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Iodoarene-Catalyzed Stereospecific Intramolecular sp^3 C–H Amination: Reaction Development and Mechanistic Insights

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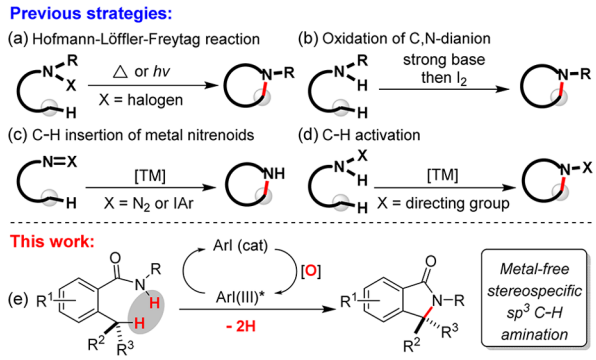
Supporting Information

ABSTRACT: A new strategy is reported for intramolecular sp^3 C–H amination under mild reaction conditions using iodoarene as catalyst and *m*-CPBA as oxidant. This C–H functionalization involving iodine(III) reagents generated in situ occurs readily at sterically hindered tertiary C–H bonds. DFT (M06-2X) calculations show that the preferred pathway involves an iodonium cation intermediate and proceeds via an energetically concerted transition state, through hydride transfer followed by the spontaneous C–N bond formation. This leads to the experimentally observed amination at a chiral center without loss of stereochemical information.

Intramolecular C–H amination, an atom-economical strategy to access N-heterocycles, has found widespread applications for the construction of alkaloid natural products and pharmaceuticals.[1] This transformation can be traced back to the Hofmann–Löffler–Freytag (HLF) reaction in the early 1880s, which employed N-halogenated amines as starting materials via a free radical pathway (Scheme 1a).[2] Another efficient variation is the C,N-dianion oxidation via tandem deprotonation of the N–H and C–H bonds and oxidative coupling under strongly basic conditions (Scheme 1b).[3] In the past few years, transition-metal-catalyzed C–H activation strategies provide more efficient routes to these heterocycles. Among them, the intramolecular C–H insertion of metal nitrenoids has been applied to the synthesis of highly complex alkaloids (Scheme 1c).[4] Recently, several groups have developed transition-metal-catalyzed aliphatic C–H amination/cyclization reactions utilizing different types of N-protected amides (Scheme 1d).[5] Nevertheless, the development of new methods for the efficient construction of C–N bonds from C–H bonds under mild conditions is still in high demand.

Iodoarene-catalyzed C–C,[6] C–O,[7] and C–N[8] bond formations have recently increased in importance as an alternative to transition-metal-catalyzed cross-couplings.[9,10] Kita et al. developed the first ArI-catalyzed C–N amination/cyclization process via dearomatization of arenes.[11] Recently, the Antonchick group explored ArI-catalyzed or $PhI(OAc)_2$-mediated sp^2 C–N bond formation to construct the azaheterocyclic skeletons including carbazoles,[12a] isoquinolones,[12b] and pyrido[1,2-*a*]benzimidazoles.[12c] We now report the first iodoarene-catalyzed intramolecular aliphatic C–H amination to synthesize γ-lactams (Scheme 1e). Through density functional theory (DFT) calculations, we find that the key C–H activation/C–N bonding proceeds via a concerted mechanism, allowing the stereospecific construction of chiral quaternary centers.

Scheme 1. N-Heterocycle Construction via Intramolecular sp^3 C–H Aminations



Initial studies involved the evaluation of the oxidative cyclization of 2-cyclohexyl-*N*-methoxybenzamide (**1a**) (Table 1). Our trials using a variety of common oxidants such as TBHP, DDQ, and *m*-CPBA at 60 °C in HFIP all failed. Switching the oxidant to $PhI(OAc)_2$ afforded the desired product (2′-methoxyspiro[cyclohexane-1,1′-isoindolin]-3′-one, **3a**) in 58% yield (Table 1, entry 1). We then focused on the development of a catalytic procedure using iodobenzene (**2a**) as the catalyst. We found that *m*-CPBA is a suitable oxidant, providing product **3a** in 75% yield at the room temperature (Table 1, entry 3). To further improve the reaction, a variety of iodoarenes (**2b**-**k**) were investigated as potential catalysts. Among them, 2-iodobiphenyl (**2h**) is best, affording **3a** in 95% yield in 15 min (Table 1, entry 4).[13] The use of DCE and TFE as solvents resulted in reduced yields (Table 1, entries 5–6). We also examined the effect of the nitrogen substituents. *N*-phenyl-benzamide **1a**′ showed lower reactivity, and extending the reaction time to 3 days improved the yield to 78% (Table 1, entry 7). However, *N*-methyl-benzamide **1a**″ did not work under these conditions (Table 1, entry 8).[14]

