



A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

www.angewandte.org

Accepted Article

Title: Nickel-Catalyzed Stereospecific C-H Coupling of Benzamides with Epoxides

Authors: Masahiro Miura, Shibo Xu, Kazukata Takamatsu, and Koji Hirano

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201807664
Angew. Chem. 10.1002/ange.201807664

Link to VoR: <http://dx.doi.org/10.1002/anie.201807664>
<http://dx.doi.org/10.1002/ange.201807664>

Nickel-Catalyzed Stereospecific C–H Coupling of Benzamides with Epoxides

Shibo Xu,^[a] Kazutaka Takamatsu,^[a] Koji Hirano,^{*[a]} and Masahiro Miura^{*[a]}

Dedication ((optional))

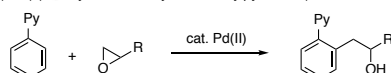
Abstract: An Ni(OAc)₂-catalyzed C–H coupling of 8-aminoquinoline-derived benzamides with epoxides has been developed. The reaction proceeds with concomitant removal of 8-aminoquinoline auxiliary to form the corresponding 3,4-dihydroisocoumarins directly. Additionally, the nickel catalysis is stereospecific; both *cis*- and *trans*-epoxides are converted to the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of configuration, which is complementary to the previous palladium catalysis. Moreover, while still preliminary, the C_{sp3}–H functionalization is also achieved in the presence of modified NiCl₂ catalysts.

In recent few decades, metal-promoted C–H coupling reactions have received significant attention because of their higher atom and step economies compared to conventional cross-coupling protocols with organic halides and organometallic reagents.^[1] Various electrophilic and nucleophilic components can be coupled with C–H bonds under appropriate conditions to form the corresponding C–C and C–X bonds. However, the alkylation reaction with epoxides as alkylating reagents is less explored. As limited successful examples, in 2015 the research group of Kuninobu and Kanai,^[2] and Yu^[3] independently reported Pd(II)-catalyzed C–H alkylations of arylpyridines and benzoic acids (Scheme 1a and 1b). These strategies can address traditional β-hydride elimination problems associated with alkyl halide electrophiles. Additionally, in the latter work, a unique stereoinvertive C–C bond formation was observed when internal epoxides were used. More recently, Dong also successfully employed epoxides in the Pd/norbornene-catalyzed direct annulation reaction with aryl iodides.^[4] A related cobalt-catalyzed C–H coupling of benzoic acids with C–C unsaturated molecules for the synthesis of lactone derivatives was also developed by Daugulis.^[5]

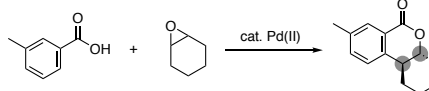
Meanwhile, well-designed bidentate directing groups now enable the functionalization of otherwise difficult C_{sp2}–H and even more challenging C_{sp3}–H bonds. To date, many combinations of bidentate coordination groups and transition metal catalysts have been developed.^[6] Our group also focused on the high potential of abundant Cu salts, and succeeded in the development of unique C–H arylation, alkylation, and amination with the assistance of suitable *N,N*-bidentate coordination groups.^[7] During continuous interest in this chemistry, we paid

attention to the C–H alkylation with epoxides. Although we could not find optimal Cu-based conditions, a similar base metal, Ni,^[6d,e,8] showed the promising reactivity. Herein, we report a Ni(II)-catalyzed C–H coupling reaction of 8-aminoquinoline-derived benzamides, which was originally developed by Daugulis,^[6a] with epoxides: the directed C–H alkylation is followed by intramolecular alcoholysis to deliver the corresponding 3,4-dihydroisocoumarins in one synthetic operation (Scheme 1c). Namely, the 8-aminoquinoline group is spontaneously removed and recovered, which deserves significant attention because the removal of bidentate directing groups is often tedious and problematic.^[9] Thus, the present Ni catalysis can provide a potentially more effective approach to the 3,4-dihydroisocoumarin structure frequently found in natural products and bioactive molecules.^[10] Additionally notable is the stereospecificity: the *cis*-epoxide can be converted to the *cis*-dihydroisocoumarin whereas the *trans* isomer is selectively formed from the *trans* epoxide. The unique stereochemical outcome with retention of configuration is complementary to that observed in previous Pd(II) catalysis (Scheme 1b).^[3]

