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# The Nickel-Catalyzed Reaction of C-H Bonds in Amides with I: ortho-Iodination via the Cleavage of C(sp2)-H Bonds and Oxidative Cyclization to #-Lactams via the Cleavage of C(sp3)-H Bonds

Yoshinori Aihara, and Naoto Chatani

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# The Nickel-Catalyzed Reaction of C-H Bonds in Amides with $I_2$: *ortho*-Iodination via the Cleavage of C($sp^2$)-H Bonds and Oxidative Cyclization to β-Lactams via the Cleavage of C($sp^3$)-H Bonds

*Yoshinori Aihara and Naoto Chatani**

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

C-H activation, bidentate directing group, iodination, nickel, oxidative cyclization

**ABSTRACT.** The first example of the nickel(II)-catalyzed reaction of amides using inexpensive and milder molecular iodine ($I_2$) as an iodinating reagent is reported. The reaction of aromatic amides having an 8-amino-5-choloroquinoline as a directing group with $I_2$ resulted in the production of *ortho*-iodination products. Deuterium labeling experiments indicate that the cleavage of C-H bonds is irreversible and is likely the rate-determining step, which is in sharp contrast to the previously reported transformation using the same Ni(II) catalyst/8-aminoquinoline chelation system. The reaction is applicable to the synthesis of β-lactams from

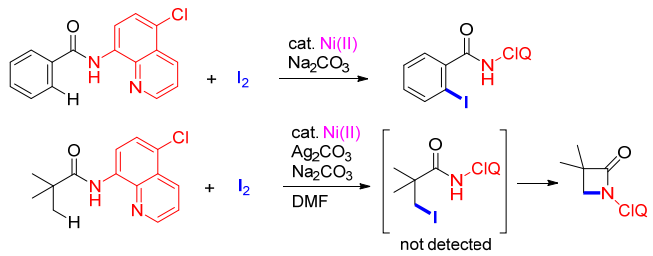
aliphatic amides as the substrate, in which C($sp^3$)-H bonds are activated. The results of deuterium labeling experiments indicate that the cleavage of C($sp^3$)-H bonds is also irreversible.

## 1. INTRODUCTION

Aryl halides are extensively utilized as important starting materials in organic synthesis for constructing a variety of useful compounds in the fields of material science and medicinal chemistry.[1] An electrophilic aromatic substitution reaction, the Sandmeyer reaction or directed lithiation are widely used in the synthesis of aryl halides. However, all of these strategies have some limitations including (i) a low functional group tolerance, (ii) a low regioselectivity, and (iii) the use of tedious and/or hazardous reagents.[2] To address these limitations, the direct, transition metal-catalyzed halogenation of C-H bonds is a particularly valuable transformation.[3] The direct, palladium-catalyzed halogenation of C-H bonds has been extensively studied as an alternate method for the preparation of aryl halides.[4,5] Rh(III),[6] Ru(II),[7] Cu(I),[8] and Co(III)[9] complexes have been shown to have a high catalytic activity for the direct halogenation of arenes. In cases of the iodination of C-H bonds reported so thus, various iodinating reagents, including NIS,[5c,m,p, 6a,c, 7a, 8d, 9] IOAc, generated by the reaction of $I_2$ with PhI(OAc),[5b,f,g] $KIO_3/K_2S_2O_8$,[5n] cyclic iodine(III),[5o] or NaI/$PhI(OAc)_2$[6e] have been used as an iodinating reagent. Yu recently reported on the direct, Pd-catalyzed iodination of C-H bonds using the inexpensive and milder molecular $I_2$ as an iodinating reagent.[10] Prompted by this finding, we envisioned the development of an iodination methodology in which earth-abundant metals, such as nickel and inexpensive $I_2$ could be used as an iodinating reagent.

Our efforts have recently focused on the direct, Ni-catalyzed functionalization of C-H bonds utilizing a 2-pyridinylmethyl moiety or an 8-aminoquinoline moiety as a directing group.[11,12] The 8-aminoquinoline directing group was first used by Daugulis in the Pd-catalyzed functionalization of C-H bonds.[13,14] Since we reported on the first example of the Ni-catalyzed functionalization of C-H bonds using 8-aminiquinoline chelation assistance in 2013,[12b] many groups have followed this approach for the Ni(II)-catalyzed functionalization of C-H bonds,[11,15] because this represents the first general system for the Ni-catalyzed chelation-assisted functionalization of C-H bonds. Herein, to expand the utility of this chelation system we report on the Ni-catalyzed direct iodination of aromatic C-H bonds using molecular $I_2$ as the iodinating reagent (Scheme 1). This reaction represents the first example of the Ni-catalyzed iodination of arenes. The reaction is also applicable to the synthesis of $\beta$-lactams from aliphatic amides, which involves the activation of C($sp^3$)-H bonds.

Scheme 1. Reactions of C-H Bonds with $I_2$

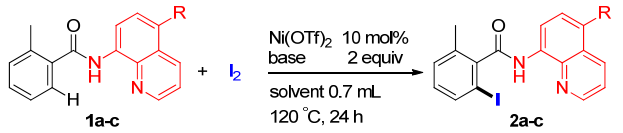



## 2. RESULTS AND DISCUSSION

2.1. **ortho-Iodination of C($sp^2$)-H Bonds.** The reaction of the aromatic amide **1a** (0.15 mmol) possessing an 8-amino-5-chloroquinoline moiety[12d,g, 16] and $I_2$ (0.3 mmol) in the presence of $Ni(OTf)_2$ (0.015 mmol) as the catalyst in 1,2-dichloroethane (0.7 mL) at 120 °C for 24 h gave a

