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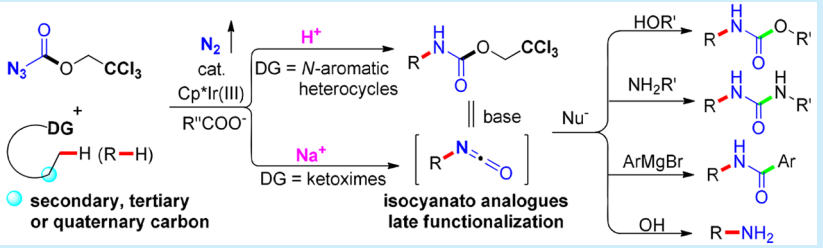
Iridium-Catalyzed Unreactive C(sp^3)−H Amination with 2,2,2-Trichloroethoxycarbonyl Azide

Tao Zhang,[†] Xuejiao Hu,[†] Xunqing Dong,[†] Guigen Li,[†,‡] and Hongjian Lu*[,†]

[†]Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

[‡]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

Supporting Information



ABSTRACT: An additive-assisted iridium-catalyzed directed C(sp^3)−H amination with 2,2,2-trichloroethoxycarbonyl azide as an amino source is reported. Both carboxylate anions and the corresponding cations in the additives are crucial to achieve satisfactory efficiency. Sodium acetate or *n*-pentanoic acid can promote the amination of various primary C(sp^3)−H bonds adjacent to secondary, tertiary, and quaternary carbons in ketoximes or *N*-aromatic heterocycles, respectively, providing a practical route to versatile *β*-amino ketoxime and *N*-heteroaryl ethanamine derivatives. The amination products can be treated as isocyanate analogues and can be converted to other useful amino functionalities. An iridacyclic compound was isolated and identified as a plausible intermediate.

Transition-metal catalyzed direct amination of alkanes via C−H activation is receiving attention because it favors amination of primary C(sp^3)−H bonds[1] and is thus an excellent complement to C−H insertion chemistry in which amination of secondary and tertiary C(sp^3)−H bonds is preferred.[2] However, the high bond dissociation energy of primary C(sp^3)−H bonds, the absence of filled high-energy orbitals or empty low-energy orbitals,[3] and the coordination ability of newly formed amino groups[4] all contribute to the low efficiency of this transformation. To overcome the inherently low reactivity and poor selectivity in intermolecular C(sp^3)−H amination reactions, the use of a coordinated directing group[5−8] at the appropriate site relative to the targeted C−H bond is critical. Ketoxime derived from ketone,[6] and a pyridine moiety,[7] which are commonly found in natural products, have been evaluated for use as representative directing groups (DGs). With the ketoxime unit as a DG, Che's group[6a] reported pioneering work on Pd-catalysis with amides under oxidative conditions. Chang et al.[6b−d] developed the first Ir-catalysis with TsN_3 and $BocN_3$, and the Li group[6e] reported Rh-catalysis with 3-substituted 1,4,2-dioxazol-5-ones (Figure 1A). With pyridine as a DG, Li's[7b] and Loh's[7c] groups reported Rh-catalyzed amination with anthranils or amidobenzo-dioxolones, respectively, as amination reagents. In both these cases, C−H bonds with adjacent tertiary or quaternary carbons could be aminated (Figure 1B). In addition to the limited catalytic systems that have been developed for C(sp^3)−H amination,[5−8] substrates with different directing groups must use different catalysts or amino sources due to the diverse coordination ability and basicity of the DGs. You's Rh catalytic system is effective for both ketoximes and pyridines when $NsNH_2$ is used as an amino source under oxidative conditions, in which only C(sp^3)−H bonds with neighboring quaternary carbons[7a] are effective through tuning the coordination ability of directing groups and facilitating the formation of five-membered metallacyclic intermediates by a Thorpe−Ingold

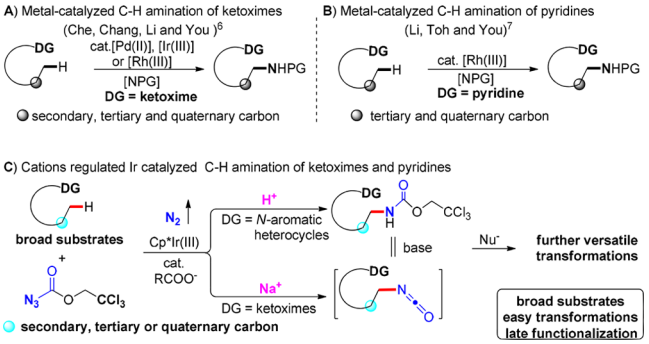


Figure 1. Metal-catalyzed unactivated C(sp^3)−H amination of ketoximes and *N*-aromatic heterocycles