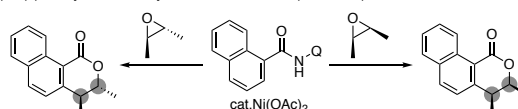
a) Pd(II)-catalyzed C–H alkylation of arylpyridines (Kuninobu and Kanai)



b) Pd(II)-catalyzed C–H alkylation of benzoic acids (Yu)



c) Ni(II)-catalyzed C–H alkylation of benzamides (this work)



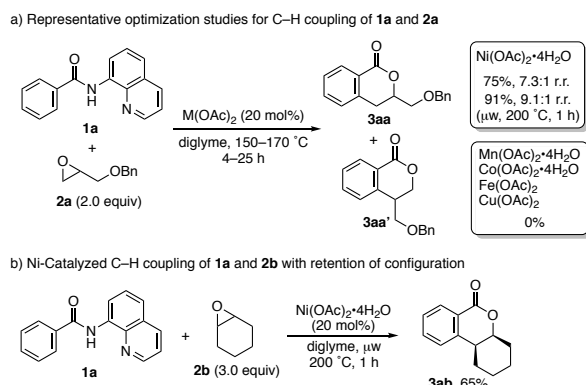
Scheme 1. Metal-catalyzed C–H alkylations with epoxides. Py = 2-pyridyl. Q = 8-quinoliny.

Our optimization studies commenced with 8-aminoquinoline-derived benzamide **1a** and terminal epoxide **2a** as model substrates (Scheme 2a). We tested several base metal acetate catalysts in heated diglyme (150–170 °C), and found that only Ni(OAc)₂·4H₂O showed catalytic activity to form 3,4-dihydroisocoumarins **3aa** and **3aa'** in 75% combined yield with 7.3:1 regioselectivity. While not detected, the simply alkylated products, i.e., alcohols shown in Scheme 1a can be initial products, and subsequent intramolecular alcoholysis forms the observed **3aa** and **3aa'** (vide infra). Other metal acetates including Mn(OAc)₂·4H₂O, Co(OAc)₂·4H₂O, Fe(OAc)₂, and Cu(OAc)₂ gave no detectable amount of coupling products. Although the subsequent screening of various reaction parameters such as solvent, additives, and ligands did not further improve the reaction efficiency, microwave irradiation (200 °C) dramatically accelerated the reaction to deliver **3aa** and

[a] S. Xu, K. Takamatsu, Prof. Dr. K. Hirano, Prof. Dr. M. Miura
Department of Applied Chemistry
Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-7362
E-mail: k_hirano@chem.eng.osaka-u.ac.jp;
miura@chem.eng.osaka-u.ac.jp

Supporting information for this article is available on the WWW
under <http://www.xxx>.

3aa' in 91% yield with somewhat higher regioisomeric ratio (9.1:1 r.r.).^[11] Additionally, the notable stereochemical outcome was observed when cyclohexene oxide (**2b**) was used instead of **1a** (Scheme 2b): the corresponding dihydroisocoumarin **3ab** was obtained as the single *cis* isomer. The observed stereochemistry with retention of configuration is in sharp contrast to that in the previous Pd catalysis, where the internal epoxide was coupled with C–H bonds in a stereoinvertive manner.^[3]