trace amount of ortho-iodination product **2a** along with the recovery of the unreacted amide **1a** in 99% yield (entry 1, Table 1). The addition of $Na_2CO_3$ (0.3 mmol) as a base dramatically increased the yield of **2a** to 74% NMR yield (entry 2). The reaction was found to be significantly affected by the nature of the base used. The results indicate that $Na_2CO_3$ is the choice of base (entries 2-5). The efficiency of the reaction was also affected by the solvent used (entries 2 and 6-8). Toluene was found to be the optimal solvent for this reaction, with **2a** being produced in 76% isolated yield (entry 6). The yield of the product was decreased when the reaction was run at 100 °C (entry 9). The use of *N*-iodosuccinimide (NIS) or iodosobenzene diacetate (PIDA)/NaI as an iodinating reagent resulted in negligible product yields (entries 10 and 11). Other Ni(II) complexes, such as $Ni(OAc)_2$, $NiI_2$, $NiBr_2$, and $NiCl_2$, also gave the iodination product, but the yields were lower than when $Ni(OTf)_2$ was used as the catalyst. No iodination product was produced in reaction of the aromatic amide **1b** having an 8-aminoqunoline directing group instead of **1a**, and a side product, which involved iodination at the 5-position on the quinoline ring was produced (entry 12). The reaction using the aromatic amide **1c** containing a methoxy group instead of chloro group gave a decreased yield of iodination product, indicating that the chloro group at the 5 position, not only prevents the substitution reaction at the 5-position on the quinoline ring but also facilitates the reaction (entry 13).

**Table 1. Optimaization of the Direct, Nickel-Catalyzed Iodination of the Aromatic Amide 1a with Iodine**




1a-c 2a-c

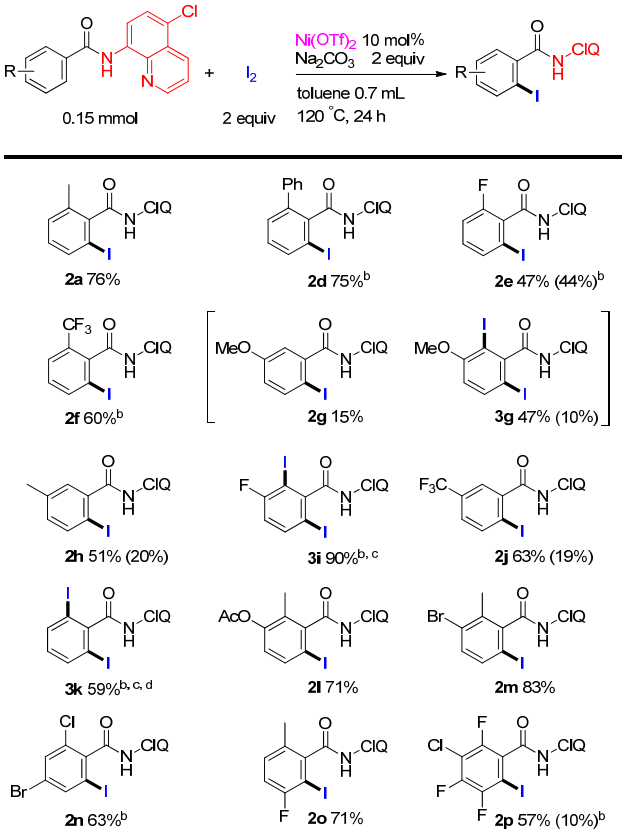
| entry | R | iodine source | base | solvent | yields [%](**2a**/**1a**)[b] |
|---|---|---|---|---|---|
| 1 | Cl | $I_2$ | none | DCE | trace / 99 |
| 2 | Cl | $I_2$ | $Na_2CO_3$ | DCE | 74 (65) / 0 |
| 3 | Cl | $I_2$ | $Cs_2CO_3$ | DCE | 52 / 15 |
| 4 | Cl | $I_2$ | $K_2CO_3$ | DCE | 13 / 17 |
| 5 | Cl | $I_2$ | LiO$^t$Bu | DCE | 27 / 42 |
| **6** | **Cl** | **$I_2$** | **$Na_2CO_3$** | **toluene** | **83 (76) / trace** |
| 7 | Cl | $I_2$ | $Na_2CO_3$ | dioxiane | 42 / 19 |
| 8 | Cl | $I_2$ | $Na_2CO_3$ | DMF | 8 / 29 |
| 9[c] | Cl | $I_2$ | $Na_2CO_3$ | DCE | 34 / 48 |
| 10 | Cl | NIS | $Na_2CO_3$ | DCE | 0 / 75 |
| 11 | Cl | PIDA, NaI | $Na_2CO_3$ | DCE | 19 / 56 |
| 12 | H (**1b**) | $I_2$ | $Na_2CO_3$ | toluene | 0 / 0 |
| 13 | OMe (**1c**) | $I_2$ | $Na_2CO_3$ | toluene | 52 / 28 |

[a] Reaction conditions: amide **1a** (0.15 mmol), iodine source (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), base (0.3 mmol) in solvent (0.7 mL) at 120 °C for 24 h. [b] NMR yields. The number in parenthesis denotes the isolated yield. [c] The reaction was run at 100 °C for 24 h.

Table 2 provides information concerning the scope of aromatic amides under the standard reaction conditions. The use of ortho-substituted amides gave good yields of iodination products (**2a**, **2d**, **2e** and **2f**). Although the reaction of meta-methyl and meta-trifluoromethyl aromatic amides resulted in selective iodination at the less hindered C-H bonds (**2h** and **2j)**, the reaction of meta-methoxy aromatic amides gave a mixture of mono-iodination products **2g** and di-iodination products **3g**. In the case of a meta-fluoro aromatic amide, the di-iodination product **3i** was selectively formed when 2.5 equivalents of iodine were used at a reaction temperature of 140 °C. Some functional groups, such as esters, fluorides, chlorides and bromides survived under the reaction conditions employed. Polyhalo-substituted aromatic amides also reacted with $I_2$ to give the corresponding ortho-iodination products, as in **2n** and **2p**.

