C–H Activation

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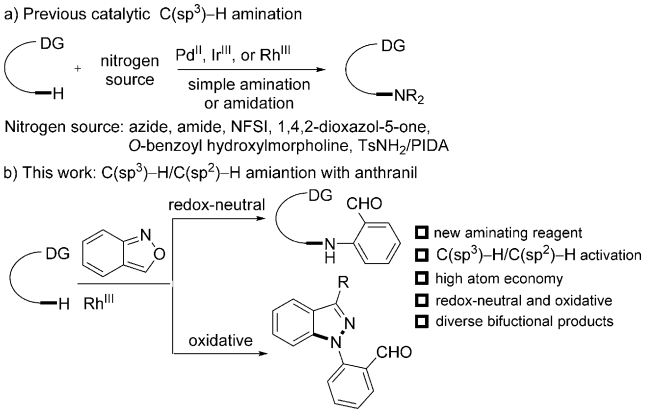
Anthranil: An Aminating Reagent Leading to Bifunctionality for Both C(sp^3)–H and C(sp^2)–H under Rhodium(III) Catalysis

Songjie Yu, Guodong Tang, Yingzi Li, Xukai Zhou, Yu Lan, and Xingwei Li**

Abstract: *Previous direct C–H nitrogenation suffered from simple amidation/amination with limited atom-economy and is mostly limited to C(sp^2)–H substrates. In this work, anthranil was designed as a novel bifunctional aminating reagent for both C(sp^2)–H and C(sp^3)–H bonds under rhodium(III) catalysis, thus affording a nucleophilic aniline tethered to an electrophilic carbonyl. A tridendate rhodium(III) complex has been isolated as the resting state of the catalyst, and DFT studies established the intermediacy of a nitrene species.*

Amines are ubiquitous in a range of biologically active molecules.[1] Atom-economic construction of C–N bonds has been recognized as one of the central topics in synthesis.[2] In addition to the Buchwald–Hartwig[3] and the Chan–Lam aminations,[4] direct amination of C–H bonds constitutes an ideal protocol.[5] Transition metals have exhibited profound potential in catalytic nitrogenation of C(sp^2)–H bonds.[6] However, only limited examples of C(sp^3)–H amination/amidation[7] have been reported using azides,[8] amides,[9] NFSI,[10] 1,4,2-dioxazol-5-ones,[11] and *O*-benzoyl hydroxylmorpholine[12] as nitrogen sources (Scheme 1 a). For such protocols stoichiometric amounts of external oxidants are often required[9a] and there is often formation of byproducts such as N_2,[8a] acids/salts,[10] and CO_2.[11]

Recently Chang and co-workers reported the amidation of arenes using 1,4,2-dioxazol-5-ones as versatile amidating reagents with the loss of CO_2.[13] Despite this success, the system is limited to simple amidation. Ideally, the introduction of multiple functional groups (FGs) simultaneously allows molecular diversity and synthetic versatility. However, this remains a formidable challenge, possibly because of the limited FG compatibility and possible product inhibition. We reasoned that anthranil may serve this purpose in that it is sufficiently coordinating[14] and the N–O bond is polarized and cleavable.[15] Significantly, amination using anthranils could deliver a nucleophilic amino group tethered to an electrophilic formyl group, which can be hard to introduce, and the formyl group may experience compatibility issues in many coupling systems.[16] Notably, the resulting skeleton containing an amino and a carbonyl group represents an important synthetic building block.[17] Although anthranil has been previously shown to couple with organozinc reagents under nickel catalysis,[18] C–H amination using anthranil is unprecedented possibly because of low reactivity and lack of a sufficient driving force. We now report our findings on rhodium(III)-catalyzed direct C(sp^3)–H and C(sp^2)–H amination using anthranils (Scheme 1 b).



Scheme 1. Transition metal catalyzed amination/amidation. DG = directing group.

Our proof-of-concept studies were initiated with the screening of the reaction parameters of the coupling of 8-methylquinoline[19] (**1a**) and anthranil (**2a**; Table 1). Using [{$RhCp^*Cl_2$}$_2$]/$AgSbF_6$ as a catalyst, the coupling proceeded to afford the desired product **3aa** (entry 1). Introduction of PivOH (1.0 equiv) significantly improved the GC yield (entry 2). The GC yield remained essentially unaffected when the catalyst was switched to [$RhCp^*(MeCN)_3$](SbF_6)$_2$ (entries 3 and 4). We identified DCM as the optimal solvent (entries 5–8), from which the product was isolated in 84% yield (entry 5). Lowering either the catalyst loading or the reaction temperature all resulted in slightly reduced yields (entries 9 and 10).

