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Rh-Catalyzed, Regioselective, C−H Bond Functionalization: Access to Quinoline-Branched Amines and Dimers

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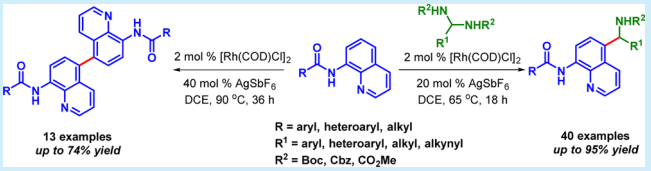
Supporting Information

ABSTRACT: Rh-catalyzed, chelation-induced, C-5 regioselective C−H functionalization of 8-amidoquinolines with a range of *N*-Boc aminals is reported for the first time. The addition of in situ generated imines to C(sp^2)−H bonds afforded branched amines in good to excellent yields. Moreover, this transformation features good functional group compatibility, broad substrate scope, and mild reaction conditions and is suitable for gram-scale synthesis. In addition, an unprecedented, chelation-induced, site-selective, remote dimerization of quinolines led to the formation of dimer frameworks in moderate yields under Rh-catalyzed conditions.



Metal catalyzed C−H functionalization has emerged as a powerful tool due to its ability to enable the direct introduction of complex functional groups into an assortment of organic molecules in an environmentally benign and efficient manner.[1] Among the rich array of metal catalysts that mediate C−H functionalization, rhodium complexes have particularly attracted considerable attention as versatile agents for C−H bond activation due to their high functional group compatibility and catalytic efficacy.[2] While substantial progress has been made for the directing group-assisted dimerization (eq 1, Figure 1)[3] and

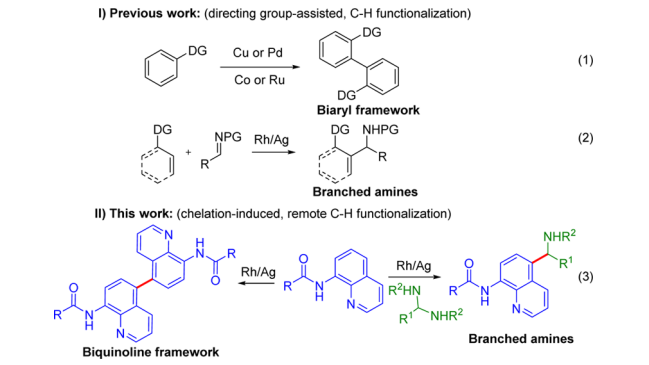


Figure 1. Directing group assisted and remote C−H functionalization reactions.

addition of C(sp^2)−H bonds to polarized π-bonds for the synthesis of amines and other heterocycles (eq 2, Figure 1),[4,5] site-selective functionalization of unactivated, remote C−H bonds remains a fundamental and ongoing challenge in synthetic chemistry.[6] To this end, Stahl et al. reported the Cu-catalyzed, remote C5-selective chlorination of 8-amidoquinolines.[7] Subsequently, Cu- or Co-catalyzed C−heteroatom bond formation at the C5 and/or C7 positions of quinoline has been reported by various research groups.[8−10] However, an efficient method for C−C bond formation at the remote C5 position of quinoline is still rare.[11] The remote C5−H functionalization remains unsatisfied with regard to the development of novel transformations, mild conditions, and selectivity.

Branched amines are an important class of organic molecules due to their prevalence in natural products, pharmaceuticals, and agrochemicals.[12] One of the principle approaches to these molecules is the addition of organometallic reagents to an imine.[13] Recently, directing group-assisted addition of unactivated C−H bonds to imines has been developed and provides a powerful alternative for the synthesis of branched amines via mild and atom-economic conditions.[4] *N*-Boc aminal is an appropriate precursor for in situ generation of the imine due to its stability and ease of accessibility.[14] To the best of our knowledge, there is no report of chelation-induced, site-selective, remote C−H bond functionalization of quinoline derivatives with imines. In continuation of our efforts on C−H functionalization reactions,[15] herein we report the first Rh-catalyzed, site-selective, remote C−H bond functionalization with *N*-Boc aminals (eq 3, Figure 1).