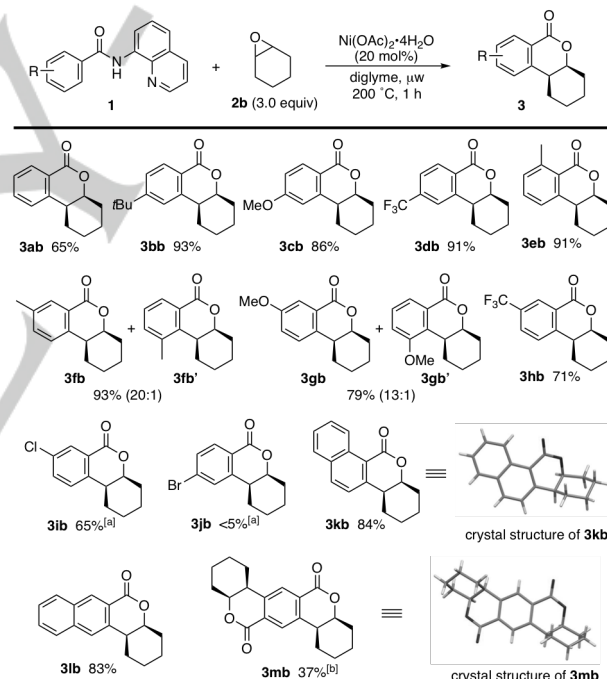


Scheme 2. a) Representative optimization studies and unique stereochemistry under Ni catalysis. Isolated yields are given. Bn = benzyl.

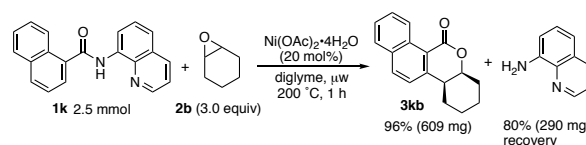
To check the generality of aforementioned unique stereochemistry, we investigated the scope of benzamides **1** with cyclohexene oxide (**2b**). Gratifyingly, the reaction proceeded uniformly with retention of configuration, and all products **3** were obtained as the *cis* isomers (Scheme 3). The reaction was compatible with electron-donating *tert*-butyl and methoxy groups as well as electron-withdrawing trifluoromethyl group to furnish the corresponding *cis*-3,4-dihydroisocoumarins **3bb–3db** in 86–93% yields. The sterically demanding ortho substitution was also tolerated under the standard conditions (**3eb**). In cases of meta-substituted benzamides, more sterically accessible C–H bonds were preferably coupled with **2b** (**3fb–3hb**). The chloro-substituted benzamide **1i** was also converted to the dihydroisocoumarin **3ib** with an acceptable yield. However, the C–Br moiety was detrimental, and competitively reduced product was also observed (**3jb**). However, this result is somewhat informative to an oxidation state of active Ni species (vide infra). On the other hand, condensed 1- and 2-naphthamides **1k** and **1l** could participate in the reaction without any difficulties (**3kb** and **3lb**): the latter reaction occurred selectively at the less congested C3 position. Moreover, the double cyclization of terephthalamide derivative **1m** was possible, forming the *syn* product **3mb** as the major isomer. The structure and stereochemistry of products **3kb** and **3mb** were unambiguously determined by the single crystallographic X-ray analysis.^[12] The Ni-catalyzed reaction could be easily conducted on a 2.5 mmol scale, and the removed 8-aminoquinoline was also recovered in this case (**3kb**: 96%, 8-aminoquinoline 80%), thus indicating good reproducibility and reliability of this process (Scheme 4).

The scope of epoxide **2** was also examined with the 1-naphthamide **1k**. The product structures are illustrated in Figure

1. As shown in Scheme 2a, terminal epoxides generally gave a regiomixture (**3kc–3ke**) but in good combined yields with synthetically useful regioisomeric ratios (6:1–15:1 r.r.). On the other hand, the chloro- and phthalimide-substituted epoxides underwent the C–H coupling exclusively at the more accessible terminal position to deliver **3kf** and **3kg** as the single isomers. Internal epoxides other than 6-membered cyclohexene oxide (**2b**) were also tested. Both the smaller (**2h**) and larger (**2i**) ring systems were accommodated, and the corresponding *cis*-dihydroisocoumarins **3kh** and **3ki** were obtained in 81% and 90% yields, respectively. Notably, in case of the indene oxide (**2j**), the regioselective benzylic C–O cleavage occurred to afford **3kj** as the single regio- and stereoisomer. Its structure was confirmed by X-ray analysis.^[12] The newly developed Ni catalysis can provide rapid and concise access to various 3,4-dihydroisocoumarins particularly bearing alkyl substituents at the C3 and C4 positions, which deserves significant attention in the C–H functionalization chemistry because some related O-heterocycles can be accessed by metal-catalyzed oxidative C–H coupling of benzoic acids with alkenes, but attempts to apply unactivated, aliphatic alkenes still remains a challenge.^[1a,5]