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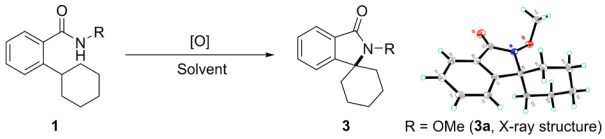
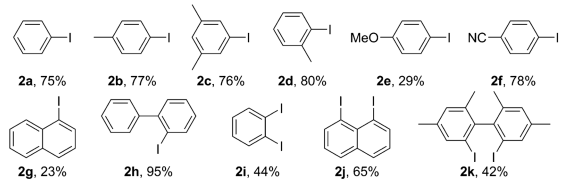
Table 1. Reaction Optimization[a]



entry	R	[cat]	oxidant (1.5 equiv)	solvent	T (°C)	time	yield (%)[b]
1	OMe (**1a**)	-	$PhI(OAc)_2$	HFIP	60	1 h	58
2	OMe (**1a**)	**2a**	AcOOH	HFIP	60	1 h	0
3	OMe (**1a**)	**2a**	*m*-CPBA	HFIP	rt	15 min	75
4	**OMe (1a)**	**2h**	***m*-CPBA**	**HFIP**	**rt**	**15 min**	**95**
5	OMe (**1a**)	**2h**	*m*-CPBA	DCE	rt	1 h	42
6	OMe (**1a**)	**2h**	*m*-CPBA	TFE	rt	1 h	57
7	Ph (**1a'**)	**2h**	*m*-CPBA	HFIP	rt	3 d	78
8	Me (**1a''**)	**2h**	*m*-CPBA	HFIP	rt	3 d	0

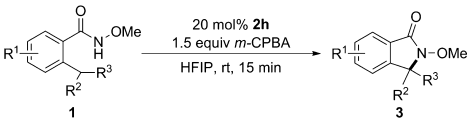


[a]Conditions: all the reactions were run at a 0.20 mmol scale with 20 mol % iodoarene in 1.0 mL of solvent, and open in air; HFIP = hexafluoro-2-propanol, TFE = trifluoroethanol. [b]Isolated yield.

With the optimal conditions in hand, we examined the scope of this intramolecular aliphatic C−H amination reaction (Table 2). We first evaluated the effect of substituents on the phenyl ring of benzamides. Electron-neutral and electron-deficient molecules **1a** and **1c−g** react well with good yields, but electron-rich substrate **1b** gives a poor yield due to some side reactions (Table 2, entries 1−7). The substrates **1h−j** with five- to seven-membered rings are compatible and afforded the desired products **3h−j** in 70−79% yields (Table 2, entries 8−10). The amination reactions also worked well for acyclic tertiary C−H bonds in substrates **1l−o** (Table 2, entries 12−15). However, the direct amination of the secondary C−H bond, such as ethyl group of substrate **1k**, only gave a trace amount of product with nearly fully decomposed starting material (Table 2, entry 11).[15] This suggests that the secondary C−H amination has a significantly higher barrier as compared with the tertiary one.[16] Reaction of naphthamide **1p** afforded lactam **3p** in 81% yield, and larger-scale transformation without notable erosion of yield proved the practicality of this new method (Table 2, entry 16). Considering that the fused lactams are widespread in drugs and natural products, substrate **1q** was synthesized and tested. Gratifyingly, the desired product **3q** was obtained with good yield (Table 2, entry 17). The reaction also works well with more complex substrates: benzamide **1r** derived from (+)-totarol reacted smoothly under the optimal conditions, affording the corresponding polycyclic lactam in an excellent yield (Table 2, entry 18).