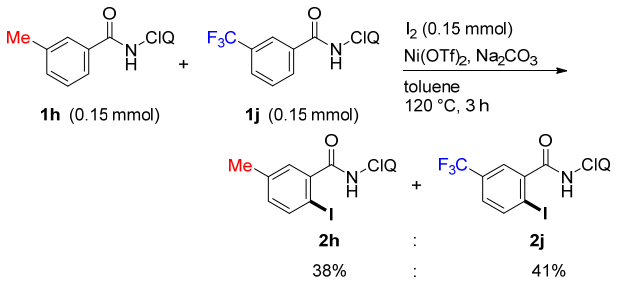
To examine the electronic effect of substituents, we performed a competition experiment using a 1:1 mixture of **1h** and **1j** in a reaction with $I_2$ (Scheme 2). The reaction gave nearly a 1:1 mixture of the products **2h** and **2j**, indicating that the electronic nature of substituents had no significant effect on the efficiency of the reaction. This is in sharp contrast to the our previous results showing that the presence of an electron withdrawing group on an aromatic amide dramatically facilitated the nickel-catalyzed arylation and alkylation of aromatic amides, in which reductive elimination was proposed to be the rate-determining step.[12b,e,h,i] The difference between the results shown in Scheme 2 and our previous results indicates that reductive elimination is not a rate-determining step in the present iodination reaction.

**Table 2. The Direct, Nickel-Catalyzed Iodination of Aromatic Amides with Iodine**



[a] Reaction conditions: amide (0.15 mmol), iodide (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), $Na_2CO_3$ (0.3 mmol) in toluene (0.7 mL) at 120 °C for 24 h. The number is isolated yields. The number in parenthesis is the yields of recovered starting amide. [b] The reaction was run at 140 °C for 24 h. [c] 2.5 Equivalents of iodide were used. [d] $Ni(OTf)_2$ (20 mol%) and 4 equivalents of $Na_2CO_3$ were used.

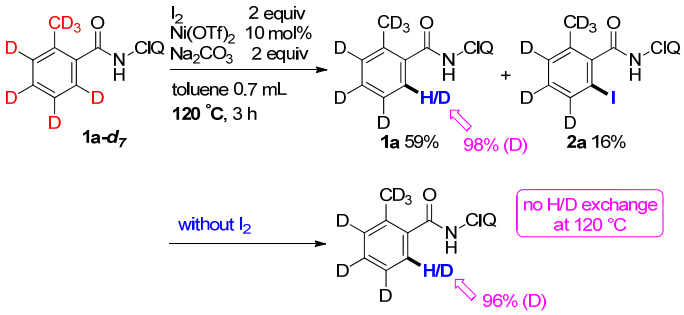
Scheme 2. Competition Experiment: Electronic Effect



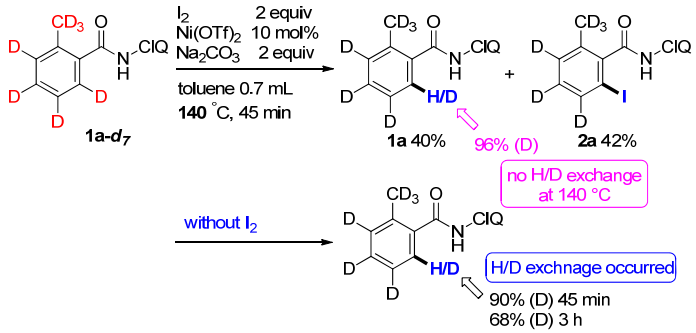

We next performed deuterium labeling experiments to gain more information on the rate-determining step. The deuterated amide **1a-*d*$_7$** was reacted with $I_2$ at 120 °C for 3 h (Scheme 3). No H/D exchange was observed in the *ortho* position on the recovered amide **1a**. In addition, no H/D exchange was observed in the absence of $I_2$ when the reaction was carried out at 120 °C, although there was a significant amount of H/D exchange in our previously reported reaction at the ortho position, when the reaction temperature was 140 or 160 °C.[12b,d,e,h] To determine whether or not H/D exchange occurs at 140 °C, the deuterated amide **1a-*d*$_7$** was reacted with $I_2$ at 140 °C (Scheme 4). No H/D exchange was detected in the recovered starting amide, although H/D exchange occurred in the absence of $I_2$. These results indicate that (i) the cleavage of C-H bonds takes place, even at 120 °C, (ii) the cleavage of C-H bond is irreversible at 120 °C, (iii)

the cleavage of C-H bond is reversible at 140 °C in the absence of $I_2$, (iv) the cleavage of C-H bonds is irreversible, even at 140 °C in the presence of $I_2$. In other words, the cleavage of C-H bonds occurs prior to the reaction with $I_2$ and the reaction of the metallacycle, which is formed by the cleavage of C-H bonds, with $I_2$ proceeds much faster than the protonation of the metallacycle, thus leading to H/D exchange.