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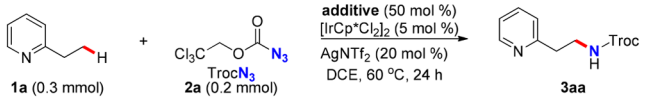
effect. Herein, we report a method of Ir-catalyzed intermolecular C(sp^3)−H amination with 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$)[9,10] (Figure 1C). Using different additives to match the coordinative ability of directing groups with the metal catalyst and the basicity of the reaction system, this method is applicable to both ketoximes and *N*-aromatic heterocycles with a broad scope of C(sp^3)−H bonds. The NHTroc group introduced to the products can be directly transformed to other useful amino functionalities.

Our investigation started with 2-ethylpyridine (**1a**) as the substrate, $TrocN_3$ (**2a**) as the amino source, and $[IrCp^*Cl_2]_2$ as the catalyst and was based on the following considerations. First, pyridine-directed catalytic C−H amination reactions would be the most efficient and direct method to produce 2-(2-aminoethyl)pyridine derivatives, a type of motif that is important in medical and bioactive molecules.[11] However, the amination of C−H bonds adjacent to secondary carbons has not been reported (Figure 1B).[7] Second, amines containing a strong electron-withdrawing sulfonyl group represent perhaps the most widely used amine sources in C−H amination reactions.[1] $TrocN_3$, containing a strongly electron-withdrawing 2,2,2-trichloroethoxycarbonyl group,[12] which can easily be deprotected or transformed,[13] may be a suitable amino source for development of a general catalytic C(sp^3)−H amination reaction. Third, since it has been reported that iridium can catalyze the C(sp^3)−H amination of ketoximes[6b−d] and shows higher reactivity than rhodium in certain C(sp^2)−H amination reactions,[14] it is necessary to investigate the substrate scope of Ir-catalyzed C(sp^3)−H aminations.

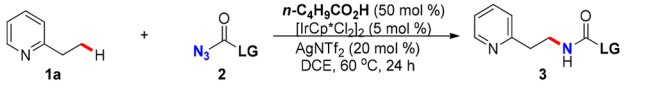
Our investigation was focused on the additives (Table 1, see the details in Table S1 in Supporting Information (SI)).[15] The

Table 1. Selected Results of Pyridine 1a[a]



entry	1	2	3	4	5	6
additive	-	LiOAc	NaOAc	KOAc	CsOAc	CsOPiv
yield (%)	-	trace	10	trace	0	0

entry	7	8	9	10	**11**
additive	AcOH	PivOH	MesCOOH	2-NAA[b]	***n*-$C_4H_9CO_2H$**
yield	25%	trace	35%	45%	56%,60%,[c] **67%**,[d,e] 45%[f]



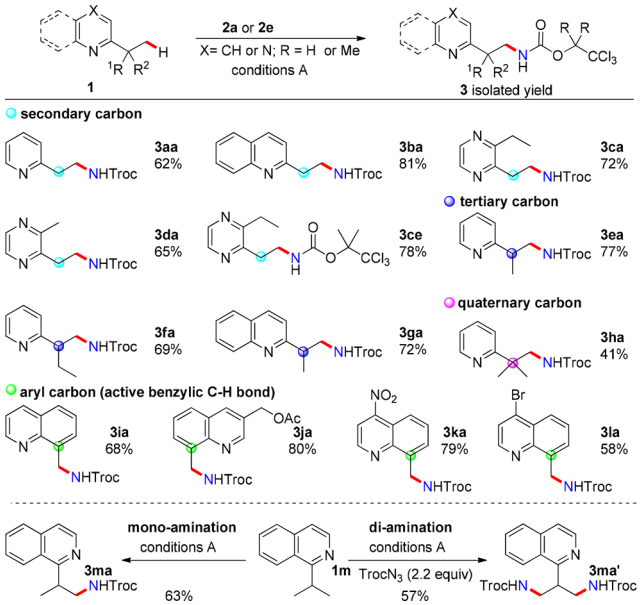
entry	12	13	14	15
LG	OCH_2Ph	$O(CH_2)_6CH_3$	$OC(CH_3)_3$	$OC(Me)_2CCl_3$
3, yield	**3ab**, 65%	**3ac**, 60%	**3ad**, 33%	**3ae**, 75%