Scheme 3. Nickel-catalyzed stereospecific C–H coupling of various benzamides **1** with cyclohexene oxide (**2b**). Conditions: **1** (0.25 mmol), **2b** (0.75 mmol), $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.050 mmol), diglyme (1.5 mL), microwave irradiation (200 °C), 1 h, N_2 . Isolated yields are given. [a] The hydrodechlorinated product **3ab** was also formed in ca. 5% yield. [b] With $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.10 mmol) and **2b** (1.50 mmol). The *anti*-**3mb** and regioisomer were also detected in the crude mixture (<5%), but they could not be isolated in the pure forms.



Scheme 4. Reaction on 2.5 mmol scale.

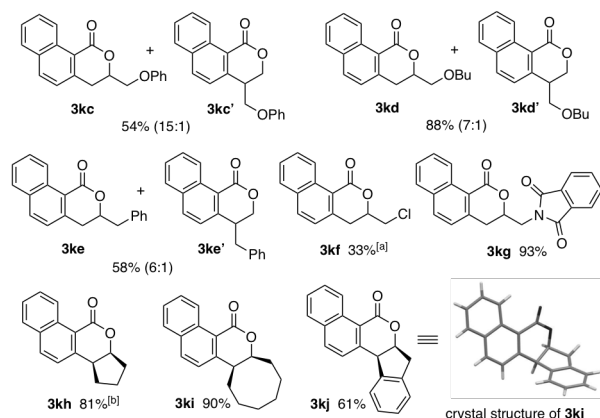
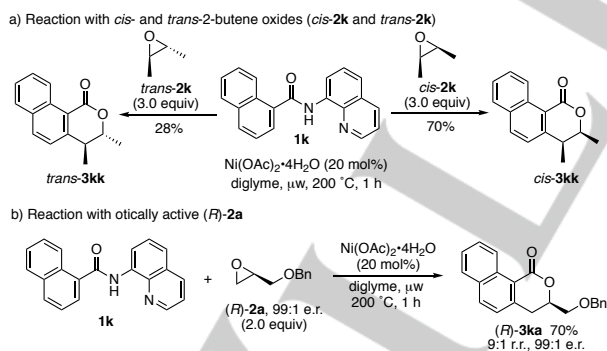


Figure 1. Product structures of nickel-catalyzed C–H coupling of 1-naphthamide **1k** with various epoxides **2**. Conditions: **1k** (0.25 mmol), **2** (0.50 mmol), Ni(OAc)₂·4H₂O (0.050 mmol), diglyme (1.5 mL), microwave irradiation (200 °C), 1 h, N₂. Isolated yields are given. [a] With 1.0 mmol of **2f**. [b] With 0.75 mmol of **2h**.