Scheme 3. Deuterium Labeling Experiments at 120 °C



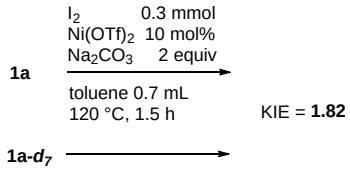

Scheme 4. Deuterium Labeling Experiments at 140 °C




We next conducted parallel experiments using amide **1a** and deuterated amide **1a-*d*$_7$** (Scheme 5). The results showed that the rate of consumption of deuterated amide **1a-*d*$_7$** was slower than

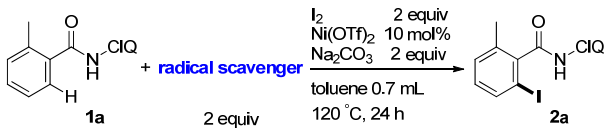
that for amide **1a. A k**inetic isotope effect (KIE) of 1.82 was observed at 120 °C. These results suggest that the cleavage of C-H bonds is the rate-determining step in the catalytic cycle.

Scheme 5. Competition Experiment for Kinetic Isotope Effect: Parallel Reaction




In order to obtain mechanistic information regarding a radical species, reactions were carried out in the presence of radical scavengers (Scheme 6). The addition of TEMPO (2 equivalents) dramatically decreased the yield of the product to 9% yield. In the use of BHT and 1,4-cyclohexadiene, no reactions were detected. These results suggest that a radical species participates in this reaction. However, the involvement of background reaction that radical scavengers were reacted with $I_2$ cannot be excluded, this background reaction would be expected to consume most of the $I_2$.[17]

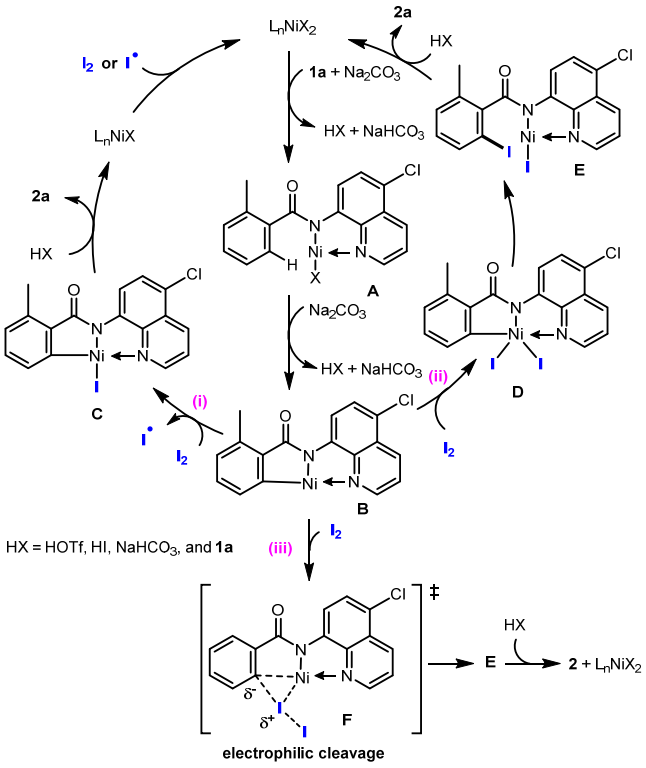
Scheme 6. Reactions with Radical Scavengers




| radical scavenger | NMR yield (**2a / 1a**) |
|---|---|
| TEMPO | 9% / 91% |
| BHT | 0% / 74% |
| cyclohexadiene | 0% / 77% |
| none | 83% / trace |

A proposed mechanism for the reaction is shown in Scheme 7. Amide **1a** coordinates to $NiX_2$ followed by a ligand exchange with the generation of HX, this step is accelerated by $Na_2CO_3$, to give the nickel complex **A**. Complex **A** undergoes cyclometalation to give complex **B** via a concerted metalation deprotonation (CMD) mechanism, which is also accelerated by the presence of $Na_2CO_3$. Based on the deuterium labeling experiments shown in Schemes 3 and 4, this step is an irreversible and a rate-determining step. There are three possible pathways for the reaction of cyclometalated complex **B** and $I_2$. The first pathway (i) proceeds via an iodine atom transfer[18] to give the Ni(III) species **C** (left cycle in Scheme 7).[19] The complex **C** undergoes reductive elimination and protonation to give the iodination product **2a** with the generation of the Ni(I) complex. The Ni(II) catalyst is regenerated by the reaction of Ni(I) and an iodine radical or $I_2$. The second pathway (ii) involves the oxidative addition of $I_2$ to complex **B** to give Ni(IV) species **D** (right cycle in Scheme 7).[20,21] This oxidative addition may take place via SET and a recombination pathway (or the homolysis and recombination of a two iodine radical pathway). The reductive elimination from **D** for the formation of a C-I bond and successive protonation gives the iodination product **2a** and with the regeneration of the Ni(II) species. Finally, a third pathway (iii) involves the direct electrophilic cleavage of the Ni-Ar bond (bottom scheme in Scheme 7).[22] The reaction of the Ni(II) complex **B** and $I_2$ directly gives the Ni(II) intermediate **E** through the transition state **F** without increasing the oxidation state of the Ni center. Sanford reported on a study of the formation of an Ar-X bond at a nickel center by using a stoichiometric amount of a nickel complex, and an electrophilic pathway is unlikely based on the experimental results reported in this paper.[19b] On the basis of these results and seminal work, we propose that an electrophilic cleavage pathway is not likely, but the reaction would likely proceed through a Ni(I)/Ni(III) catalytic cycle, such as pathway (i).[23]

Scheme 7. Proposed Mechanism




2.2. **Intramolecular Oxidative Cyclization of C($sp^3$)-H Bonds.** We next examined the reaction of aliphatic amides with $I_2$ in an attempt to extend the utility of this new iodination reaction. However, the reaction of aliphatic amides and $I_2$ did not give the expected *β*-iodinated products, but instead *β*-lactams were formed via the cleavage of C($sp^3$)-H bonds (Scheme 8). This type of transformation was achieved by utilizing a bidentate chelation system and various strong oxidants in conjunction with palladium,[24] copper[25] or cobalt[26] catalysts. Ge recently reported on the Ni-catalyzed amidation of C($sp^3$)-H bonds using TEMPO as an oxidant.[27] In all

of these reports, the formation of *β*-lactams was proposed to proceed via C-N bond forming reductive elimination.