Previous study by Antonchick et al. showed that sp^2 C−H aminations smoothly occur in the presence of iodine(III) reagents.[12a] To test the chemoselectivity between sp^3 and sp^2 C−H amination in the current system, we investigated the substrate **1s** containing two competing sites (a and b, Scheme 2) for the direct amination. Under the standard conditions shown in Table 2, both sp^3 and sp^2 C−H amination products **3s** and **4s** were obtained with a ratio of 42/58 (Scheme 2). This suggests

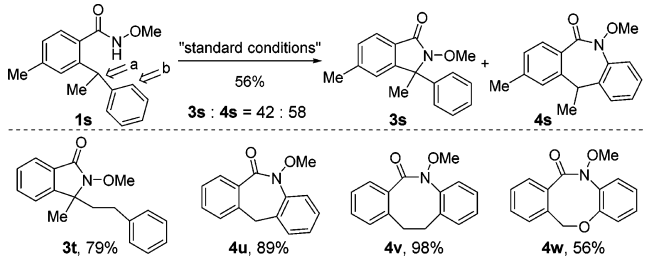
Table 2. Substrate Scope[a]



entry	substrate	product	yield[b]
1	R = H, **1a**	R = H, **3a**	95%
2	R = 4-OMe, **1b**	R = 4-OMe, **3b**	27%
3	R = 5-Me, **1c**	R = 5-Me, **3c**	74%
4	R = 4-F, **1d**	R = 4-F, **3d**	73%
5	R = 4-Cl, **1e**	R = 4-Cl, **3e**	93%
6	R = 4-COOMe, **1f**	R = 4-COOMe, **3f**	86%
7	R = 4,5-$(CH_2)_4$, **1g**	R = 4,5-$(CH_2)_4$, **3g**	90%
8	n = 1, **1h**	n = 1, **3h**	70%
9	n = 2, **1i**	n = 2, **3i**	75%
10	n = 3, **1j**	n = 3, **3j**	79%
11	R = H, **1k**	R = H, **3k**	trace
12	R = Me, **1l**	R = Me, **3l**	83%
13	R = Et, **1m**	R = Et, **3m**	84%
14	R = *n*-Bu, **1n**	R = *n*-Bu, **3n**	94%
15	**1o**	**3o**	56%
16	**1p**	**3p**	81% (79%)[c]
17	**1q**	**3q**	78%
18	**1r**	**3r**	91%

[a]Conditions: **1** (0.20 mmol), 20 mol % **2h**, *m*-CPBA (0.3 mmol) in HFIP (1.0 mL) at room temperature, and open in air. [b]Isolated yield. [c]2.5 mmol scale transformation.

Scheme 2. Chemoselectivity between sp^3 and sp^2 C−H Amination



that the barrier for the seven-membered lactam formation via aromatic C−H amination is close to that for the five-membered lactam formation via tertiary C−H amination. However, substrate **1t** with two-carbon chain extension in the tether, greatly increasing the barrier for the sp^2 C−H amination to form the nine-membered lactam, and thus only the sp^3 C−H amination product **3t** was generated in 79% yield (Scheme 2). As mentioned before, the secondary C−H amination is much more difficult than the tertiary one. Therefore, in the case of substrate **1u**, the seven-membered aromatic C−H amination product **4u** was the only detectable product.[17] In addition, substrates **1v** and **1w** without tertiary C−H bonds can smoothly