Initially, *N*-(quinolin-8-yl)benzamide (**1a**) and di-*tert*-butyl (phenylmethylene)dicarbamate (**2a**) were chosen as model substrates for the optimization of reaction parameters (Table 1). When the reaction was carried out in the presence of catalytic $Pd(OAc)_2$ and $AgSbF_6$ at 100 °C for 24 h in toluene, the corresponding branched amine **3a** was isolated in 12% yield as a result of C5-selective addition of **1a** to *N*-Boc-aminal **2a** (entry 1). The structure of **3a** was unambiguously determined by single-crystal X-ray diffraction (Scheme 1). Exposure of **1a** and **2a** to a catalytic amount of $Pd(OAc)_2/Cu(OAc)_2$ afforded the desired amine **3a** in 16% yield (Table 1, entry 2). A variety of metal

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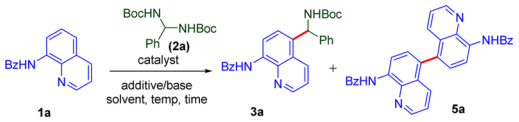
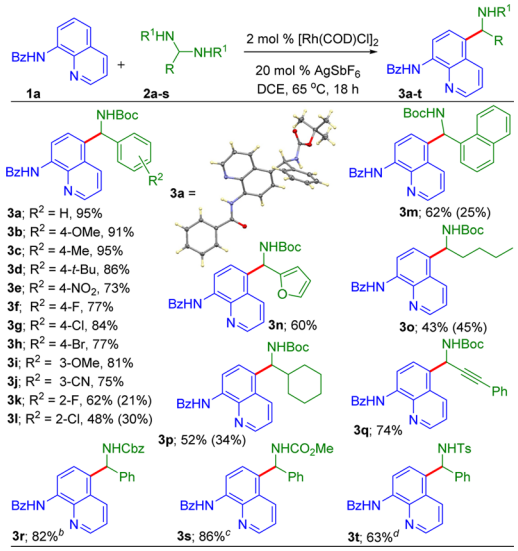
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive/base	solvent	temp/time (°C/h)	yield[h] (3a/5a)
1	$Pd(OAc)_2$	$AgSbF_6$	toluene	100/24	12/0
2[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	100/24	16/0
3[c]	CuI	K_2CO_3	DMF	100/24	0/0
4	[Ru(*p*-cymene)Cl_2]$_2$	$AgSbF_6$	toluene	100/24	35/8
5	[Rh(COD)Cl]$_2$	$AgSbF_6$	toluene	100/24	68/14
6[d]	$Ni(OTf)_2$	$AgSbF_6$	toluene	100/24	0/0
7[e]	$Fe(OTf)_3$	$AgSbF_6$	toluene	100/24	0/0
8	[Rh(COD)]OTf	$AgSbF_6$	DCE	65/18	65/2
9	$Rh_2(esp)_2$	$AgSbF_6$	DCE	65/18	42/3
10	[Rh(COD)Cl]$_2$	$AgNO_3$	DCE	65/18	74/0
11	[Rh(COD)Cl]$_2$	Ag_2CO_3	DCE	65/18	6/0
12	[Rh(COD)Cl]$_2$	AgOTf	DCE	65/18	75/4
13	[Rh(COD)Cl]$_2$	AgOAc	DCE	65/18	11/2
14	**[Rh(COD)Cl]$_2$**	**$AgSbF_6$**	**DCE**	**65/18**	**95/0**
15	[Rh(COD)Cl]$_2$		DCE	65/24	0/0
16		$AgSbF_6$	DCE	65/24	0/0
17[f]	[Rh(COD)Cl]$_2$	$AgSbF_6$	DCE	65/24	69/0
18[g]	[Rh(COD)Cl]$_2$		DCE	65/24	trace