[a]Yield was calculated based on crude ^1H NMR using CH_2Br_2 as the standard. [b]2-NAA = 2-naphthylacetic acid. [c]80 °C. [d]100 °C. [e]Isolated yield. [f]120 °C.

reaction failed to proceed without additives, and little pyridine **3aa** was formed under basic conditions (Table1, entries 1−6). After a screening of different acids and temperatures, **3aa** was obtained in 67% yield under 100 °C with *n*-pentanoic acid as the additive (Table 1, entries 7−11). $TrocN_3$ and its analogue **2e** have proven to the best of all the different azidoformates (Table 1, entries 12−15).

The scope of *N*-aromatic heterocycles was then explored, giving the results shown in Scheme 1. In addition to pyridine, quinoline, isoquinoline, and even pyrazine could be used as

Scheme 1. Substrate Scope of *N*-Aromatic Heterocycles 1[a]

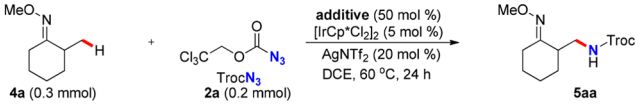


[a]Conditions A: **1** (0.3 mmol), **2** (0.2 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), *n*-$C_4H_9CO_2H$ (50 mol %), DCE, 100 °C, 24 h; isolated yield.

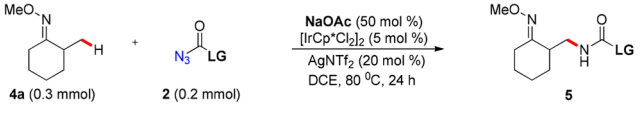
DGs. The C−H bonds adjacent to secondary carbons were aminated efficiently (**3aa**−**da**, **3ce**), implying the uniqueness of this catalytic system among the known methods.[7] The amination of C−H bonds adjacent to tertiary and quaternary carbons provided the desired products **3ea**−**3ha** in moderate to good yields. Benzylic C(sp^3)−H amination of 8-methylquinolines was observed with high functional group tolerance (**3ia**−**3la**). The desired monoamination of an isoquinoline **1m** was achieved selectively producing **3ma**, but a reasonable yield of the diamination product **3ma′** was also produced when excess $TrocN_3$ was used. Such double C−H aminations are challenging due to the formation of an intramolecular hydrogen bond in other catalytic systems.[4]

Then, the C(sp^3)−H amination using ketoxime **4a** as the substrate and $TrocN_3$ as the amino source was tested. The amination product **5aa** was achieved, albeit in moderate yield, using Chang's conditions.[6d] The results from optimization of the reactions are shown in Table 2 (see the details in Table S2

Table 2. Selected Results of Ketoxime 4a[a]



entry	1	2	3	4	5
additive	LiOAc	**NaOAc**	KOAc	CsOAc	HOAc
yield	10%	88%, 83%,[b] 92%,[c] **99%**[d]	20%	55%	45%



entry	6	7	8	9[e]	10
LG	OCH_2Ph	$O(CH_2)_6CH_3$	$OC(CH_3)_3$	$OC(Me)_2CCl_3$	OPh
5, yield	**5ab**, 62%	**5ac**, 66%	**5ad**, 37%	**5ae**, 92%[e]	**5af**, 34%

[a]Yield was calculated based on crude ^1H NMR using CH_2Br_2 as the standard. [b]80 °C. [c]40 °C. [d]20 °C; isolated yield. [e]60 °C.

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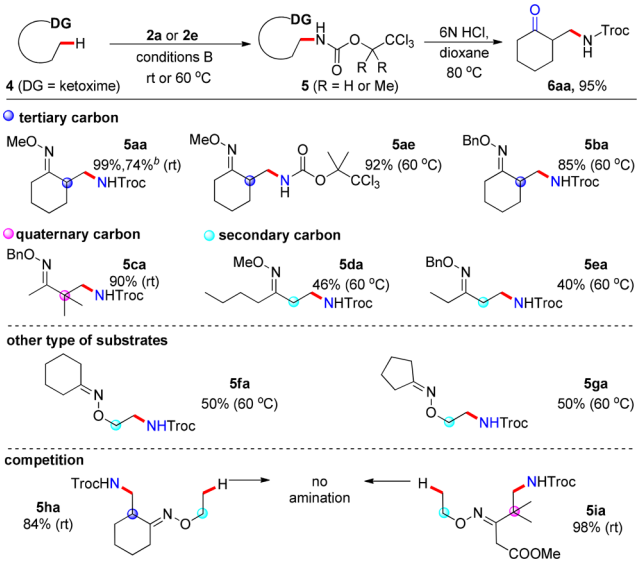
in SI). Among the different alkali metal acetates, NaOAc was shown to be the best, giving **5aa** in 99% yield, even at room temperature (Table 2, entries 1−5). In screening the different azidoformates, $TrocN_3$ and its analogue **2e** gave the best yields (Table 2, entries 6−10).

