C–H Activation

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Rhodium(III)-Catalyzed Amidation of Unactivated C(sp^3)–H Bonds

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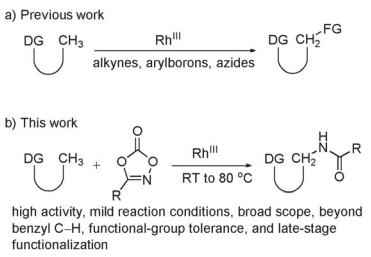
Abstract: *Nitrogenation by direct functionalization of C–H bonds represents an important strategy for constructing C–N bonds. Rhodium(III)-catalyzed direct amidation of unactivated C(sp^3)–H bonds is rare, especially under mild reaction conditions. Herein, a broad scope of C(sp^3)–H bonds are amidated under rhodium catalysis in high efficiency using 3-substituted 1,4,2-dioxazol-5-ones as the amide source. The protocol broadens the scope of rhodium(III)-catalyzed C(sp^3)–H activation chemistry, and is applicable to the late-stage functionalization of natural products.*

The significance of C(sp^3)–H activation leading to C–N bond formation has been extensively exemplified because C–N linkages are ubiquitous in pharmaceuticals, biologically active compounds, and natural products.[1] Consequently, the direct amination/amidation of unactivated C(sp^3)–H bonds has received increasing attention.[2] In the past decade, only limited examples of direct amination of C(sp^3)–H Bonds has been reported by using palladium,[3,4] rhodium(II),[5] copper,[6] iridium,[7] and other catalysts.[8] Recently, rhodium(III)-catalyzed[9] C–H activation has been increasingly explored, and provides unique synthetic methodologies with high activity, selectivity, broad substrate scope, and functional-group tolerance. Despite these attractive processes, the coupling reactions are mostly based on C(sp^2)–H activation.[10,11] Thus, there are only a few examples on the functionalization of unactivated C(sp^3)–H bonds using rhodium(III) catalysis, as in the coupling with alkynes,[12] activated forms of arenes,[13] and azides[14] (Scheme 1 a). Recently, Chang and co-workers reported an elegant iridium(III)-catalyzed amidation for a broad scope of C(sp^3)–H bonds using organic azides.[7] Despite the progress, rhodium(III)-catalyzed C(sp^3)–H activation reactions, especially amidation reactions, typically suffer from limited substrate scope and harsh reaction conditions, and only amidation of benzylic C–H bonds, such as that in 8-methylquinolines, has been realized.[14]

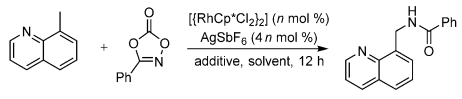


Scheme 1. C–H activation of unactivated C(sp3)–H bonds. DG = directing group, FG = functional group.

The challenges associated with C(sp^3)–H bond activation can be ascribed to the steric hindrance of C(sp^3)–H bonds and the low reactivity of the resulting Rh–C(alkyl) species. Therefore, the stability, coordinating capacity, and reactivity of the coupling partner are major criteria for our design. We now report a mild rhodium(III)-catalyzed C(sp^3)–H amidation for a broad scope of substrates, including 8-alkylquinoline and aliphatic cyclic and acyclic ketoximes. This amidation reaction utilizes 3-substituted 1,4,2-dioxazol-5-ones[15] as the amide sources, and they are particularly attractive nitrene-transfer reagents owing to their high activity, stability, and synthetic accessibility (Scheme 1 b).[16]

We initiated our studies with the screening of reaction conditions in the coupling of 8-methylquinoline (**1a**) with 3-phenyl-1,4,2-dioxazol-5-one (**2a**; Table 1). Using [{RhCp*Cl$_2$}$_2$]/AgSbF$_6$ as a catalyst, coupling occurred in DCE (entry 1) to afford the product **3aa** in 76% yield. The reaction efficiency was slightly lower in CH_2Cl_2 at 25 °C (entry 2). Further introduction of a catalytic amount of

Table 1: Optimization Studies.[a]



Entry	*n*	Additive (mol%)	Solvent	*T* [°C]	Yield [%][b]
1	4	–	DCE	60	76
2	4	–	CH_2Cl_2	25	69
3	4	AgOAc (8)	CH_2Cl_2	25	91
4	2	AgOAc (4)	CH_2Cl_2	25	70
5	2	AgOAc (4)	CH_2Cl_2	40	74
6	4	AgOAc (8)	CH_2Cl_2	25	15[c]
7	4	AgOAc (8)	CH_2Cl_2	25	n.d.[d]
8	4	AgOAc (8)	CH_2Cl_2	25	n.d.[e]
9	4	AgOAc (8)	CH_2Cl_2	25	n.d.[f]
10	4	AgOPiv (8)	CH_2Cl_2	25	90
11	4	AgOAc (8)	1,4-dioxane	25	63
12	4	AgOAc (8)	toluene	25	59
13	4	AgOAc (8)	MeOH	25	47
14	4	AgOAc (8)	CH_2Cl_2	25	73[g]

