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Iridium-Catalyzed Intermolecular Amidation of sp^3 C–H Bonds: Late-Stage Functionalization of an Unactivated Methyl Group

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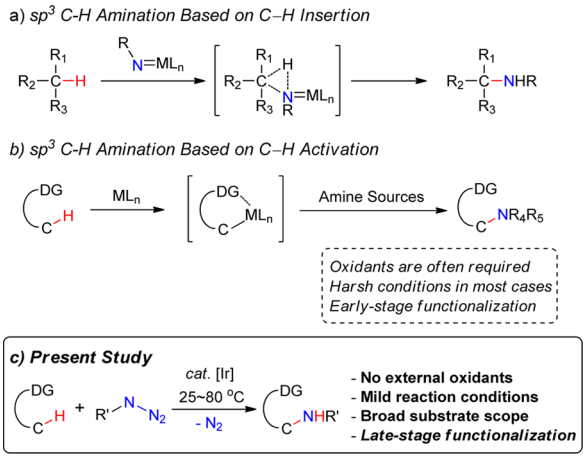
Supporting Information

ABSTRACT: Reported herein is the iridium-catalyzed direct amidation of unactivated sp^3 C–H bonds. With sulfonyl and acyl azides as the amino source, the amidation occurs efficiently under mild conditions over a wide range of unactivated methyl groups with high functional group tolerance. This procedure can be successfully applied for the direct introduction of an amino group into complex compounds and thus can serve as a powerful synthetic tool for late-stage C–H functionalization.

Nitrogen-containing molecules are widely present in both natural products and synthetic compounds of high utility in pharmaceutical, agrochemical, and materials chemistry.[1] As a result, the development of efficient and selective amination procedures has been the focus of intensive research. While synthetic tools enabling sp^2 C–N bond formation have been well-established,[2] facile amination at unreactive sp^3 C–H bonds under mild conditions still remains a great challenge in synthetic chemistry. In the past decades, notable advances were made in metal-catalyzed aliphatic amination relying on a nitrenoid C–H insertion approach (outer-sphere mechanism, Scheme 1a),[3]

Scheme 1. Direct sp^3 C–H Amination



which was successfully demonstrated in the amination of aliphatic, benzylic, or allylic sp^3 C–H bonds. Intermolecular reactions based on this strategy are often designed toward activated methylene C–H bonds positioned at benzylic, allylic, or α-heteroatomic groups, leaving room for improvement.[4]

Another approach that has also been scrutinized involves an inner-sphere pathway for the key C–H bond activation,[5,6] in which an in situ-generated metallacyclic intermediate is allowed to react with amino precursors (Scheme 1b).[7−10] Although this method has received special attention because of its high regioselectivity and atom efficiency,[11] there are several limitations, especially in the intermolecular amination reactions, including the requirement of external oxidants for unactivated amino precursors and/or relatively harsh reaction conditions.[10] In addition, most of the precedent examples utilizing this approach were employed in early-stage C–H aminations and thus worked only on simple substrates. As a result, synthetic applications to complex molecules are not feasible.

In continuing efforts to develop efficient and selective amination reactions,[12] we recently disclosed metal-catalyzed direct sp^2 C–H amination protocols using organic azides as the amino source.[13] The chelation-guided direct C–N bond formation occurs in the absence of external oxidants to release N_2 as a single byproduct. Described herein is the Ir-catalyzed intermolecular amidation of *unactivated methyl sp^3 C–H bonds* under mild conditions using azides as the amino source (Scheme 1c). Notable features of the developed procedure include a broad substrate scope, high selectivity, mild conditions, and excellent functional group tolerance. An especially significant aspect of this study is the successful application to *late-stage functionalization*, thus enabling mild direct C–H amidation of complex natural products or synthetic compounds.