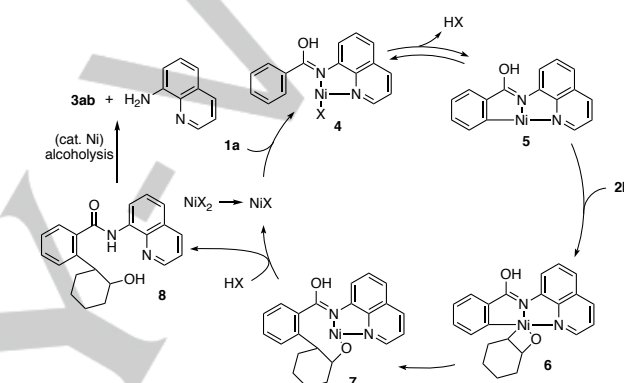
To get more insight into the stereochemistry, we then subjected *cis*- and *trans*-2-butene oxides (*cis*-**2k** and *trans*-**2k**) to the identical conditions with **1k** (Scheme 5a). To our delight, the reaction proceeded with perfect stereospecificity: *cis*-**2k** gave the dihydroisocoumarin *cis*-**3kk** exclusively while *trans*-**3jk** was formed as the sole product from *trans*-**2k**. Again, the structure of *cis*-**3kk** was unambiguously determined by X-ray analysis.^[12] Moreover, the optically active chiral epoxide (*R*)-**2a** was converted to the chiral 3,4-dihydroisocoumarin (*R*)-**3ka** without erosion of enantiomeric ratio (Scheme 5b). Thus, regardless of the structural and stereochemical information of starting epoxides (i.e., cyclic or acyclic as well as terminal or internal), the present Ni catalyst is stereospecific and operative with retention of configuration.



Scheme 5. Stereospecific nickel-catalyzed C–H coupling of 1-naphthamide **1k** with a) *cis*- and *trans*-2-butene epoxides (*cis*-**2k**, *trans*-**2k**) and b) chiral epoxide (*R*)-**2a**.

Although the detail still remains unclear, on the basis of the literature information and our findings,^[13] we are tempted to assume the reaction mechanism of **1a** with **2b** as follows (Scheme 6). Given the incompatibility of C–Br moiety (**3jb** in Scheme 3), an active Ni catalyst is believed to be Ni^I rather than Ni^{II}.^[8] Thus, the initial reduction from Ni^{II} precatalyst to Ni^I is followed by *N,N*-bidentate coordination with benzamide **1a** to

form the intermediate **4**. The facile and reversible C–H cleavage generates a metalacycle **5** with the liberation of HX. Subsequent oxidative addition with cyclohexene oxide (**2b**; **5** to **6**) and reductive elimination (**6** to **7**) to form the C_{sp2}–C_{sp3} bond. Final protonolysis with HX regenerates the starting Ni^I to complete the catalytic cycle. The concurrently formed alkylation product **8** undergoes the intramolecular alcoholysis to deliver the observed dihydroisocoumarin **3ab** and recovered 8-aminoquinoline. We confirmed that this ring-closing process spontaneously occurred but was largely accelerated also by the nickel catalyst.^[14] Additionally, the observed stereospecificity (retention of epoxide configuration) supports the net retention process in the Ni^I/Ni^{III} redox event; namely, the stereoinvertive oxidative addition/stereoinvertive reductive elimination^[15] or stereoretentive oxidative addition/stereoretentive reductive elimination^[16] can be operative.

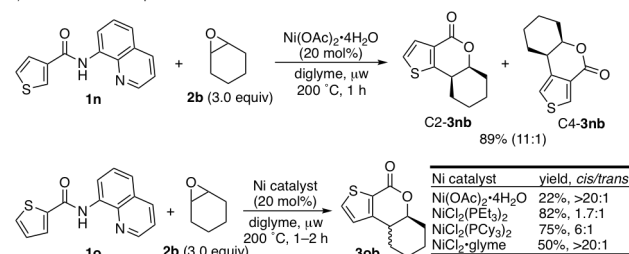


Scheme 6. Plausible mechanism.

