent (Scheme 5, equation 2). Under this reaction condition, **3a** was observed in 32% yield. This experiment proves the fate of HCOOH formed during the reaction from $AgBF_4$ and DMF. Finally, the reaction carried out in the presence of Rh(I) and HCOOH without using $AgBF_4$ in DMF as solvent provided 85% yield of **3a** (Scheme 5, equation 2).

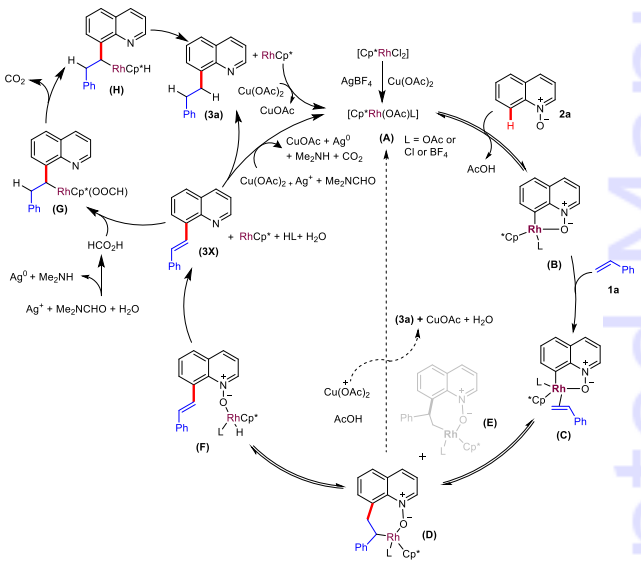


Scheme 5. Intermediate study.

Competition experiment revealed that electron-rich quinoline *N*-oxide is favored over electron deficient suggesting that former is kinetically favored.[22] In our earlier report, for the first time we have characterized a five remembered rhodacycle with quinoline *N*-oxide.[20c] This metallacycle might be an intermediate in current reaction also as it was able to catalyze the current reaction, albeit in low yield.[22]

Based on the above experiments and literature report, we proposed a plausible mechanistic cycle (Scheme 6).[20c,30] The reaction is probably initiated by C(8)-H bond activation of **2a** by active rhodium species (**A**)[31] leading to a five-membered rhodacycle (**B**). Further, coordination of **1a** with rhodacycle initiate its 1,2-insertion in linear/ branched fashion giving intermediate **D** and **E**, however, *β*-hydride elimination takes place from more favorable product **D** leading to intermediate **F**. Reductive elimination of acid from **F** can lead to the formation of intermediate **3X** along with the generation of Rh(I) species. Intermediate **3X** can undergo a reduction in the presence of Rh(I) and HCOOH generated from DMF to provide final product and Rh(I) species.[29] This is supported by the experiment where the reduction of olefin intermediate was observed in the presence of Rh(I), DMF and $AgBF_4$ (Scheme 5, equation 1).[22] Silver salt ($AgBF_4$) must be involved in the oxidation of DMF to formic acid. The Rh(III) active catalytic species is regenerated by oxidation of Rh(I) with $Cu(OAc)_2$. In an alternate pathway, intermediate **D** could also provide the final product **3a** in the presence of $Cu(OAc)_2$ and AcOH.

In summary, a Rh-catalyzed strategy has been developed for the regioselective C-8 alkylation of quinoline using olefin as alkyl source. In this report, *N*-Oxide enables the site selective C-H activation and act as a traceless directing group. The generality and usefulness of the developed catalytic method was established by synthesizing 37 C-8 alkylated quinolines and Ep4 agonist, respectively. Mechanistic study showed that DMF is not only acting as reaction media but also crucial for the reduction of olefin intermediate.



Scheme 6. Probable reaction pathway.

Experimental Section

Procedure for C-8 alkylation of Quinoline *N*-Oxides with olefins: To an oven-dried screw cap reaction vial charged with a spinvane magnetic stir-bar, $[Cp^*RhCl_2]_2$ (5 mol%) and $AgBF_4$ (1 equiv.) were added. Depending on the physical state of the quinoline *N*-oxide (0.1 mmol) and olefin (0.2 mmol), solid compounds were weighed along with the other reagents, whereas liquid reagents, AcOH (2 equiv.) were added by micropippete and DMF was added by laboratory syringe, respectively. The reaction vial was closed with screw cap and kept for vigorous stirring on a preheated oil bath at 140°C for 24h. After completion, the reaction mixture was allowed to cool and extracted with ethyl acetate. Ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography using silica

gel (230-400 mesh size) and appropriate mixture of *n*-hexane: EtOAc as eluent.

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[22] See supporting information for more detail.

[23] CCDC 1487039 (**4f**), contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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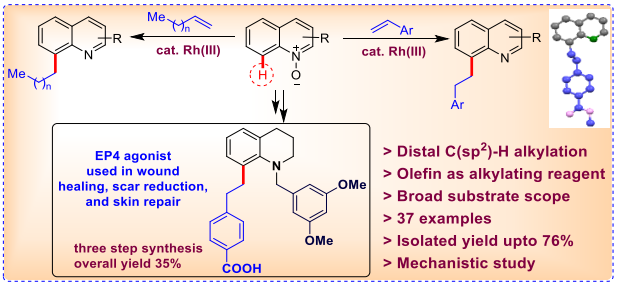
UPDATE

Rhodium-Catalyzed Remote (C-8) alkylation of Quinolines with Activated and Unactivated Olefins: Mechanistic Study and Total Synthesis of EP4 Agonist



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