Nickel-Catalyzed Regio- and Stereospecific C–H Coupling of Benzamides with Aziridines

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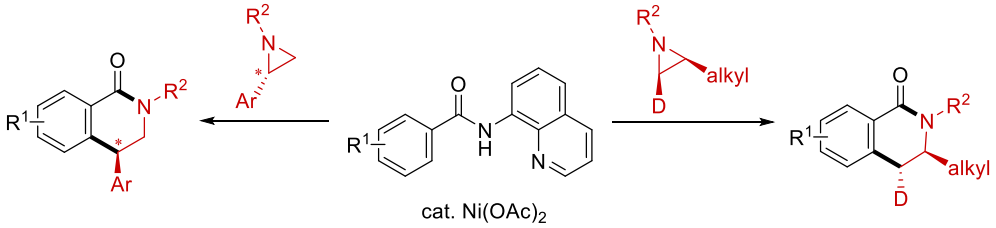
Supporting Information Placeholder



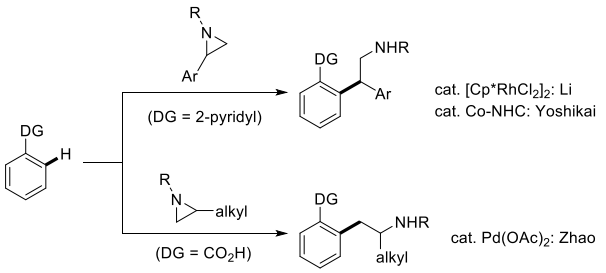
ABSTRACT: A nickel-catalyzed C–H coupling of 8-aminoquinoline-derived benzamides with aryl- and alkyl-substituted aziridines has been disclosed. The current strategy provides direct access to benzolactams by the C–H alkylation-intramolecular amidation cascade event with the concomitant removal of the aminoquinoline auxiliary. The regioselectivity of ring opening of aziridines can be controlled by the substituents. The reaction with chiral aziridines proceeds with inversion of configuration, thus suggesting an S_N2-type nucleophilic ring-opening pathway.

Due to the innate ring strain, aziridines have been regarded as important building blocks for the construction of structurally complex *N*-containing compounds via ring-opening reactions.[1] Among them, the Lewis-acid-promoted Friedel-Crafts alkylation[2] of electron-rich aromatic rings and the metal-catalyzed cross-coupling reaction with aryl halides[3] or organometallic reagents[4] have witnessed a significant progress in C–C bond formation. In particular, as an efficient and step- and atom-economical strategy, metal-catalyzed C–H coupling of arenes[5] with aziridines to furnish the β-arylethylamine skeleton has attracted growing attention. As a seminal work, the research group of Li reported the Cp*Rh(III)-catalyzed pyridine-directed *ortho*-C–H alkylation of 2-arylpyridines with aziridines.[6] The same transformation was subsequently disclosed with the Co-NHC catalytic system by the Yoshikai group (Scheme 1a, top).[7] However, these protocols are limited to the relatively activated aryl-substituted aziridines that favor the benzylic C–N cleavage, and the C–H coupling reaction with alkyl-substituted aziridines is less explored. As only one successful example, Zhao's group recently developed the Pd-catalyzed carboxylic-acid-assisted *ortho*-C–C coupling of benzoic acids with alkyl-substituted aziridines (Scheme 1a, bottom), in which the more sterically accessible C–N bond is selectively cleaved.[8]