Scheme 8. Oxidative Cyclization of C(sp3)-H Bonds

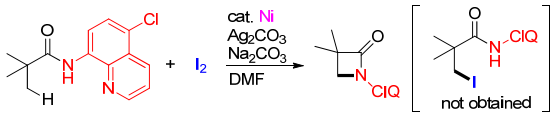
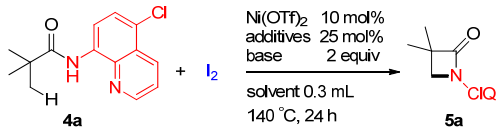



**Table 3. Optimization of the Nickel-Catalyzed Formation of *β*-lactam via cleavage of C(sp$^3$)-H Bonds**[a]

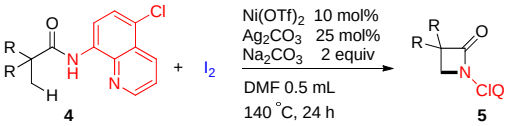


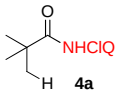
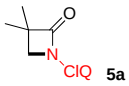
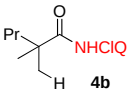
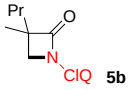
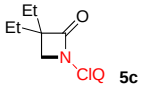
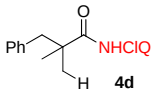
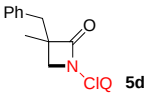
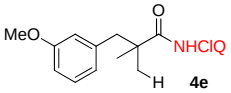
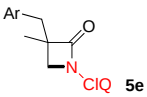
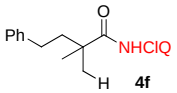
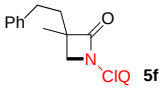
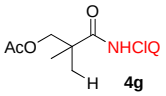
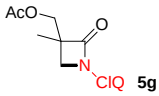
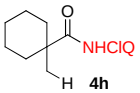
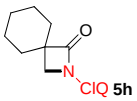
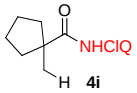
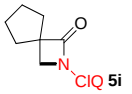

| entry | additives | base | solvent | yields [%] (**5a**/**4a**)[b] |
|---|---|---|---|---|
| 1 | none | $Na_2CO_3$ | toluene | 8 / 68 |
| 2 | none | $Na_2CO_3$ | DCE | 5 / 41 |
| 3 | none | $Na_2CO_3$ | DMSO | 6 / 44 |
| 4 | none | $Na_2CO_3$ | DMF | 53 (53) / 38 |
| 5 | none | $Cs_2CO_3$ | DMF | 0 / 45 |
| 6 | none | $K_2CO_3$ | DMF | 39 / 40 |
| 7 | none | NaOAc | DMF | 0 / 70 |
| 8 | $Ag_2CO_3$ | $Na_2CO_3$ | DMF | 63 (62) / 39 |
| 9[c] | none | $Na_2CO_3$ | DMF | 82 / 8 |
| **10**[c] | **$Ag_2CO_3$** | **$Na_2CO_3$** | **DMF** | **92 (91) /trace** |

[a] Reaction conditions: amide **1a** (0.15 mmol), iodine (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), additive (0.0375 mmol), base (0.3 mmol) and solvent (0.3 mL) were added in the sealed tube, and heated at 140 °C for 24 h. [b] NMR yields. The number in parenthesis represents the isolated yield. [c] Reaction conditions: amide **1a** (0.15 mmol), iodine (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), additive (0.0375 mmol), base (0.3 mmol) and solvent (0.5 mL) were added in the two-necked flask equipped with a condenser, and heated at 140 °C for 24 h.

The aliphatic amide **4a** was reacted under the standard reaction conditions used for the iodination of aromatic C-H bonds to give the *β*-lactam **5a** in 8% (Table 3, entry 1). The choice of solvent had a significant effect on the yield of the *β*-lactam **5a** (entries 1-4). The reaction of the aliphatic amide **4a** and $I_2$ in the presence of $Ni(OTf)_2$, $Na_2CO_3$ with DMF as the solvent in a sealed tube gave the *β*-lactam **5a** in 53% yield, along with 38% of unreacted **4a** being recovered (entry 4). This reaction was also dependent on the choice of base (entries 4-7). The addition of a catalytic amount of $Ag_2CO_3$ improved the yield of *β*-lactam **5a** to 63% yield. The yield of *β*-lactam **5a** was increased to 82% yield, when the reaction was conducted in an open system instead of a closed system. Finally, the combined use of $Ag_2CO_3$ and an open system gave the *β*-lactam **5a** in 91% isolated yield (entry 10).

Table 4. The Nickel-Catalyzed Formation of *β*–Lactams with Iodine [a]




| substrate | product [%][b] |
|---|---|
|  4a |  5a 91 |
|  4b |  5b 74[c] |
|  4c |  5c 79 (16)[c] |
|  4d |  5d 75 |
|  4e |  5e 64 (24) |
|  4f |  5f 74 (7)[c] |
|  4g |  5g 50 (22) |
|  4h |  5h 27 (46) |
|  4i |  5i 47 (30)[c] |

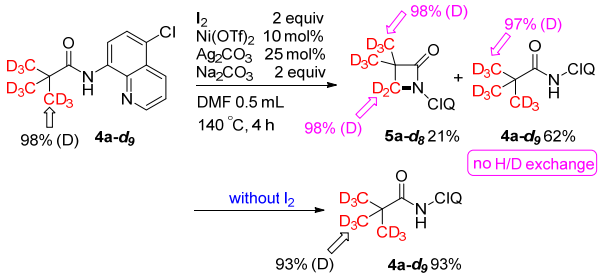
[a] Reaction conditions: amide **1a** (0.15 mmol), iodine (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), $Ag_2CO_3$ (0.0375 mmol), $Na_2CO_3$ (0.3 mmol) and DMF (0.5 mL) were added in a two-necked flask equipped with a condenser, and heated at 140 °C for 24 h. [b] Isolated yields. The number in parenthesis is the yield of the recovered starting amide. [c] Reaction run at 160 °C for 24 h.