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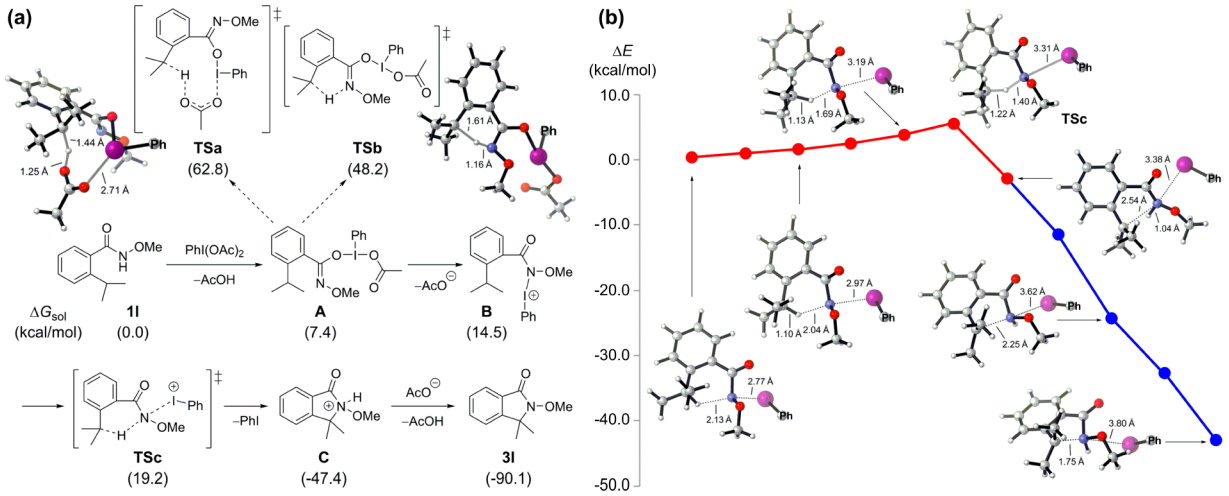


Figure 1. (a) DFT-computed free energies in TFE for the reaction between benzamide **1l** and $PhI(OAc)_2$ and structures of unfavorable transition states **TSa** and **TSb**. (b) IRC plot of the key sp^3 C−H amination transition state **TSc** with representative structures; carbon: gray, hydrogen: white, oxygen: red, nitrogen: blue, and iodine: purple.

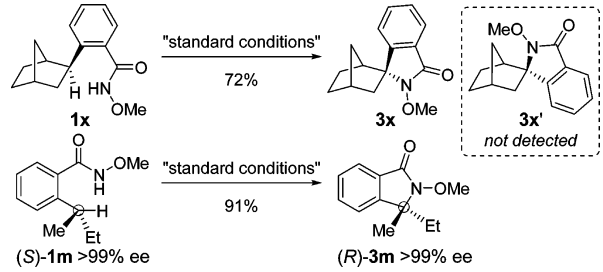
yield the corresponding eight-membered lactams **4v** and **4w** via sp^2 C−H aminations exclusively (Scheme 2).

To better understand the mechanism of this sp^3 C−H amination,[18] DFT calculations were performed on the reaction of benzamide **1l** and $PhI(OAc)_2$ (Figure 1).[19,20] As shown in Figure 1a, intermediate **A** is generated from benzamide **1l** and $PhI(OAc)_2$ through ligand exchange on hypervalent iodine. This step is endergonic by 7.4 kcal/mol in TFE. From intermediate **A**, the electrophilic sp^3 C−H activation was evaluated, but calculations show that the intramolecular deprotonation by acetate via transition state **TSa** has a very high overall barrier (62.8 kcal/mol, Figure 1a). The nucleophilic C−H activation transition state **TSb** was also located, but the 1,5-hydride migration requires an overall activation free energy of 48.2 kcal/mol, which is still too high for a reaction under mild conditions. Alternatively, the dissociation of acetate from intermediate **A** generates an iodonium intermediate **B**, predicted to be endergonic by 7.1 kcal/mol in TFE (Figure 1a).[21] The cation **B** is predicted to be much more reactive toward nucleophilic sp^3 C−H activation. The hydride transfer from tertiary carbon to nitrogen via an S_N2-like transition state **TSc** requires an activation free energy of only 4.7 kcal/mol.[22] This is in agreement with recent discovery that iodonium cation is the active intermediate in the iodine(III)-promoted C−C coupling.[20c]

Figure 1b shows the intrinsic reaction coordinate (IRC) for the reaction of iodonium **B** through transition state **TSc**. This reaction directly gives protonated lactam **C** without the involvement of a carbocation intermediate. As shown in Figure 1b, the hydride gradually moves to the electron-deficient nitrogen along the red line, accompanied by the N−I bond cleavage. When the N−H bond is fully formed with a distance of 1.04 Å, the C−N distance is still quite long (2.54 Å, Figure 1b). The C−N bonding then occurs spontaneously along the blue line with high exothermicity. This sp^3 C−H amination proceeds via an energetically concerted mechanism, where the hydride transfer is followed by the spontaneous C−N bond formation, akin to the well-known "oxygen rebound" mechanism.[23]