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.5 mmol), Rh or Ru catalyst (2 mol %), $Pd(OAc)_2$ (10 mol %), CuI (20 mol %), additive (20 mol %), solvent (4 mL). [b]$Cu(OAc)_2$ (0.4 mmol). [c]K_2CO_3 (0.4 mmol). [d]$Ni(OTf)_2$ (10 mol %). [e]$Fe(OTf)_3$ (10 mol %). [f]$AgSbF_6$ (4 mol %). [g][Rh(COD)Cl]$_2$ (100 mol %). [h]Isolated yields.

Scheme 1. Remote C-5 Functionalization of 1a with *N*-Boc Aminals[a]



[a]Reaction conditions: **1a** (0.4 mmol), **2a–s** (0.5 mmol), [Rh(COD)Cl]$_2$ (2 mol %), $AgSbF_6$ (20 mol %), 1,2-dichloroethane (DCE) (4 mL), 65 °C, 18 h. [b]Dibenzyl (phenylmethylene)dicarbamate (**2r**) used as a coupling partner. [c]Dimethyl (phenylmethylene)dicarbamate (**2s**) used as a coupling partner. [d](*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide (**2t**) used as a coupling partner. The values in parentheses refer to the amount of recovered starting material.

catalysts and additives were examined (entries 3–7). Under ruthenium catalysis, compound **3a** was isolated in 35% yield along with the dimer **5a** in 8% yield (entry 4). With the [Rh(COD)Cl]$_2$/$AgSbF_6$ catalytic system at 100 °C in toluene, a mixture of amine **3a** (68%) and dimer **5a** (14%) was isolated (entry 5). Cu, Fe, and Ni catalytic conditions were ineffective in this transformation (entries 3, 6, and 7). By careful analysis of remote C5-selective functionalization reaction outcomes with these metal catalysts, Rh catalysis was shown to exhibit favorable efficiency and the best yield toward remote functionalization. This advantage inspired us to conduct further screening with Rh as the optimal catalyst. Further investigation and optimization involved changing the solvent to DCE and lowering the reaction temperature as well as utilizing various Rh catalysts (entries 8–10) and diverse silver salts (entries 11–14). These studies revealed that [Rh(COD)Cl]$_2$ in combination with $AgSbF_6$ was excellent for improving the reaction efficiency and gave **3a** in 95% yield as a single product (entry 14). Other rhodium catalysts and silver salts such as $AgNO_3$, Ag_2CO_3, AgOAc, and AgOTf were found to be less effective in this transformation. The reaction failed in the absence of either [Rh(COD)Cl]$_2$ or $AgSbF_6$ (entries 15 and 16).[16] Additionally, the reaction also proceeded smoothly with 4 mol % of $AgSbF_6$ (entry 17), and no product was observed with 100 mol % of [Rh(COD)Cl]$_2$ (entry 18).[17]

Having determined the optimized reaction conditions, we initially probed the versatility of site-selective, remote C–H functionalization with regard to a diverse class of *N*-Boc aminals using **1a** as the coupling partner (Scheme 1). *N*-Boc aminals bearing various functional groups, including electron-donating or electron-withdrawing groups, all gave the corresponding branched amines in good to excellent yields (Scheme 1, **3a–e**). Notably, halogenated aminals (**2f–h**) were also well-tolerated in this protocol and provided the corresponding amines in good yields (**3f–h**). Moreover, *meta*-substituted *N*-Boc aminals were successful under the reaction conditions, delivering branched amines in 81% (**3i**) and 75% (**3j**) yields, respectively. Importantly, *ortho*-substituted aminals were compatible in the reaction, furnishing the desired products in good, although lower, yields (**3k**, 62%; **3l**, 48%). Di-*tert*-butyl (naphthalen-1-ylmethylene)-dicarbamate (**2m**) reacted well under the Rh-catalyzed conditions and provided the corresponding product **3m** in 62% yield. Similarly, a heteroaromatic aminal (**2n**) was also well-tolerated and furnished the expected branched amine **3n** in 60% yield. Besides the aromatic aminals, aliphatic *N*-Boc aminals (**2o** and **2p**) were also suitable for this transformation, delivering the aliphatic amines **3o** in 43% and **3p** in 52% yields, respectively. Surprisingly, di-*tert*-butyl (3-phenylprop-2-yne-1,1-diyl) dicarbamate (**2q**) was compatible with these conditions and afforded the propargylamine derivative (**3q**) in 74% yield. It is worth noting that the remote C–H functionalization was also suitable with aminals (**2r** and **2s**) prepared from Cbz-NH_2 and methyl carbamate, respectively, and gave the desired products (**3r** and **3s**) in good yields. The *N*-Ts-branched amine (**3t**) was prepared using the imine (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**2t**) as a coupling partner with **1a** under optimal conditions.