With the optimized reaction conditions in hand, we examined the scope of the substrate (Table 4). *α,α,α*–Trisubstituted amides gave the corresponding *β*-lactams in good yields. In all cases, the reactions proceeded exclusively at the methyl group in a highly regioselective manner, and *β*-

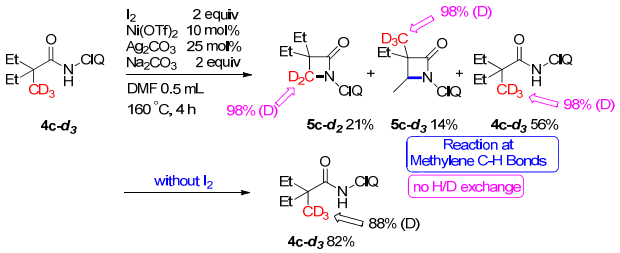
methylene C-H bonds in **4b** and **4c**, cyclic $\beta$-methylene C-H bonds in **4h** and **4i** and $\gamma$-aromatic C-H bonds in **4d** and **4e** did not react with $I_2$. In contrast to Ge's finding that the reaction of amide **4d** in the presence of a Ni(II) catalyst and TEMPO as an oxidant gave a mixture of the $\beta$-lactam **5d** and another $\beta$-lactam which was obtained via the cleavage of benzylic C-H bonds,[27] aliphatic amides containing a benzylic C-H bonds, as in **4d** and **4e** gave only the product, in which methyl C-H bonds reacted. The reaction was applicable to the synthesis of $\beta$-lactams having a spiro motif, as in **5h** and **5i**.

Deuterium labeling experiments using **4a-*d*$_9$** at 140 °C were carried out (Scheme 9). Similar to the case of an aromatic system, the cleavage of C-H bonds was found to be irreversible in the presence of $I_2$. Next, deuterium labeling experiments using **4c-*d*$_3$** were carried out (Scheme 10). No H/D exchange was observed in the presence of $I_2$. In addition, the activation of a methylene C-H bond in **4c-*d*$_3$** was observed, as in **5c-*d*$_3$**, although methylene C-H bonds in **4c** did not react, as shown in Table 4. These results suggest that the cleavage of C-H bonds is the rate-determining step in this reaction.

Scheme 9. Deuterium Experiments at 140 °C

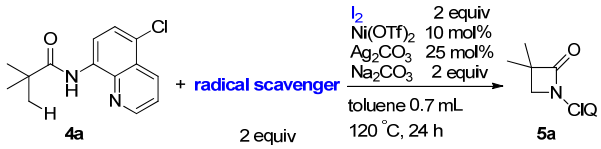



Scheme 10. Deuterium Experiments at 160 °C




The addition of radical scavengers, such as TEMPO and BHT resulted in no reaction (Scheme 11), similar to aromatic iodination reactions, as shown in Scheme 6. These results indicate that a radical is involved in the reaction.

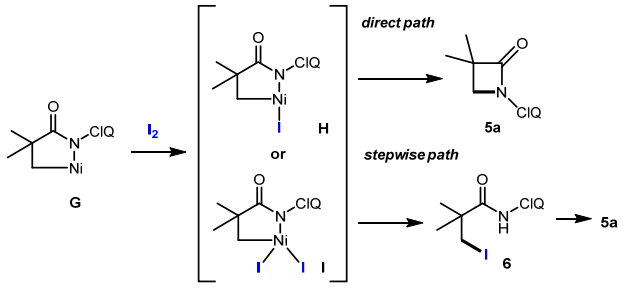
Scheme 11. Reactions with Radical Scavengers



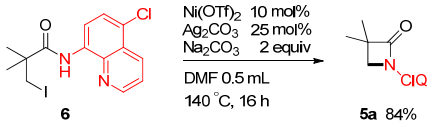

| radical scavenger | NMR yield (**5a** / **4a**) |
|---|---|
| TEMPO | 5% / 81% |
| BHT | 0% / 83% |
| none | 92% / trace |

The most important issue to be addressed is how the *β*-lactam is formed. There are two possible pathways for the formation of a β-lactam as shown in Scheme 12. One possibility is a direct pathway, in which the *β*-lactam is directly formed through the C-N bond reductive elimination from the Ni(III) intermediate **H** or the Ni(IV) intermediate **I**, which are generated by the reaction of the metallacycle **G** with $I_2$. All of the β-lactam synthesis reactions involving a cleavage of C($sp^3$)-H bonds reported so thus are proposed to proceed through this direct path.[23-26] The other possibility is a stepwise pathway, involving the direct *β*-iodination of the aliphatic amide to **6** and a facile intramolecular cyclization of the resulting **6** to form the *β*-lactam.