In order to explore the Ir-catalyzed amidation of unactivated sp^3 C–H bonds, ketoxime derivative **1a** was chosen as a model substrate to react with *p*-toluenesulfonyl azide (**2a**) (Table 1). Whereas the previously developed catalytic system[13e] was not effective for this conversion (entry 1), catalytic amounts (0.1 equiv) of acetate additive provided a dramatic improvement in the reaction efficiency when a cationic iridium catalyst, generated in situ by the addition of a silver species, was employed. Among various acetate ions screened (entries 2–8), silver acetate was most efficient in leading to excellent product yields (entries 8 and 9). Solvents other than 1,2-dichloroethane (1,2-DCE) were less effective (entries 10 and 11).[14] In addition, other catalytic systems, including $[RhCp^*Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$, were not operative (entries 12 and 13). It was also interesting to see that a palladium catalyst system that was previously employed for the sp^3 C–H amidation reaction with sulfonamide in the presence

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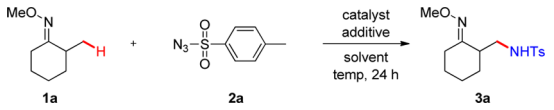
Table 1. Optimization of the Reaction Conditions[a]



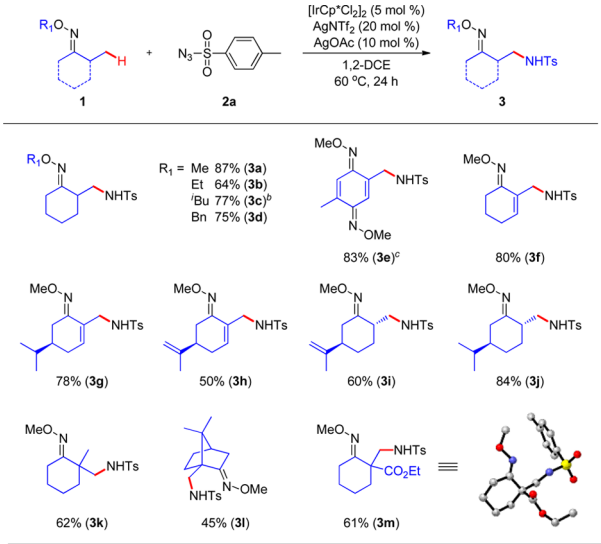
entry	catalyst	additive	solvent	temp (°C)	yield (%)[b]
1	$[IrCp^*Cl_2]_2/AgNTf_2$	-	1,2-DCE	60	<1
2	$[IrCp^*Cl_2]_2/AgNTf_2$	NaOAc	1,2-DCE	60	56
3	$[IrCp^*Cl_2]_2/AgNTf_2$	LiOAc	1,2-DCE	60	70
4	$[IrCp^*Cl_2]_2/AgNTf_2$	KOAc	1,2-DCE	60	60
5	$[IrCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2$	1,2-DCE	60	66
6	$[IrCp^*Cl_2]_2/AgNTf_2$	CsOAc	1,2-DCE	60	80
7	$[IrCp^*Cl_2]_2/AgNTf_2$	HOAc	1,2-DCE	60	43
8	**$[IrCp^*Cl_2]_2/AgNTf_2$**	**AgOAc**	**1,2-DCE**	**60**	**90**
9	$[IrCp^*Cl_2]_2/AgNTf_2$	AgOAc	1,2-DCE	80	91
10	$[IrCp^*Cl_2]_2/AgNTf_2$	AgOAc	DCM	60	81
11	$[IrCp^*Cl_2]_2/AgNTf_2$	AgOAc	*t*-AmylOH	60	n.r.
12	$[RhCp^*Cl_2]_2/AgSbF_6$	AgOAc	1,2-DCE	80	n.r.
13	$[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$	AgOAc	1,2-DCE	80	<1
14[c]	$Pd(OAc)_2$	$K_2S_2O_8$	1,2-DCE	100	n.r.
15[c]	$Pd(OAc)_2$	NFSI[d]	1,2-DCE	100	n.r.