[a] Reactions were carried out by using [{RhCp*Cl$_2$}$_2$] (4.0 mol%)/AgSbF$_6$ (16 mol%), AgOAc (8 mol%), 8-methylquinoline (0.2 mmol) and 3-phenyl-1,4,2-dioxazol-5-one (0.24 mmol) in a solvent (3 mL) under nitrogen at 25 °C for 12 h. [b] Yield of product isolated after column chromatography. [c] Reaction was performed with 5-phenyl-1,3,2,4-dioxathiazole 2-oxide. [d] Reaction was performed with 5,5-dimethyl-3-phenyl-1,4,2-dioxazole. [e] No AgSbF$_6$ was used. [f] No rhodium catalyst was used. [g] [{IrCp*Cl$_2$}$_2$] was used to replace [{RhCp*Cl$_2$}$_2$]. Cp* = C$_5$Me$_5$, DCE = 1,2-dichlorethane.

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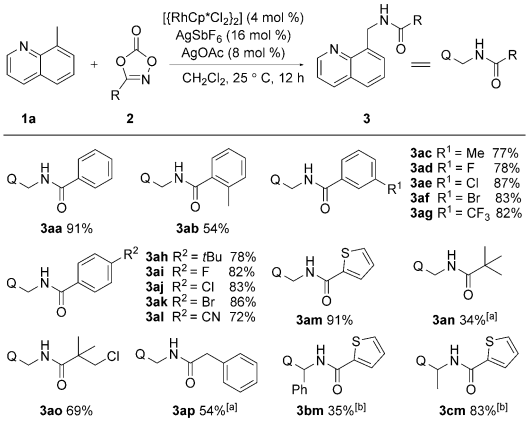
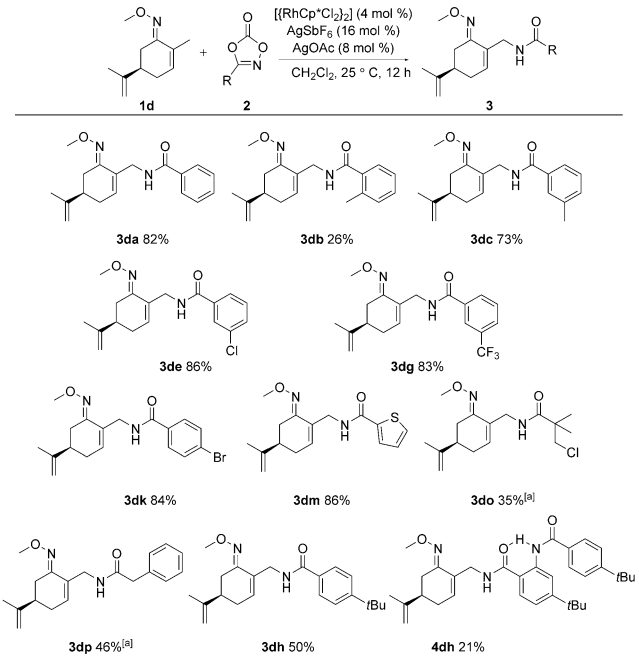
AgOAc significantly improved the yield to 91% (entry 3), and a similarly high yield was realized using AgOPiv (entry 10). Using CsOAc or NaOAc as an additive only slightly increased the yield (see the Supporting Information). Thus, these silver salts likely both facilitate C–H activation and activate the amidating reagent. Decreasing the catalyst loading gave inferior results, even at higher temperature (entries 4 and 5). Poor or no conversion was observed when the amidating reagent was replaced by either 5-phenyl-1,3,2,4-dioxathiazole 2-oxide or 5,5-dimethyl-3-phenyl-1,4,2-dioxazole (entries 6 and 7). Control experiments revealed that both [{RhCp*Cl_2}$_2$] and $AgSbF_6$ are necessary (entries 8 and 9). A screening of solvents indicated that other solvents afforded inferior results (entries 11–13). Other transition metals, such as [{IrCp*Cl_2}$_2$], only exhibited lower efficiency (entry 14).