With the optimized reaction conditions in hand, we next explored the scope and generality of this amination system (Scheme 2). Introduction of a variety of alkyl, halo, aryl, alkenyl, and alkynyl groups to different positions of **1a** is fully tolerated, and the aminated product was isolated in 75–96% yield (**3aa**–**qa**). The reaction was not limited to amination of a methyl group, as 8-ethylquinoline coupled efficiently in high yield (**3ra**). Anthranils bearing electron-donating, electron-withdrawing, and halogen groups at different positions all

[*] Dr. S. Yu, G. Tang, X. Zhou, Prof. X. Li
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
Dalian 116023 (China)
E-mail: xwli@dicp.ac.cn
Y. Li, Prof. Y. Lan
School of Chemistry and Chemical Engineering
Chongqing University
Chongqing 400030 (China)
E-mail: lanyu@cqu.edu.cn

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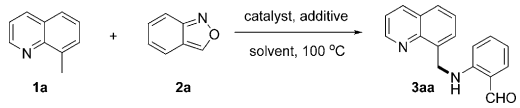
Table 1: Optimization studies.[a]

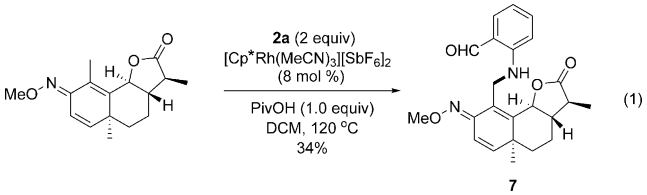


Entry	Cat. (mol%)	Solvent	Yield [%][b]
1[c]	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (20)	DCE	35
2	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (20)	DCE	75
3	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	DCE	76
4[d]	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	DCE	73
5	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	DCM	(84)
6	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	toluene	37
7	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	THF	45
8	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	acetone	31
9	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (4)	DCM	69
10[e]	[RhCp*(MeCN)$_3$](SbF_6)$_2$ (8)	DCM	79

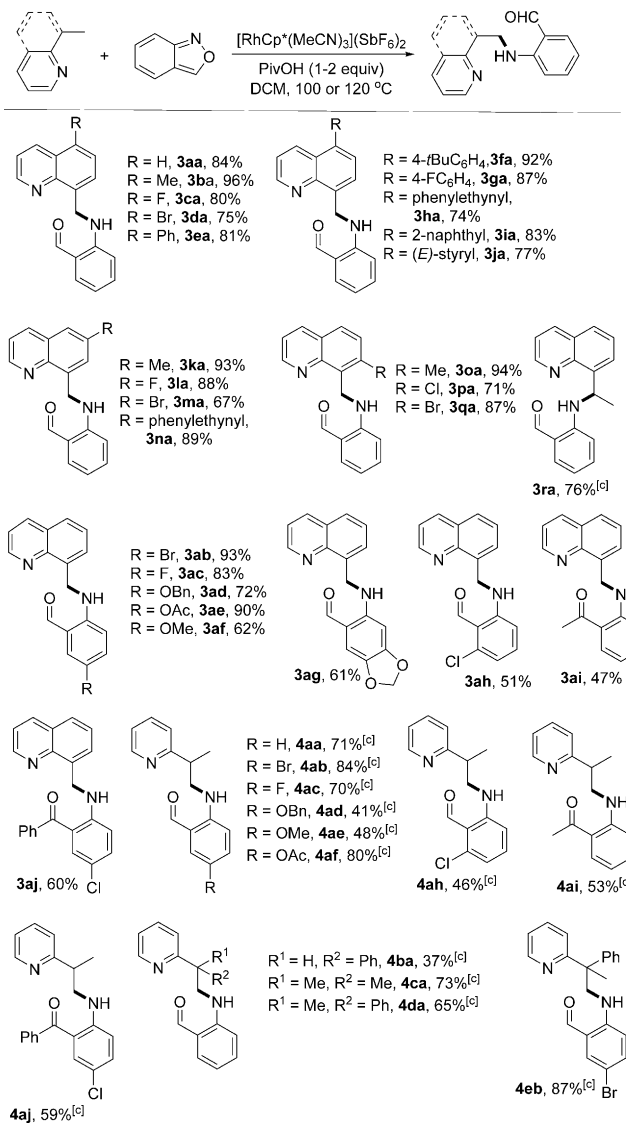
[a] The reaction was carried out using 8-methylquinoline (0.2 mmol), anthranil (0.4 mmol), catalyst, and PivOH (0.2 mmol) in a solvent (3 mL) at 80–100 °C. [b] Determined by GC analysis using biphenyl as a standard. Yield of isolated product given within parentheses. [c] No PivOH. [d] 0.4 mmol PivOH. [e] 80 °C. Cp* = C_5Me_5. DCE = 1,2-dichloroethane, DCM = dichloromethane, Piv = pivaloyl, THF = tetrahydrofuran.