[a]Substrate **1a** (0.2 mmol), **2a** (2 equiv), catalyst (5 mol %), $AgNTf_2$ or $AgSbF_6$ (20 mol %), and additive (10 mol %) in solvent (0.5 mL) at the indicated temperature for 24 h. [b]Determined by GC. [c]2 equiv of additive. [d]*N*-Fluorobenzenesulfonimide.

of oxidants[10] did not perform the present direct C–N bond formation (entries 14 and 15).

With the optimized conditions in hand, we next investigated the substrate scope of α-methyl cyclic ketoximes using **2a** as the amino source (Table 2). We observed that variation at the

Table 2. Substrate Scope of Cyclic Ketoximes[a]



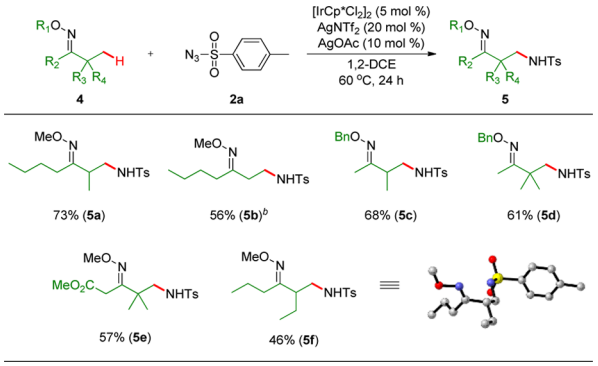
[a]Cyclic substrate **1** (0.2 mmol), **2a** (2 equiv), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), and AgOAc (10 mol %) in 1,2-DCE (0.5 mL). [b]At 80 °C. [c]Azide **2a** (1.1 equiv) was used.

O-alkyl moiety of ketoximes, such as methyl, ethyl, isobutyl, and benzyl groups, did not significantly affect the reaction efficiency (**3a**–**d**). While a vinylic methyl group was selectively amidated in high yields (**3e**–**h**), it was noteworthy that potentially reactive neighboring sp^2 C–H bonds were totally inert (**3e**).[15]

Ketoxime derivatives prepared from (*R*)-carvone, a versatile starting material in numerous asymmetric total syntheses of complex natural products,[16] all smoothly reacted under the optimized conditions (**3g**–**j**). In these amidations, the presence of olefinic double bonds did not deteriorate the reaction efficiency (**3g**–**i**), thereby demonstrating the excellent functional group tolerance of the present procedure. Stereogenic methyl groups were amidated with retention of stereochemistry, as judged by NMR spectroscopy of the obtained products (**3i** and **3j**). Sterically bulky methyl groups bonded to quaternary carbon centers were also readily amidated without difficulty (**3k**–**m**). The successful amidation of a substrate containing an ester group again exhibits the high functional group compatibility of the present conditions, and the structure of the product (**3m**) was unambiguously determined by X-ray crystallographic analysis.

The scope of acyclic ketoximes was subsequently investigated since those compounds were predicted to be more challenging than cyclic analogues because of the presumably more flexible nature of acyclic conformers.[10a,17] We were pleased to see that methyl groups of acyclic substrates were also efficiently and selectively amidated under the optimized conditions (Table 3).

Table 3. Substrate Scope of Acyclic Ketoximes[a]



[a]Acyclic substrate **4** (0.2 mmol), **2a** (2 equiv), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), and AgOAc (10 mol %) in 1,2-DCE (0.5 mL). [b]A mixture of *E* and *Z* ketoxime isomers was obtained.

Again, the reaction occurred exclusively at the methyl group without amidating any secondary C–H bonds. The functional group tolerance was also observed to be high (**5e**). It was interesting to observe that the amidation occurred highly selectively, involving only a five-membered iridacycle pathway rather than a six-membered route, as demonstrated by the formation of **5f**.