The scope of ketoximes was then explored (Scheme 2). C−H bonds adjacent to tertiary or quaternary carbons reacted

Scheme 2. Substrate Scope of Ketoximes[a]

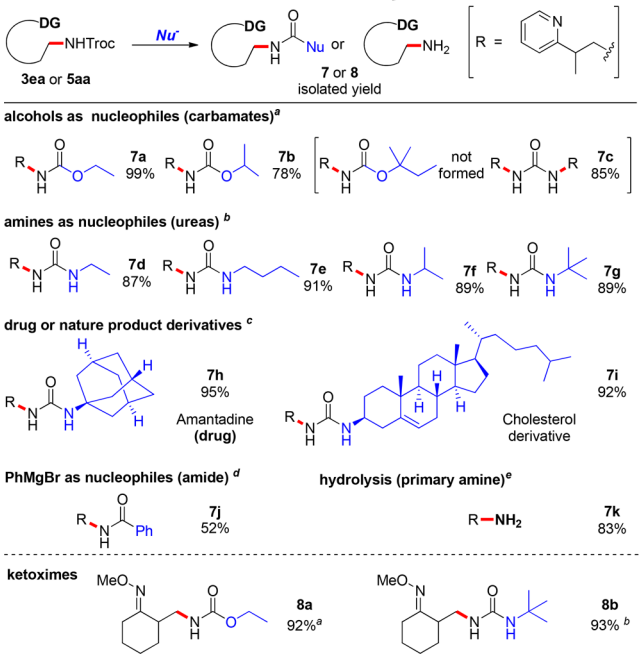


[a]Conditions B: **4** (0.3 mmol), **2** (0.2 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), NaOAc (50 mol %), DCE, 24 h; isolated yield. [b]2.0 mmol scale.

smoothly even at room temperature, giving products **5aa**−**5ca** and **5ae**. The amination of C−H bonds adjacent to secondary carbons proceeded slowly, generating the desired products **5da**−**ea** in moderate yields. Compounds **5fa** and **5ga**, important precursors of 1,2-amino alcohols, were obtained in moderate yields. Finally, the competing reactions at different C−H bonds were investigated, and the results show that C−H bonds adjacent to tertiary or quaternary carbon were greatly favored as a result of the Thorpe−Ingold effect, providing the desired products (**5ha**−**ia**) exclusively. Interestingly, the ketoxime (**5aa**) was easily deprotected without affecting the Troc functional group, producing a ketone derivative (**6aa**) in 95% yield.

The products formed in this reaction could be treated as analogs of isocyanates and directly transformed to compounds bearing other important and functional amino groups (Scheme 3). Using ethanol and isopropanol as nucleophiles, different carbamates were formed efficiently (**7a**−**b**). When *tert*-amyl alcohol was used, the symmetric urea (**7c**) was obtained instead of a carbamate. When different amines containing secondary, tertiary, or quaternary carbons were used, various asymmetric urea compounds were obtained directly (**7d**−**g**). The reactions of amantadine, an antiviral and an antiparkinsonian medication, and an amine derivative of cholesterol could provide urea derivatives of the drug or natural product directly (**7h**−**i**). With PhMgBr as a nucleophile, the amide **7j** could be obtained directly. Under basic conditions, **3aa** was efficiently converted to the free primary amine **7k**. Ketoximes can also go through similar transformations, forming carbamate and urea derivatives **8a**−**b** without affecting the ketoxime group.