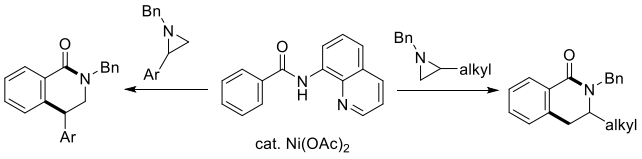
Meanwhile, our research group has recently reported the nickel-catalyzed C–H coupling of benzamides[9] with small-sized *O*-heterocycles, including epoxides and oxetanes.[10] The reactions proceeded with the assistance of the *N,N*-bidentate aminoquinoline auxiliary, which was originally introduced by Daugulis,[11] and the corresponding six- and seven-membered benzolactones were directly formed with the spontaneous removal of the aminoquinoline directing group. Particularly notable is the stereochemistry observed in the reaction with internal epoxides: the C–C bond formation occurred with retention of configuration.[10a] During our continuing interest in this chemistry, we herein describe a nickel-catalyzed C–H coupling of benzamides with aziridines (Scheme 1b). The *N,N*-bidentate chelation-promoted C–H alkylation was followed by the intramolecular amidation to form the corresponding six-membered lactam derivatives with concomitant removal of the directing group. Both the 2-aryl- and alkyl-substituted aziridines were successfully accommodated to afford the functionalized 3,4-dihydroisoquinolinones. Notably, the nickel catalysis was stereospecific,[12] and the chiral aziridines were converted into the corresponding products with inversion of configuration, suggesting a redox-neutral S_N2-type ring-opening pathway, which is in contrast to the reaction with epoxides.[10a]

Scheme 1. Metal-Catalyzed Directed C–H Transformations Involving Ring Opening of Aziridines

a) Previous work: Metal-catalyzed C-H coupling of aromatic compounds with aziridines

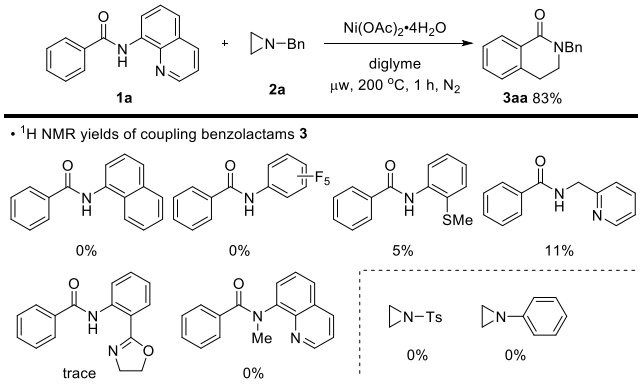


b) **This work:** Ni-catalyzed C-H coupling of benzamides with aziridines



We selected benzamide **1a** and *N*-benzyl aziridine (**2a**; 3.0 equiv) as model substrates and started optimization studies (Scheme 2). After extensive screening of various reaction parameters,[13] we pleasingly found that the reaction proceeded smoothly in the presence of a $Ni(OAc)_2$ catalyst with microwave irradiation (200 °C) in diglyme for 1 h to form the corresponding benzolactam **3aa** in 83% ^{1}H NMR yield. Due to the dimerization side reaction of the aziridine, an excess amount (3.0 equiv) of aziridine is necessary to maintain the satisfactory yield. The evaluation of directing groups demonstrated that the aminoquinoline auxiliary was indispensable, and other monodentately and bidentately coordinating amide substrates resulted in no or much less formation of product **3aa** under the present conditions. On the other hand, the *N*-benzyl protecting group of aziridines was also critical for the success: *N*-Ts substitution resulted in just decomposition of the aziridine, whereas the *N*-Ph substituted aziridine showed no reactivity.

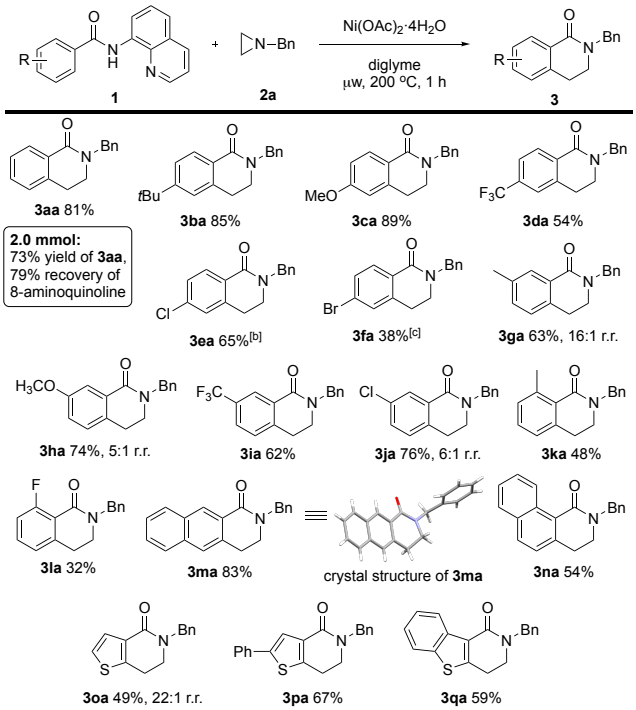
Scheme 2. Effects of Directing Groups and *N*-Substituents in Nickel-Catalyzed C–H Coupling of Benzamides with Aziridines[a]



[a]Conditions: **1** (0.10 mmol), **2** (0.30 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.020 mmol), diglyme (0.5 mL), microwave irradiation (200 °C), 1 h, N_2. ^{1}H NMR yields are shown.