The optimized amidation procedure was next applied to a range of organic azides in reaction with **1a** (Table 4). The broad scope of arenesulfonyl azides helped accommodate various substituents bearing different electronic properties, giving amidated products in good yields (**6a**–**f**). Naphthalenesulfonyl azide was smoothly reacted as well (**6g**). The fact that alkane- and alkenesulfonyl azides were facile amino sources (**6h**–**l**) proves that the present protocol is a powerful synthetic tool for accessing diverse amidated compounds. It was noteworthy that acyl azides were also successfully applied to the current Ir-catalyzed conditions to afford acylamido products (**6m**–**p**), albeit in moderate yields, thus enabling the direct installation of an amide group at unactivated sp^3 methyl C–H bonds.

As functionalization of quinoline(s) is important because of the resulting biological properties,[18] direct C–H amidation of 8-methylquinolines was examined (Table 5). We were delighted

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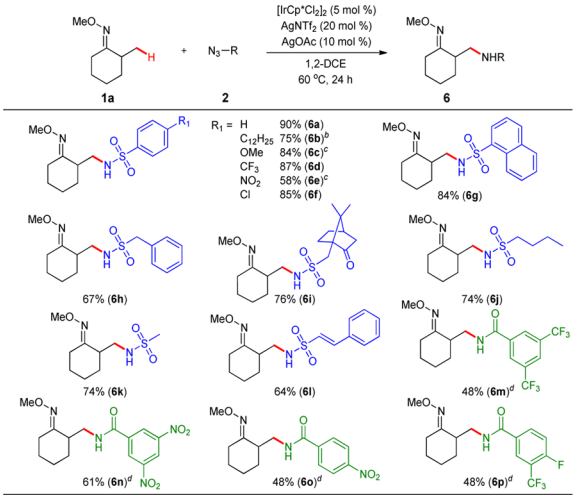
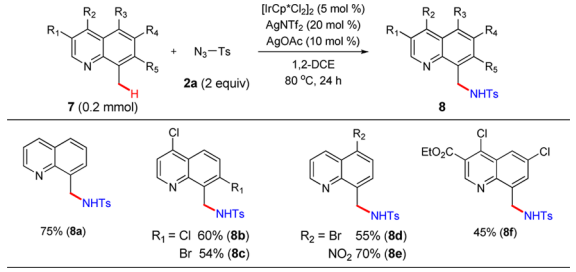
Table 4. Substrate Scope of Organic Azides[a]



[a]**1a** (0.2 mmol) and **2** (2 equiv) in 1,2-DCE (0.5 mL). [b]At 80 °C. [c]A mixture of *E* and *Z* ketoxime isomers was obtained. [d]At 50 °C.

Table 5. C−H Amidation of 8-Methylquinoline Derivatives

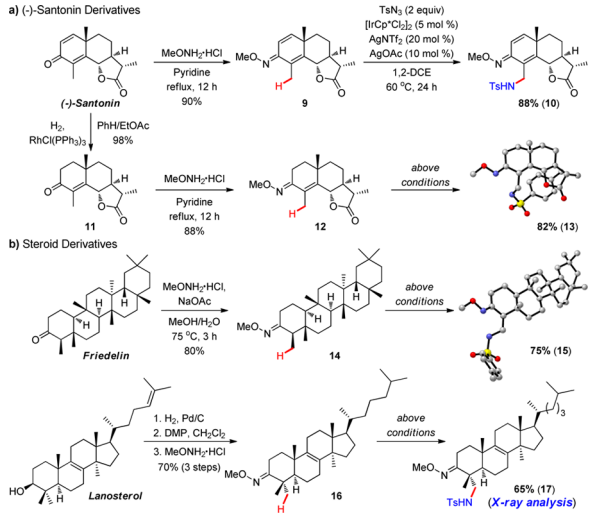


to see that the quinoline nitrogen atom was effective in guiding the desired methyl amidation using the same catalyst system, albeit at slightly higher temperatures. A range of substituents at different positions of the quinoline were compatible with the conditions. Indeed, substrates bearing halide, nitro, or ester groups were smoothly amidated to furnish highly functionalized products (**8b−f**), thus allowing the potential for further derivatization.