The scope with respect to the amidating reagent was examined next in the coupling of **1a** (Scheme 2). Thus, amidating reagents bearing different electron-donating and electron-withdrawing groups at different positions of the phenyl ring all coupled smoothly with **1a**. Furthermore, the 3-substituent in the amidating reagent is not limited to a phenyl ring, as 3-(thiophen-2-yl)-1,4,2-dioxazol-5-one also coupled to afford the product **3am** in 91% yield. 3-Alkyl-substituted amidating reagents are also viable (RT–60 °C), although somewhat lower yields (34–69%) of the products were isolated (**3an**–**ap**). Furthermore, amidation of a benzylic methylene C–H bond took place to afford **3bm** in 35% yield. In contrast, the methylene C–H bond in 8-ethylquinoline was amidated in high yield (**3cm**), and is indicative of the tolerance of steric hindrance.

To further define the scope and limitations of this reaction, amidation of the oxime ether of L-(−)-carvone has been examined (Scheme 3). Amidating reagents bearing different electron-withdrawing and electron-donating groups at the *ortho* and *meta* positions of the phenyl ring are fully tolerated, and the reaction proceeded with selectivity for



Scheme 2. C–H amidation of 8-methylquinoline (**1a**). Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), AgOAc (8 mol%), [{RhCp*Cl_2}$_2$] (4 mol%), $AgSbF_6$ (16 mol%), CH_2Cl_2 (3 mL), 25 °C, 12 h, sealed tube under nitrogen. Yield is that of product isolated after column chromatography. [a] Reaction was performed with AgOPiv (8 mol%) at 60 °C. [b] Reaction was performed at 80 °C.



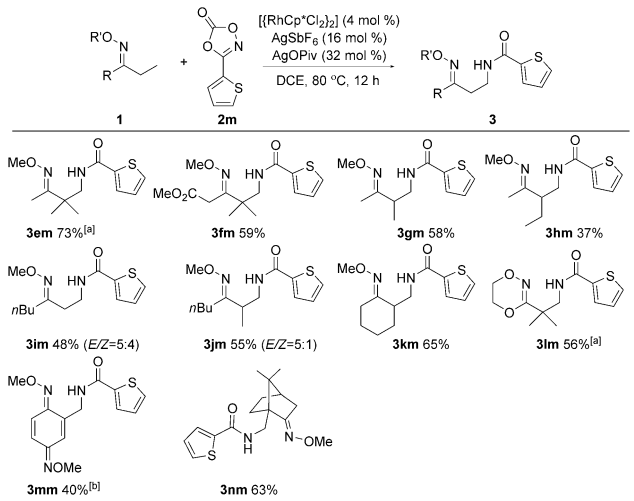
Scheme 3. C–H amidation of aliphatic O-methyl ketoxime. Reaction conditions: oxime ether of L-(−)-carvone (0.2 mmol), 2 (0.21 mmol), AgOAc (8 mol%), [{RhCp*Cl_2}$_2$] (4 mol%), $AgSbF_6$ (16 mol%), CH_2Cl_2 (3.0 mL), 25 °C, 12 h, sealed tube under nitrogen. Yield is that of product isolated after column chromatography. [a] Reaction was performed at 60 °C.

monoamidation. In contrast, a small amount of the diamidation product was observed when amidating reagents bearing either a simple or *para*-substituted phenyl ring were employed, wherein the second amidation refers to additional *ortho* C–H amidation at the phenyl ring. Thus, the diamidation product **4dh** was isolated in 21% yield together with the monoamidation product **3dh**.

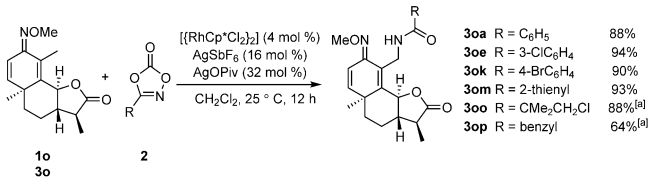
This amidation reaction can be further extended to aliphatic cyclic and acyclic ketoximes which are embedded within other backbones (Scheme 4). Thus, the amidation of primary C–H bonds in methyl, ethyl, isopropyl, and *tert*-butyl groups all proceeded smoothly (25–80 °C), and the products were isolated in moderate to good yields. In these reactions, a high loading of AgOPiv is mostly necessary to ensure higher activity, and only traces of the diamidation product could be detected. Clearly, the C(alkyl)–H bonds are not restricted to benzylic and allylic C–H ones, and these unactivated C–H bonds are typically encountered for the late-stage functionalization of value-added molecules.

To further demonstrate the applicability of this protocol to the late-stage functionalization of natural products, the oxime ether of (−)-santonin (**1o**) was synthesized and subjected to the optimal reaction conditions (60–80 °C; Scheme 5). The amidation reaction proceeded exceptionally well to afford the desired products **3oa**–**op** in 64–94% yield.