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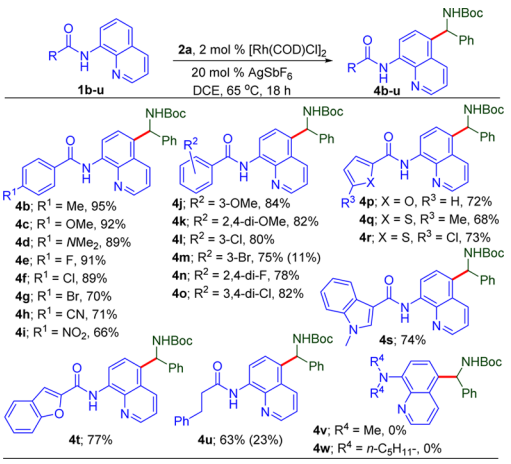
Next, the scope and generality of substituted 8-amidoquinolines were explored under the optimal reaction conditions (Scheme 2). A range of quinoline amides bearing various

Scheme 2. Substrate Scope of 8-Amidoquinolines for Remote Functionalization.[a]

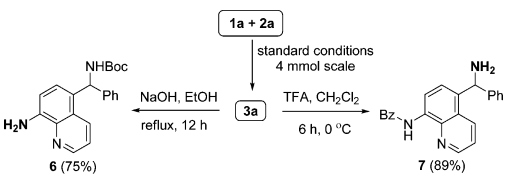


[a]Reaction conditions: **1b−w** (0.4 mmol), **2a** (0.5 mmol), [Rh(COD)Cl]$_2$ (2 mol %), $AgSbF_6$ (20 mol %), DCE (4 mL) and 65 °C, 18 h. The values in the parentheses refer to the amount of recovered starting material.

electron-donating, electron-withdrawing, or halogen substituents at the *para* position all reacted smoothly with **2a**, and the desired branched amines were isolated in 66−95% yields (**4b−i**). In a similar way, *meta*-substituted amides (**1j,l,m**) and disubstituted quinoline benzamides (**1k,n,o**) were also tolerated. Electron-rich substrates gave slightly higher yields than electron-poor substrates. A diverse class of heterocyclic amides could generate the corresponding branched amines in moderate to good yields (**4p−t**, 68−77%). Surprisingly, the aliphatic amide (**1u**) proved amenable to the standard conditions, delivering **4u** in 63% yield. An examination of the 8-amidoquinolines with rhodium-catalyzed conditions revealed that the reaction is compatible with variously substituted aromatic amides, heteroaromatic amides, as well as aliphatic amides. *N,N*-Dialkylquinolin-8-amines (**1v** and **1w**) failed to give the corresponding products under standard conditions.