coupled smoothly with **1a** (**3ab**–**aj**), however the electron-donating groups tend to slightly lower the coupling efficiency. The amination reaction was been extended to 3-substituted anthranils, thus affording the desired product with a pendent ketone group (**3ai** and **3aj**). In contrast, subjecting a simple isoxazole to the standard reaction conditions gave no desired product, thus indicating that an aromatization driving force plays a vital role. We next extended the directing group to a pyridine ring. 2-Isopropylpyridine, which failed to undergo C–H activation in previous studies,[11] coupled smoothly with various anthranils, thus leading to desymmetrization in good to high yields (**4aa**–**ai**). The C–H substrate has been extended to a methyl group appended to other tertiary (**4ba**) and quaternary carbon centers (**4ca**–**4eb**). In contrast to these couplings, poor reactivity was observed for 2-ethylpyrine.

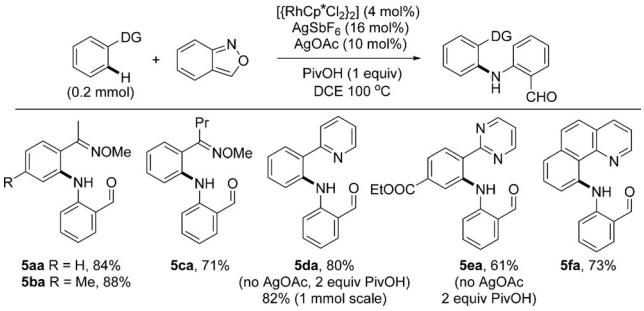
Extension of the C–H substrate to other types of arenes proved successful (Scheme 3). Under modified reaction conditions, the amination of arenes assisted by an oxime ether, pyridine, and pyrimidine all proceeded smoothly in good to high yields (**5aa**–**fa**). Anthranils were also used as aminating reagents for oxidative synthesis of indazoles (**6aa**–**ah**) by C–H activation of protic imines, amidines, and imidate esters (Scheme 4). The reaction is assisted by a the functionalizable NH directing group and both electron-donating and electron-withdrawing groups are tolerated.[20] An oxime ether also proved to be an applicable directing group in the late-stage amination of the oxime derivative of (−)-santonin [Eq. (1)].



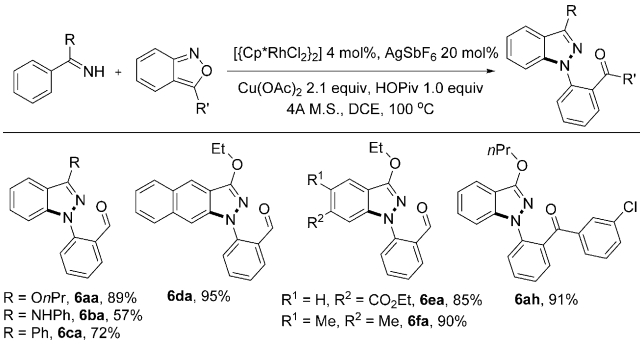
(1)



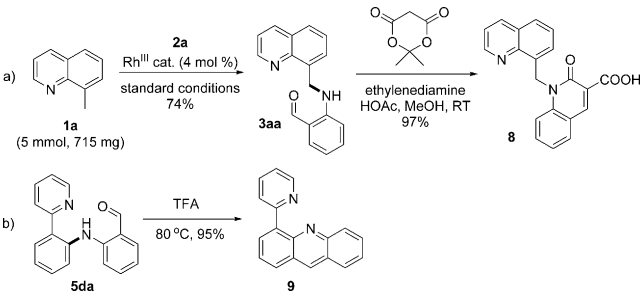
Scheme 2. Amination of C(sp^3)–H bonds. Reaction conditions: 8-alkylquinoline (0.2 mmol), anthranil (0.4 mmol), [RhCp*(MeCN)$_3$](SbF_6)$_2$ (8 mol%), PivOH (0.2 mmol), DCM (3 mL), 100 °C, 20 h. [b] Yield of product isolated after column chromatography. [c] PivOH (0.4 mmol), 120 °C.