Scheme 12. Proposed Mechanism for the Formation of β-Lactams



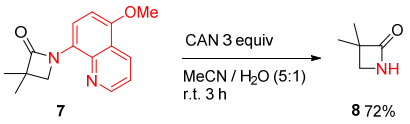

Scheme 13. Conversion of **6** to **5a**




In order to confirm which of these pathways is operative, the β-iodinated amide **6** was independently prepared and reacted under the standard reaction conditions in the absence of $I_2$ (Scheme 13). The β-lactam **5a** was obtained in 84% yield. In addition, the cyclization took place even in the absence of $Ni(OTf)_2$ and $Ag_2CO_3$. This result suggests that the β-lactam is formed via a stepwise pathway, and not via a direct pathway.[28] However, these results do not completely exclude the possibility of a direct pathway because **6** was not detected in the catalytic reaction of **4a**.

β-Lactams are an important structure for natural products and pharmaceutical compounds, such as penicillin and ezetimibe.[29] The deprotection of 8-aminoqunoline moieties in the products increases the potential of this transformation. Treatment of the β-lactam **7** containing an 8-amino-5-methoxyquinoline with ceric ammonium nitrate (CAN) gave the deprotected β-lactam **8** in 72% yield (Scheme 14).[30]

Scheme 14. Deprotection




## 3. CONCLUSION

We report on the first example of the Ni(II)-catalyzed direct iodination of aromatic amides using molecular $I_2$ as an iodinating reagent.[31] The reaction does not require strong co-oxidants. Mechanistic experiments revealed that the cleavage of C-H bonds is irreversible and is the rate-determining step in the catalytic cycle, in sharp contrast to other Ni(II)-catalyzed functionalization of C-H bonds in amides.[12b,e,i] This reaction is applicable to the synthesis of *β*-lactams by using aliphatic amides and $I_2$, in which C($sp^3$)-H bonds are activated. The results of deuterium labeling experiments indicate that the cleavage of C($sp^3$)-H bonds is also irreversible.

## ASSOCIATED CONTENT

**Supporting Information**. Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/

## AUTHOR INFORMATION

Corresponding Author

chatani@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, F; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (c) Hartwig, J. F. *Synlett* **2006**, 1283. (d) Johansson, S.; Carin, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062.

(2) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Merkushev, E. B. Synthesis **1988**, 923. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (d) Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424.

(3) For recent reviews on halogenation of C-H bonds, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Engle K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, 50, 1478. (c) Voskressensky, L. G.; Golantsov, N. E.; Maharramov, A. M. *Synthesis* **2016**, *48*, 615.

(4) The first example of the Pd-catalyzed chelation-assisted halogenation of the *ortho* C-H bonds was developed for the synthesis of a gardening pesticide, the production of which involves *ortho* iodination. Kodama, H.; Katuhira, T.; Nishida, T.; Hino, T.; Tsubata, K. *Chem. Abstr.* 2001, 135, 344284. Patent WO 2001083421 A1.

(5) For selected examples, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (d) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc*. **2006**, *128*, 7416. (e) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 15142. (f) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2008**, *47*, 5215. (g) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (h) Zhao, X.; Dimitrijevic, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (i) Song, B.; Zheng, X.; Mo, J.; Xu, B. *Adv. Synth. Catal.* **2010**, 352, 329. (j) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524. (k) John, A.; Nicholas, K. M. *J. Org. Chem.* **2012**, *77*, 5600. (l) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440. (m) Sarkar, D.; Melkonyan, F. S.; Gulevich,

A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 10800. (n) Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Tetrahedron* **2014**, *70*, 4197. (o) Sun, X.; Yao, X.; Zhang, C.; Rao, Y. *Chem. Commun.* **2015**, *51*, 10014. (p) Yang, X.; Sun, Y.; Sun, T.-Y.; Rao, Y. *Chem. Commun*. **2016**, *52*, 3423-6426.

(6) (a) Schröder, N.; Wencel-Delord J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (b) Qian, G.; Hong, X.; Liu, B.; Mao, H.; Xu, B. *Org. Lett*. **2014**, *16*, 5294. (c) Schröder, N.; Lied, F.; Glorius, F. *J. Am. Chem. Soc.* **2015**, *137*, 1448. (d) Ding, Q.; Zhou, X.; Pu, S.; Cao, B. *Tetrahedron* **2015**, *71*, 2376. (e) Zhang, P.; Hong, L.; Li, G.; Wang, R. *Adv. Synth. Catal*. **2015**, *357*, 345.

(7) (a) Wang, L.; Ackerman, L. *Chem. Commun.* **2014**, *50*, 1083. (b) Teskey, C. J.; Lui, A. Y. W.; Greaney, M. F. *Angew. Chem., Int. Ed*. **2015**, 54, 11677. (c) Yu, Q.; Hu, L.; Wang, Y.; Zheng, S.; Huang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 15284.

(8) (a) Chen, X.; Hao, X.-S.; Goodhue, C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Lu, Y.; Wang, R.; Qiao, X.; Shen, Z. *Synlett* **2011**, 1038. (c) Urones, B.; Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044. (d) Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 5093.

(9) Yu, D.-G.; Gensch, T.; Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc*. **2014**, *136*, 17722.

(10) (a) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326. (b) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344. (c) Chu, L.; Xiao, K.-J.; Yu, J.-Q. *Science* **2014**, *346*, 451. (d)

Haines, B. E.; Xu, H.; Verma, P.; Wang, X.-C.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9022.

(11) For recent reviews on Ni-catalyzed functionalization of C-H bonds utilizing a bidentate-chelation assistance, see: (a) Misal Castro, L. C.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410. (b) Chatani, N. *Top Organomet. Chem*. **2016**, *56*, 19-46.

(12) (a) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (c) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc*. **2014**, *136*, 898. (d) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc*. **2014**, *136*, 15509. (e) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922. (f) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem*. **2014**, *79*, 11933. (g) Yokota, A.; Chatani, N. *Chem. Lett*. **2015**, *44*, 902. (h) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 438. (i) Uemura, T.; Yamaguchi, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 3162. (j) Kubo, T.; Chatani, N. submitted for publication.