With the optimal conditions in hand, the scope of benzamides **1** was first explored with **2a** as the reaction partner. As shown in Scheme 3, benzamides bearing electron-donating *tert*-butyl and methoxy substituents at the *para* position smoothly afforded the corresponding 3,4-dihydroisoquinolinones **3ba** and **3ca** in high yields. The reaction was also compatible with an electron-withdrawing trifluoromethyl group to furnish the targeted product **3da** in a moderate yield. Of note, the chloro and bromo substitutions were also tolerated, and the coupling products (**3ea** and **3fa**) were obtained along with the protodehalogenated product **3aa** in small amounts (~8%). When *meta*-substituted benzamides were employed in the reaction, the C–H coupling preferred to occur at the less sterically hindered position with good to excellent regioselectivity, regardless of the electronic nature of substituents (**3ga**-**ja**). The *ortho* substitutions were also tolerated albeit with somewhat lower efficiency (**3ka** and **3la**). Naphthalene derivatives **1m** and **1n** could also be coupled with **2a**: the reaction with 2-naphthalenecarboxamide occurred selectively at the more sterically accessible C3 position to form the corresponding **3ma** in 83% yield, whereas **3na** was obtained in a moderate yield from the congested 1-naphthyl isomer. The structure of **3ma** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 2049819). Moreover, several thiophene-derived carboxamides were also applicable for this reaction, successfully leading to thiophene-fused lactams (**3oa**-**pa**) in synthetically useful yields. Notably, the aminoquinoline directing group could be spontaneously removed and subsequently recovered.[14] The model reaction of **1a** with **2a** could be easily conducted on a 2.0 mmol scale to deliver the coupling product **3aa** in 73% yield along with 79% recovery of 8-aminoquinoline auxiliary, which exhibits remarkable reproducibility and reliability.

Scheme 3. Products of Nickel-Catalyzed Regioselective C–H Coupling of Various Benzamides 1 with *N*-Benzyl Aziridine 2a[a]

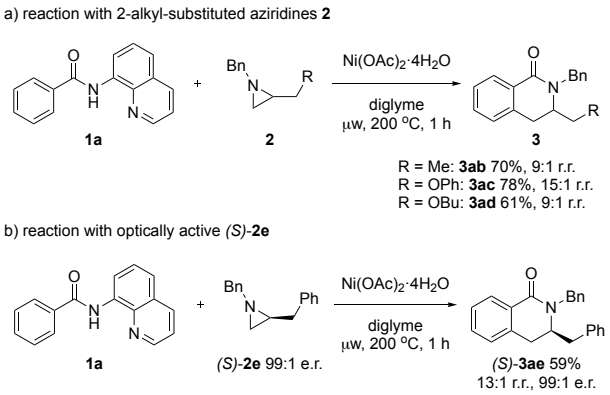


[a]Conditions: **1** (0.10 mmol), **2a** (0.30 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.020 mmol), diglyme (0.5 mL), microwave irradiation (200 °C), 1 h, N_2. Isolated yields are

shown. [b] The hydrodechlorinated product **3aa** was also formed in ~8% yield. [c] The hydrodebrominated product **3aa** was also formed in ~9% yield.