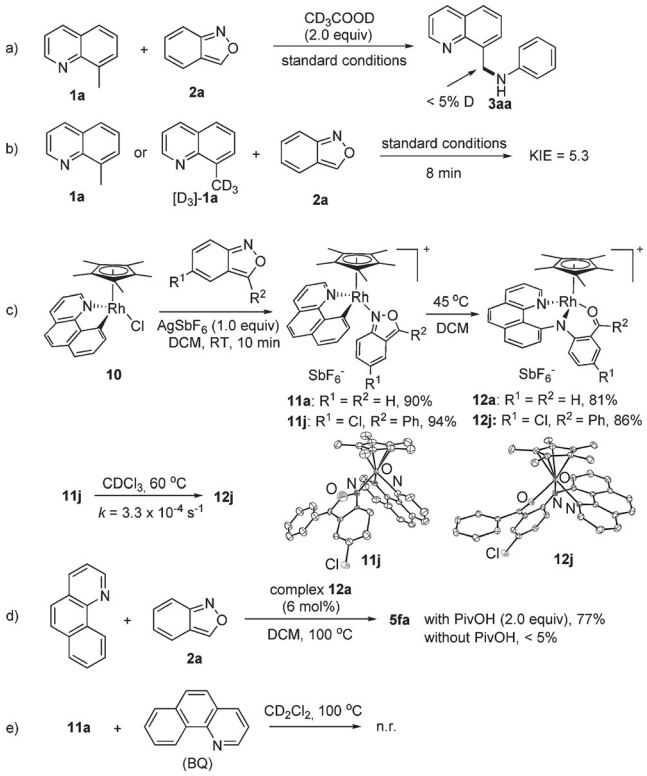
Scheme 3. Amination of arenes (see Supporting Information for details).



Scheme 4. Oxidative synthesis of indazoles (see the Supporting Information for details). M.S. = molecular sieves.



Scheme 5. Gram-scale synthesis and derivatization reactions. TFA = trifluoroacetic acid.

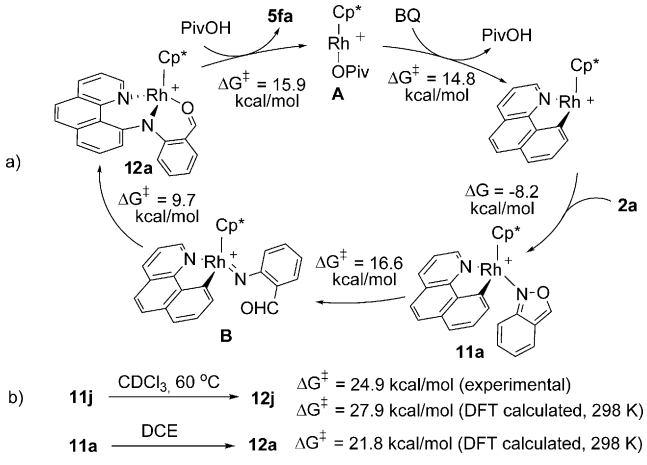


Scheme 6. Mechanistic studies.[24]

Synthetic applications of this protocol have been demonstrated (Scheme 5). Scale-up of the amination of 8-methylquinoline proved successful at a reduced catalyst loading (Scheme 5a). Derivatization of the aminated product has been achieved by taking advantage of the nucleophilic amino and the electrophilic carbonyl. Thus, condensation of **3aa** with Meldrum's acid afforded a carboxyl-functionalized 2-quinolone (**8**) in nearly quantitative yield (Scheme 5a). In another experiment, treatment of **5da** with CF_3COOH led to a Friedel–Crafts dehydrative cyclization to afford an acridine (**9**) in 95% yield (Scheme 5b).