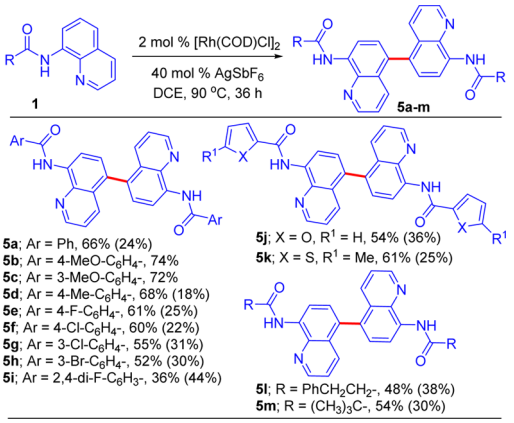
As a further demonstration of the synthetic expediency of this method, a gram-scale (4 mmol) reaction was conducted with **1a** and **2a** using standard reaction conditions to furnish the branched amide **3a** in 79% yield (Scheme 3). The amide bond was cleaved using NaOH in EtOH at 80 °C to provide the 8-aminoquinoline derivative **6** in 75% yield.[18] Furthermore, *N*-Boc-deprotection of **3a** under acidic conditions provided the corresponding benzylic amine **7** in 89% yield (Scheme 3).[19]

Scheme 3. Gram-Scale Synthesis and Functional Group Modification of 3a



With the amine derivatives of 8-amidoquinoline in hand, the feasibility of Rh-catalyzed, remote C-5 dimerization was investigated. Based on our initial results during the reaction optimization process, we knew dimerization was feasible and a consistent byproduct of the remote functionalization method. Having successfully accomplished our goal of C-5 functionalization, we set out to optimize conditions under which dimerization would predominate (see the Supporting Information). For that purpose, we performed the reaction of **1a** in the presence of 2 mol % of [Rh(COD)Cl]$_2$ and 40 mol % of $AgSbF_6$ using elevated temperatures and extended reaction times. The reaction proceeded at the remote C-5 position, and the symmetrical quinoline dimer **5a** was obtained in 66% yield (Scheme 4).[20] We

Scheme 4. Substrate Scope for the C-5 Dimerization Reaction[a]



[a]Reaction conditions: **1** (0.4 mmol), [Rh(COD)Cl]$_2$ (2 mol %), $AgSbF_6$ (40 mol %), DCE (4 mL), 90 °C, 36 h. The values in parentheses refer to the amount of recovered starting material.

then surveyed additional substrates with various groups to gauge the usefulness of the Rh-catalyzed dimerization and obtained the expected C-5 dimers (**5b−i**) in moderate yields. When heterocyclic amides were used as substrates, site-selective dimerization products were also obtained in reasonable yields (**5j**, 54% and **5k**, 61%). Gratifyingly, aliphatic amides (**1u** and **1x**) also afforded the desired products in 48% (**5l**) and 54% (**5m**) yields, respectively. The structures were confirmed using HRMS and 2D-NMR.

In conclusion, we report the first successful example of Rh-catalyzed, chelation-induced, C5-selective, remote functionalization of 8-amidoquinoline derivatives using *N*-Boc aminals as coupling partners. Further benefits include complete site selectivity, a broad substrate scope, and high functional group tolerance. We have also successfully extended the Rh-catalyzed conditions for the synthesis of a quinolone-based dimer framework. Further efforts to extend the applications of this new protocol are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02848.

General experimental procedures and spectroscopic data of all the compounds; 2D-NMR and HRMS spectral data for representative compounds; and X-ray crystallographic data for **3a** (PDF)

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Notes

The authors declare no competing financial interest.

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(16) On the basis of radical inhibition experiments with TEMPO, formation of the dimer product, and previous work,[7−11,21] the reaction appears to occur via a single-electron transfer (SET) pathway (see the Supporting Information for details).

(17) Various Lewis acids [$FeCl_3$ (10 mol % and 100 mol %), $BiCl_3$ (10 mol %), and $Sc(OTf)_3$ (10 mol %), **1a** (0.4 mmol), **2a** (0.5 mmol), DCE (4 mL), 65 °C, 24 h] were screened independently for the synthesis of **3a**. Lewis acids alone failed to effect the transformation.

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