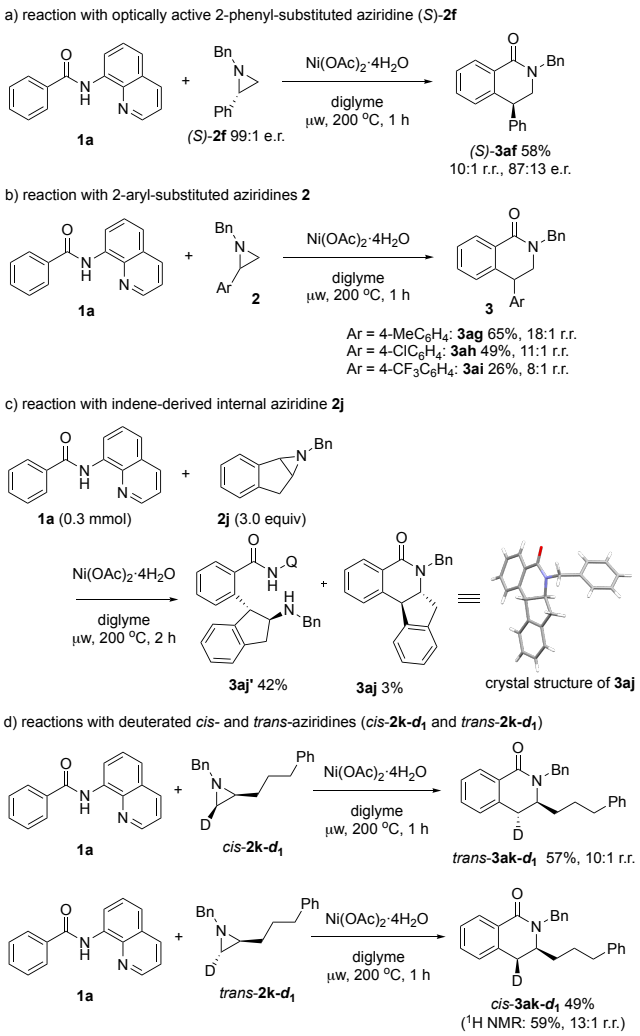
The scope of aziridines **2** was also investigated with **1a**. As shown in Scheme 4a, the 2-alkyl-substituted aziridines, which were challenging substrates under previous Cp*Rh(III)[6] and Co[7] catalysis, were successfully accommodated in the nickel-catalyzed C–C coupling protocol to deliver the 3-substituted 3,4-dihydroisoquinolinones. The reaction with 2-ethyl-substituted aziridine **2b** preferably occurred at the less hindered terminal position to furnish the desired **3ab** in 70% yield. The ether substituents were also compatible for the C–H alkylation, and the corresponding products (**3ac** and **3ad**) were isolated in good yields with high regioselectivity. Additionally, when the optically active aziridine (*S*)-**2e** was used, its chirality was successfully transferred to the product (*S*)-**3ae** without losing enantiopurity (Scheme 4b). We also tested the 2,2-dimethyl-substituted aziridine for the C–H coupling, but only decomposition of aziridine was observed, and no desired product was formed (data not shown).

Scheme 4. Nickel-Catalyzed C–H Coupling of Benzamide 1a with Substituted *N*-Benzyl Aziridines 2



To probe the possible reaction pathway, some mechanistic experiments were performed. Initially, when the enantiopure 2-phenyl aziridine (*S*)-**2f** was subjected to the reaction conditions, as observed in previous reports,[6,7] the benzylic C–N bond was primarily cleaved and coupled with **1a** to deliver the stereochemically inverted (*S*)-**3af**[15] albeit with some erosion of the enantiopurity (Scheme 5a). This result may imply that nickel-promoted accumulation of positive charge at the benzylic position leads to the prolongation and cleavage of the C–N bond, but a complete carbocation should not be involved.[6] The observed inversion of configuration suggests that the C–C coupling mainly proceeds via a redox-neutral S_N2-type nucleophilic ring-opening pathway. The observed regioselectivity was general; both the electron-rich and -deficient 2-arylaziridines provided the 4-aryl dihydroisoquinolinones **3ag**-**3ai** preferably (Scheme 5b). As shown in Scheme 5c, the indene-derived aziridine **2j** also underwent the coupling reaction via the benzylic C–N cleavage to furnish the C–H alkylated product **3aj'** as the major isomer. Although the cyclization of **3aj'** was sluggish, the lactam product **3aj** was also isolated in 3% yield, and its *trans*-stereochemistry was confirmed by X-ray crystallographic analysis (CCDC 2082069). To gain more information about the stereochemistry, deuterated *cis*- and *trans*-aliphatic aziridines were independently prepared and subjected to the standard conditions (Scheme 5d). Intriguingly, the reaction proceeded with ideal stereospecificity: *cis*-**2k-*d*$_1$** was converted to the *trans*-**3ak-*d*$_1$** as single diastereomer, whereas the *cis*-**3ak-*d*$_1$** was exclusively formed from *trans*-**2k-*d*$_1$**. Consequently, the nickel catalysis is stereospecific, and the inversion of configuration is opposite to that observed in the reaction with epoxides,[10a] which demonstrates the unique properties of a nickel catalyst in the ring-opening reactions of small-sized heterocycles.