A series of experiments have been performed to probe the mechanism. Significant H–D exchange was observed at the methyl position of **1a** in the presence of CD_3COOD and the catalyst, but in the absence of any aminating reagent. However, essentially no deuterium incorporation to the methylene of **3aa** was detected in the presence of **2a** and CD_3COOD (Scheme 6a). This result suggests irreversibility of the C–H activation in the catalytic system. To probe the C–H activation process, a kinetic isotope effect was measured on the basis of two reactions run in parallel using **1a** and [D_3]-**1a**. The rather large value of $k_H/k_D = 5.3$ indicates that cleavage of the C–H bond is likely involved in the turnover-limiting step (Scheme 6b). Moreover, introduction of TEMPO (1 equiv) to the reaction of **1a** and **2a** had only marginal influence, thus suggesting irrelevance of radical species in this system.

To further understand the interactions between the Rh–C bond and the anthranil, an equimolar reaction of **10**, anthranil, and $AgSbF_6$ was performed to rapidly afford the anthranil complex **11**, which can lead to the N,N,O tridentate



Scheme 7. DFT studies of the mostly likely reaction pathway.

complex **12** (Scheme 6c). Both **11j** and **12j** were characterized by X-ray crystallography. Moreover, the first-order rate constant for the conversion of **11j** into **12j** (60 °C, $CDCl_3$) was measured to be $3.3 \times 10^{-4}\ s^{-1}$, which corresponds to a $\Delta G^{\neq}$ value of 24.9 kcal mol^{-1} (Schemes 6c and 7). The tridentate complex proved to be an active catalyst for the coupling of benzo[*h*]quinolone (BQ) and anthranil (Scheme 6d). Of note, the PivOH additive was indispensable because only traces of **5fa** were detected when it was omitted. This outcome agrees with our observation that simple heating of a CD_2Cl_2 solution of **12a** and BQ gave essentially no

reaction (100 °C), and it stands in stark contrast to the previously observed facile interactions between the chelating intermediates and an incoming arene substrate.[21] Therefore, the role of PivOH is twofold: it both facilitates the activation of the C–H bond as a proton shuttle and protonates the N–Rh bond in **12a** to release the coupled product and generate an active rhodium(III) carboxylate species.

On the basis of these observations, four distinct pathways with respect to N–O cleavage have been proposed for the coupling of BQ and anthranil (see the Supporting Information), namely, the SN_2-type N–O cleavage, the N–O oxidative addition, the aryl migratory insertion (into the C=N bond) pathway, and the nitrenoid pathway. We applied DFT studies and established the nitrenoid[13,22] pathway as the lowest energy one (Scheme 7a). In this pathway, starting from the active catalyst **A**, C–H activation of BQ occurs with the assistance of a pivalate anion by a concerted metalation-deprotonation mechanism with a calculated activation free energy of 14.8 kcal mol^{-1}. Subsequent coordination of anthranil leads to formation of **11a** with $\Delta G = -8.2$ kcal mol^{-1}. Formation of the nitrenoid species **B** from **11a** readily occurs with an activation free energy of 16.6 kcal mol^{-1}. Subsequent migratory insertion of the aryl group in **B** carries a barrier as low as 9.7 kcal mol^{-1}. The lowest lying species is **12a** and the overall barrier for the catalytic turnover was calculated to be 35.7 kcal mol^{-1}, which seems to be in agreement with the requirement of 100 °C reaction temperature. To compare with the experimental value of $\Delta G^{\neq}$ 24.9 kcal mol^{-1} for the **11j** into **12j** conversion, this activation free energy was calculated to be 27.9 kcal mol^{-1} (Scheme 7b and the Supporting Information), thus indicating the reliability of our DFT outcomes. Comparisons of the DFT-calculated $\Delta G^{\neq}$ values for the conversions of **11a** and **11j** revealed that the kinetic barrier is higher for **11j** as a result of ground-state stabilization.

In summary, we have designed anthranil as a novel aminating reagent for rhodium-catalyzed amination of both C(sp^2)–H and C(sp^3)–H bonds by a C–H activation pathway under both redox-neutral and oxidative conditions, thus leading to the formation of an amino group tethered to a proximal carbonyl in high atom economy. A broad scope of substrates has been established. The bifunctionalization of arene substrastes has allowed facile synthesis of heterocycles.[23] A tridentate rhodium(III) complex has been isolated as a key intermediate, and DFT studies suggested the intermediacy of a nitrenoid species. This method of introducing bifunctionality under operationally simple reaction conditions may find applications in the synthesis of complex structures.

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Keywords: amination · arenes · C–H activation · reaction mechanisms · rhodium

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[24] CCDC 1455664 (**11j**) and 1455665 (**12j**)contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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