On the basis of the concerted nature of the C−H activation/C−N bonding process revealed by DFT calculations, we predict that the C−H amination at a chiral center will not lose the stereochemical information. This is later validated by the

Scheme 3. Stereospecific Tertiary C−H Amination



experiments shown in Scheme 3. The reaction of 2-*exo*-2′-(methoxycarbamoyl)phenyl-norbornane (**1x**) only gave one diastereomer **3x** in 72% yield. Remarkably, when substrate (*S*)-**1m** was employed, the lactam product (*R*)-**3m** with a chiral quaternary center was generated with complete stereochemical fidelity.[24,25] These stereospecific tertiary C−H aminations enable the utility of this method in asymmetric synthesis.[26]

In summary, we have developed a new synthesis of γ-lactams via an iodoarene-catalyzed intramolecular tertiary C−H amination. The products form efficiently using a simple organocatalyst and *m*-CPBA as oxidant under mild conditions in short times. DFT calculations show that the preferred pathway for this reaction involves an iodonium cation intermediate and proceeds via a concerted C−H activation/C−N bonding transition state. Consequently, chiral quaternary centers can be constructed stereospecifically using this method.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03488.

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Notes

The authors declare no competing financial interest.

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(13) The treatment of **3a** with sodium hydride gave the N−O bond cleavage product in 85% yield. For details, see the SI.

(14) We studied the effect of the nitrogen substituents by DFT calculations. The change of the OMe group to Ph and Me groups increases the C−H amination barrier from 19.2 kcal/mol (Figure 1a) to 24.7 and 44.3 kcal/mol, respectively. For details, see the SI.

(15) Substrates with secondary and primary C−H bonds and substrates with aliphatic tethers are unsuccessful. For details, see the SI.

(16) The computed activation free energies for the secondary (2-ethyl-*N*-methoxybenzamide) and primary (2-methyl-*N*-methoxybenzamide) C−H aminations are 22.4 and 28.5 kcal/mol, much higher than that for the tertiary one (19.2 kcal/mol, Figure 1a). For details, see the SI.

(17) For substrate **1u**, the computed activation free energy for the aromatic C−H amination is 1.9 kcal/mol lower than that for the secondary C−H amination. For details, see the SI.

(18) For the discussion of the radical mechanism, see the SI.

(19) (a) All calculations were performed with: Frisch, M. J., et al. *Gaussian 09*, Revision D.01; Gaussian Inc.: Wallingford, CT, 2013. (b) Geometry optimizations and frequency calculations were performed at the M06-2X/6-31G(d)[SDD, for I] level. Single-point energy calculations in TFE using the CPCM model were performed at the M06-2X/6-311+G(d,p)[SDD, for I] level. For details, see the SI.

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(21) The formation of oxygen-bonded iodonium cation **B′** from intermediate **A** is calculated to be endergonic by 27.9 kcal/mol in TFE.

(22) Previous study shows that the activation free energy for the dissociation process is approximately equal to the reaction enthalpy: Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *J. Am. Chem. Soc.* **2010**, *132*, 3078. Our calculations indicate that the dissociation of intermediate **B** to form nitrenium cation and iodobenzene is endothermic by 14.2 kcal/mol in terms of enthalpy and is endergonic by 1.1 kcal/mol in TFE. Therefore, the activation free energy for the dissociation of intermediate **B** is about 14 kcal/mol, higher than that for the hydride transfer via **TSc** (about 5 kcal/mol).

(23) (a) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859. (b) Zou, L.; Paton, R. S.; Eschenmoser, A.; Newhouse, T. R.; Baran, P. S.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4037.

(24) For the determination of the absolute configuration, see the SI.

(25) Under "DFT-computed conditions" [$PhI(OAc)_2$ as oxidant and TFE as solvent], the transformation of (*S*)-**1m** to (*R*)-**3m** also occurs with complete stereochemical fidelity. For details, see the SI.

(26) For recent examples of stereospecific tertiary C−H functionalization, see: (a) Bercovici, D. A.; Brewer, M. *J. Am. Chem. Soc.* **2012**, *134*, 9890. (b) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851.

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