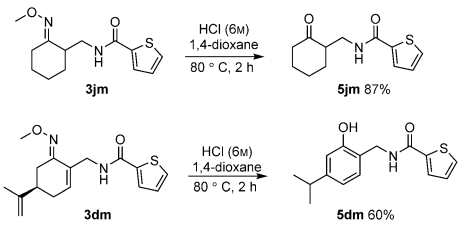
The amidated product can undergo further transformations, such as the ready removal of the DG (Scheme 6). The hydrolysis of aliphatic ketoximes **3** in HCl/1,4-dioxane generated the ketone products **5**.[17] When the oxime **3dm** was subjected to the hydrolysis conditions, further isomer-



Scheme 4. C–H amidation of other aliphatic O-methyl ketoximes. Reaction conditions: 1 (0.2 mmol), 2m (0.21 mmol), AgOPiv (32 mol%), [{RhCp*Cl_2}$_2$] (4 mol%), $AgSbF_6$ (16 mol%), DCE (3.0 mL), 80°C, 12 h, sealed tube under nitrogen. Yield is that of product isolated after column chromatography. [a] Reaction was performed with AgOAc (8 mol%) in CH_2Cl_2 at 25°C. [b] Reaction was performed with AgOAc (8 mol%) in CH_2Cl_2 at 80°C.



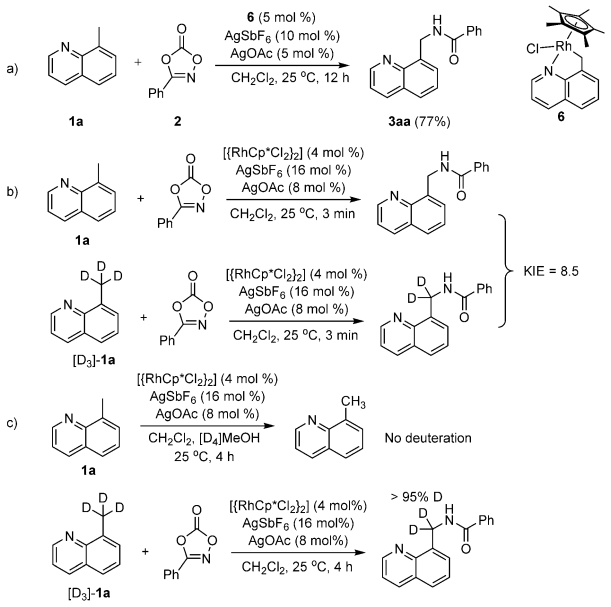
Scheme 5. Late-stage C(sp^3)–H amidation. Reaction conditions: **1o** (0.2 mmol), 2 (0.21 mmol), AgOPiv (32 mol%), [{RhCp*Cl_2}$_2$] (4 mol%), $AgSbF_6$ (16 mol%), DCE (3.0 mL), 80°C, 12 h, sealed tube under nitrogen. Yield is that of product isolated after column chromatography. [a] Reaction was performed with **2** (0.24 mmol), AgOPiv (8 mol%), CH_2Cl_2 at 60°C.



Scheme 6. Deprotection of C(sp3)–H amination products.

ization occurred and the phenol **5dm** was isolated in 60% yield.

Several experiments have been performed to explore the mechanism (Scheme 7). To probe the relevance of C–H activation, the monomeric rhodacyclic complex **6**[11] was used as a catalyst (5 mol%) for the coupling of **1a** and 3-phenyl-1,4,2-dioxazol-5-one, and **3aa** was isolated in 77% yield, thus



Scheme 7. Mechanistic studies.

indicating that C–H activation is likely involved (Scheme 7a). H–D exchange experiments have been carried out for **1a** and [D_3]-**1a** in the presence and absence of the amidating reagent (Scheme 7c). All experiments pointed to no H–D exchange, thus suggesting that the C–H activation is irreversible. Next, a kinetic isotope effect (KIE) was measured for this C–H activation process. Both an intermolecular KIE experiment and two parallel competition reactions afforded consistent results (KIE = 8.5). The large magnitude of the KIE suggests that the C–H bond cleavage is turnover-limiting in the catalytic cycle[18] (see the Supporting Information for a proposed catalytic cycle).

In summary, we have developed an efficient rhodium(III)-catalyzed C(sp^3)–H amidation of alkyl C–H bonds using 3-substituted 1,4,2-dioxazol-5-ones as an amidating reagent. This amidation reaction expands the scope of both coupling partners and proceeds with functional-group tolerance under relatively mild reaction conditions. Importantly, the alkyl C–H groups have been extended beyond benzylic and allylic C–H ones. The amidated products can be further transformed into useful products. In the context of C(sp^3)–H activation reactions, our method is applicable to the late-stage functionalization of natural products or other complex molecules. Future applications of rhodium(III)-catalyzed activation of other types of unreactive C–H bonds are underway in our laboratories.

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