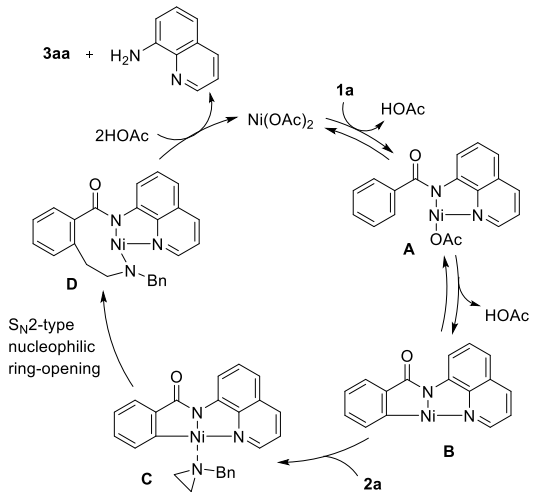
Scheme 5. Investigation of Regio- and Stereochemistry in the C–H Alkylation Step



On the basis of the experimental results and previous studies, a plausible reaction mechanism of **1a** with **2a** is proposed in Scheme 6. The initial chelation of benzamide **1a** to $Ni(OAc)_2$ generates Ni(II) complex **A**, which is followed by the reversible C–H cleavage[16] to give the nickelacycle **B**[17] with the generation of HOAc. Subsequent coordination of an aziridine nitrogen atom to the Ni(II) center leads to the prolongation of the C–N bond and promotes the C–C coupling to form intermediate **D** via an S_N2-type nucleophilic ring-opening process.[12] The carbocation-involved S_N1-type pathway and single electron transfer-type[4b] ring opening of aziridine could be ruled out based on the observed regio- and stereoselectivity. The difference of Lewis basicity between N and O

atoms may be responsible for the ring-opening pathway of aziridines and epoxides. The relatively stronger coordination of the N atom with the metal center results in a larger polarization of the C-N bond that favors the S_N2-type nucleophilic ring-opening process, while the epoxides prefer the redox-active ring-opening pathway.[10a] In the reactions of **1a** with *para*-substituted arylaziridines **2**, a negative slope of ρ = –1.09 was obtained from the Hammett plot with σ_p for the conversion of **1a**, suggesting that the C–C bond formation step is probably involved in the rate-determining step.[18] The intramolecular amidation[19] and simultaneous protonolysis with HOAc deliver the final product **3aa** and recovered 8-aminoquinoline with regeneration of the starting $Ni(OAc)_2$ to complete the catalytic cycle.

Scheme 6. Plausible Mechanism



In summary, we have developed a nickel-catalyzed, aminoquinoline-directed C–H coupling of benzamides with aziridines. This strategy provides rapid access to functionalized 3,4-dihydroisoquinolinones via a C–H alkylation-intramolecular amidation cascade process with concomitant removal of the aminoquinoline auxiliary. The reaction is compatible with both aryl- and alkyl-substituted aziridines, and the regioselectivity is controlled by the nature of the substituents. Additionally, the mechanistic studies reveal that the nickel catalyst is stereospecific, and the inversion of configuration in the C–C formation step suggests an S_N2-type nucleophilic ring-opening pathway.

ASSOCIATED CONTENT

Supporting Information

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

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, detailed optimization studies, experimental procedures, isotope-labeling experiments, Hammett studies (PDF)

Accession Codes

CCDC 2049819 and 2082069 contain 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.

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Notes

The authors declare no competing financial interest.

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