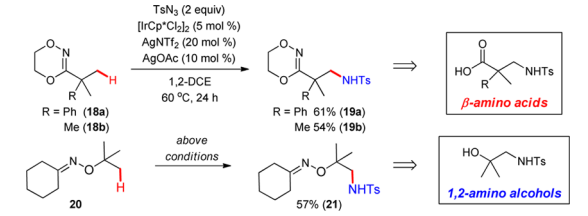
We anticipated that the present procedure might be applicable to the amidation of natural products or synthetic compounds with high complexity because of its operational convenience and mild reaction conditions. Especially in view of the fact that previous reports of sp^3 amination based on the C−H activation strategy dealt mostly with simple starting materials,[10] the utility of our method as a tool for *late-stage functionalization* would be highly significant.[19] To test this, ketoximes **9** and **12** derived from (−)-santonin were prepared and subjected to the optimized conditions (Scheme 2a). To our delight, the catalytic amidation took place smoothly at the desired methyl group to afford **10** and **13**, respectively, in high yields, and a solid-state structure of the latter product was characterized. In addition, steroidal substrates **14** and **16** prepared from friedelin and lanosterol, respectively, were also readily amidated to afford the corresponding products **15** and **17** (Scheme 2b). Notably, the amidation of **16** containing two reactive diastereotopic Me groups proceeded *in a completely selective manner* leading to amidation at the equatorial methyl moiety (as confirmed by X-ray and NMR analyses), presumably as a result of conformational bias.[20]

It was found that the present amidation protocol could readily be employed for the preparation of synthetically valuable

Scheme 2. Late-Stage sp^3 C−H Amidation

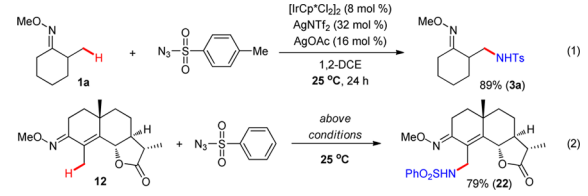


Scheme 3. C−H Amidation To Form Synthetic Building Units



building units (Scheme 3). Reactions of 3-substituted-5,6-dihydro-1,4,2-dioxazines **18a** and **18b** were facile, giving the corresponding amidated products **19a** and **19b**, which can be converted to *β*-amino acids.[21a] It needs to be addressed that, to the best of knowledge, this represents the first example of the use of dioxazines as a directing group in C−H amination reactions. In addition, it was interesting to see that an amidation of cyclohexanone *O*-(*tert*-butyl)oxime (**20**) occurred exclusively at the methyl group to afford **21**, which can serve as a precursor of 1,2-amino alcohols upon N−O bond cleavage.[21b]

To our surprise, the amidation was observed to proceed efficiently even at room temperature, albeit with a higher loading of catalyst. The model substrate **1a** was converted to the corresponding product **3a** in high yield (89%) at 25 °C (eq 1). In addition, substrate **12** derived from santonin was also amidated smoothly under ambient conditions (eq 2).



In conclusion, we have developed an Ir-catalyzed direct C−H amidation of unactivated methyl groups under mild conditions that uses organic azides as the amino source. A wide range of substrates were selectively amidated in good yields with high functional group tolerance. This protocol can serve as a new tool for late-stage C−H functionalization of complex molecules in synthetic and medicinal chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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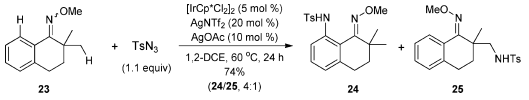
(14) See the Supporting Information (SI) for details.

(15) The amidation of dimethyltetralone derivative **23** bearing both sp^2 and sp^3 C−H bonds revealed that sp^2 C−H amidation is more favorable than sp^3 C−H amidation (see the SI for details).



23 24 25

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