(13) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(14) For recent reviews on the catalytic functionalization of C-H bonds utilizing bidentate-chelation assistance, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (c) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett*. **2016**, *57*, 819. See also ref 11.

(15) For papers on the Ni-catalyzed functionalization of C-H bonds using an 8-aminoquinoline directing group published after ref 16, see: (a) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2015,**

*137*, 4924. (b) Yang, K.; Wang, Y.; Chen, X.; Kadi, A. A.; Fun, H.-K.; Sun, H.; Zhang, Y.; Lu, H. *Chem. Commun.* **2015**, *51*, 3582.(c) Yan, S.-Y.; Liu, Y.-J.; Liu, B.; Liu, Y.-H.; Zhang, Z.-Z.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 7341. (d) Ye, X.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2015**, *51*, 7863. (e) Liu, Y.-J.; Zhang, Z.-Z.; Yan, S.-Y.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 7899. (f) Liu, Y.-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 11650. (g) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett*. **2015**, *17*, 1340. (h) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett*. **2015**, *17*, 1970. (i)Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett*. **2015**, *17*, 2482. (j) Wang, X.; Zhu, L.; Chen, S.; Xu, X.; Au, C.-T.; Qiu, R. *Org. Lett*. **2015**, *17*, 5228. (k) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett*. **2015**, *17*, 2546. (l) Yi, J.; Xia, C.; Li, F. *J. Org. Chem*. **2015**, *80*, 6213. (l) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Biomol. Chem*. **2015**, *13*, 6803. (m) Barsu, N.; Kalsi, D.; Sundararaju, B. *Chem. Eur. J*. **2015**, *21*, 9364. (n) Maity, S.; Agasti, S.; Mahammad, A.; Hazra, A.; Maiti, D. *Chem. Eur. J*. **2015**, *21*, 11320. (o) Landge, V. G.; Shewale, C. H.; Jaiswal, G.; Sahoo, M. K.; Midya, S. P.; Balaraman, E. *Catal. Sci. Technol.***2016**, *6*, 1946.

(16) Kubo, T.; Chatani, N. *Chem. Lett*. **2015**, *44*, 1365.

(17) (a) Albéniz, A. C.; Espinet, P.; López-Femández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278. (b) Miller, R. A.; Hoerrner, R. S. *Org. Lett.* **2003**, *5*, 285.

(18) Xu, Z.-Y.; Jiang, Y.-Y.; Yu, H.-Z.; Fu, Y. *Chem. Asian J.* **2015**, *10*, 2479.

(19) (a) Ceder, R. M.; Granell, J.; Muller, G.; Font-Bardía, M.; Solans, X. *Organometallics* **1996**, *15*, 4618. (b) Higgs, A. T.; Zinn, P. J.; Simmons, S. J.; Sanford, M. S. *Organometallics* **2009**, *28*,

6142. (c) Renz, A. L.; Pérez, L. M.; Hall, M. B. *Organometallics* **2011**, *30*, 6365. (d) Zheng, B.; Tang, F.; Luo, J.; Schultz, J. W.; Rath, N. P.; Mirica, L. M. *J. Am. Chem. Soc.* **2014,** *136*, 6499.

(20) Higgs, A. T.; Zinn, P. J.; Sanford, M. S. *Organometallics* **2010**, *29*, 5446.

(21) (a) Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218. (b) Bour, J. R.; Camasso, N. M.; Sanford. M. S. *J. Am. Chem. Soc.* **2015,** *137*, 8034.

(22) The electrophilic pathway is supported by computational studies of the Pd-catalyzed direct iodination of aromatic C-H bonds with iodine (ref. 10d).

(23) Suder, A.; Curran, D. P. *Angew. Chem. Int. Ed*. **2016**, *55*, 58.

(24) (a) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (b) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, *16*, 480.

(25) (a) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (b) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706.

(26) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 6462.

(27) Wu, X.; Zhao, Y.; Ge, H. *Chem. Eur. J*. **2014**, *20*, 9530

(28) Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218.

(29) Garcia-Calvo, M.; Lisnock, J.; Bull, H. G.; Hawes, B. E.; Burnett, D. A.; Braun, M. P.; Crona, J. H.; Davis Jr., H. R.; Dean, D. C.; Detmers, P. A.; Graziano, M. P.; Hughes, M.; Macintyre, D. E.; Ogawa, A.; O'neill, K. A.; Iyer, S. P.; Shevell, D. E.; Smith, M. M.; Tang, Y.

S.; Makarewicz, A. M.; Ujjainwalla, F.; Altmann, S. W.; Chapman, K. T.; Thornberry, N. A. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8132. (b) Lau, W. K.; Mercer, D.; Itani, K. M.; Nicolau, D. P.; Kuti, J. L.; Mansfield, D.; Dana, A. *Antimicrob. Agents Chemother.* **2006**, *50*, 3556.

(30) An 8-amino-5-methoxyquinoline directing group was not a superior directing group, as shown in Table 1. In fact, the compound **7** was obtained in 17% isolated yield. However, Ge reported a new and general protocol for the deprotection of an 8-aminoqunoline moiety with $PhI(OAc)_2/BF_3Et_2O$ and CAN to give β-lactams.

(31) Recently, Wu, Su, and coworkers reported the Cu-catalyzed C-H iodination of aromatic amides having an-8-aminoquinoline as the directing group with $I_2$, in which iodination took place at the quinoline ring. Wu, C.; Zhou, H.; Wu, Q.; He, M.; Li, P.; Su, Q.; Mu, Y. *Synlett* **2016**, *27*, 868.

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