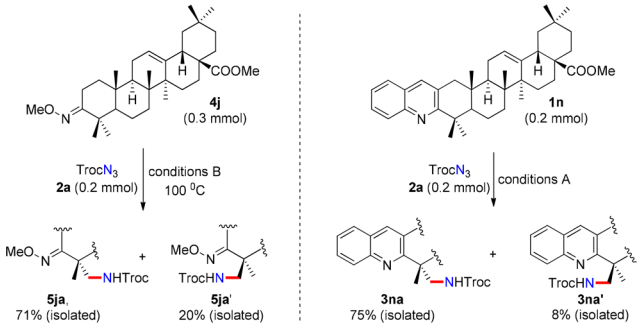
Scheme 3. Transformations of Aminated Products 3 and 5



[a]K_2CO_3 (4.0 equiv), alcohol, 100 °C, 20 h. [b]DIPEA (1.0 equiv), amine (1.5 equiv), DMSO, 100 °C, 20 h. [c]Amine (1.1 equiv). [d]PhMgBr (3.0 equiv), THF, −78 °C−rt, 10 h. [e]$LiOH·H_2O$ (5.0 equiv), $MeCN/H_2O$ (1/1), rt, 3 h.

This newly developed method has been utilized as a tool for late-stage functionalization (Scheme 4).[16] For example, the

Scheme 4. Late-Stage C(sp^3)−H Amination



ketoxime **4j**, derived from oleanolic acid, was prepared and subjected to the reaction under the optimized conditions. The catalytic amination proceeded smoothly at the methyl group affording monoaminated isomers in 91% yield (**5ja**, 71%; **5ja′**, 20%), which could be separated by column chromatography. The quinoline derivative **1n**, a member of a promising new class of antiosteoporosis compounds,[17] was readily aminated, providing **3na** in 75% isolated yield as the major product. An equal equivalent of substrate **1n** was used, showing the high efficiency of this transformation.

A series of experiments were carried out to further understand the mechanism (Scheme 5). Significant primary kinetic isotope effects were observed in an intermolecular competition experiment between $[D_6]$-**1g** and **1g** (**3ga**/$[D_5]$-**3ga** = 5.3, eq 1) and an intramolecular competion reaction of $[D_3]$-**1g** ($[D_3]$-**3ga**/$[D_2]$-**3ga** = 6.1, eq 2), while no H/D scrambling occurred in these two reactions. These results

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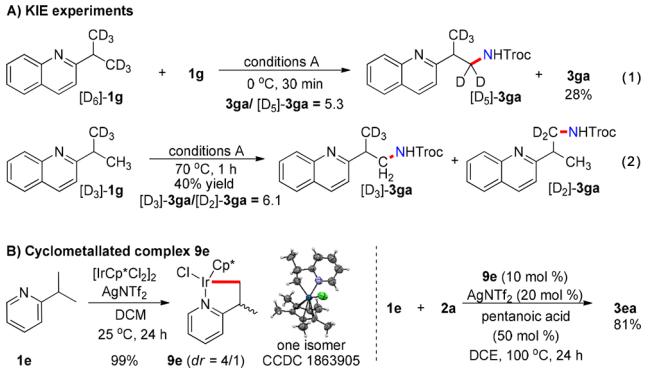
Scheme 5. Mechanistic Studies



reveal that breaking of the C−H bond may be the rate-determining step. Compound **1e** reacted stoichiometrically with $[IrCp^*Cl_2]_2$ and $AgNTf_2$ to afford the neutral iridacycle **9e** (Scheme 5B), whose structure was confirmed by X-ray crystallographic analysis. Compound **9e** could be used as the catalyst in place of $[IrCp^*Cl_2]_2$, suggesting that **9e** may be a key intermediate.

In conclusion, we have developed an Ir-catalyzed unactivated C(sp^3)−H amination reaction, which uses $TrocN_3$ as easily transformable amine source. In addition to the known effect of the carboxylate anions of additives, the cations are also crucial for promotion of the reaction and expansion of the substrate scope. With NaOAc as the additive, C(sp^3)−H amination of ketoximes can proceed even at room temperature and the yield of amination products is as high as 99%. *n*-Pentanoic acid is a vital additive with which *N*-heteroaromatic substrates can achieve satisfactory efficency. A wide range of primary C(sp^3)−H bonds adjacent to secondary, tertiary, and quaternary carbons can be aminated. The reaction does not require oxidative conditions and is therefore suitable for late-stage functionalization of bioactive compounds. The desired products can be treated as isocyanate analogues and can be converted to other useful amino functionalities. The KIE experiment and the isolation of an iridacyclic complex and study of its catalytic reactions have allowed us to gain further understanding of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02738.

Experimental details and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1863905 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hongjianlu@nju.edu.cn.

ORCID

Guigen Li: 0000-0002-9312-412X
Hongjian Lu: 0000-0001-7132-3905

Notes

The authors declare no competing financial interest.

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