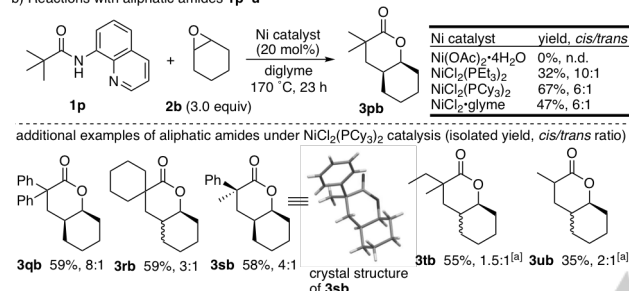
Finally, we attempted to apply conceivably more challenging heteroaromatic thiophenecarboxamides **1n** and **1o** (Scheme 7a). Under the standard conditions using the Ni(OAc)₂·4H₂O catalyst, the reaction of thiophene-3-carboxamide **1n** and cyclohexene oxide (**2b**) occurred smoothly with good regioselectivity (89%, C2-**3nb**:C4-**3nb** = 11:1) while thiophene-2-carboxamide **1o** gave the product **3ob** in only 22% yield. However, our additional optimization studies revealed that NiCl₂(PEt₃)₂ showed better performance to afford **3ob** in 82% yield albeit with a lower *cis/trans* ratio of 1.7:1.^[17] The complexes NiCl₂(PCy₃)₂ and phosphine-free NiCl₂·glyme were also effective, and **3ob** was formed in acceptable 75% and 50% yield, respectively, with better stereoselectivity (6:1 and >20:1).^[18] Moreover, the modified NiCl₂-based catalyst systems also promoted the C_{sp3}–H coupling of pivalamide **1p** with **2b** to form **3pb**, particularly with NiCl₂(PCy₃)₂ proving to be optimal (67% yield, *cis/trans* = 6:1) (Scheme 7b). Also in this case, Ni(OAc)₂·4H₂O was much less effective.^[19] The NiCl₂(PCy₃)₂ catalyzed the C_{sp3}–H coupling of some additional aliphatic amides (**1q–u**) with **2b** to deliver the corresponding lactones **3qb–ub**. When the potentially reactive methyl and methylene C_{sp3}–Hs were present, the more sterically accessible methyl C–H was selectively alkylated (**3rb** and **3tb**). Although the *cis/trans* ratio at the cyclohexyl ring fused positions was dependent on the substrate and modest in most cases, the relative stereochemistry at the position α to carbonyl was well controlled: the stereochemistry of major isomer of **3sb** was unambiguously determined by X-ray analysis.^[12] Additionally

notable is the compatibility with the somewhat acidic proton at the position α to carbonyl albeit with a moderate yield (**3ub**). While still preliminary, the obtained results demonstrate the high potential of Ni catalyst in the even more challenging C_{sp^3} –H couplings with epoxides.

a) Reactions with thiophenecarboxamides **1n** and **1o**



b) Reactions with aliphatic amides **1p–u**



Scheme 7. Nickel-catalyzed stereospecific C–H coupling of thiophenecarboxamides **1n** and **1o**, and aliphatic amides **1p–u**. n.d. = not determined. [a] The relative stereochemistry at the position α to carbonyl is not determined.

In conclusion, we have developed a Ni-catalyzed, *N,N*-bidentate coordination-assisted C–H coupling of benzamides with epoxides. The reaction occurs with the concomitant removal of 8-aminoquinoline bidentate auxiliary to form the 3,4-dihydroisocoumarins directly. Additionally, the reaction is completely stereospecific in most cases: both the *cis*- and *trans*-epoxides are converted to the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of configuration, which is in sharp contrast to previous Pd-catalyzed C–H coupling with epoxides.^[3] Moreover, the C_{sp^3} –H cleavage is also possible under NiCl₂-phosphine catalysis. The observed unique activity and stereochemistry associated with the Ni catalysis deserve significant attention from the viewpoint of C–H functionalization chemistry. Improvement of stereoselectivity in the reaction of C_{sp^3} –H, mechanistic investigation, and application to other ring system construction are currently underway in our laboratory.

Acknowledgements ((optional))

This work was supported by JSPS KAKENHI Grant Nos. 17J00349 (Grant-in-Aid for JSPS Research Fellow) to K.T., JP 15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H., and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M. S.X. thanks Japanese government (MEXT) scholarship.

We appreciate Dr. Yuji Nishii (Osaka University) for his assistance with X-ray analysis.

Conflict of Interest

The authors declare no conflict of interest.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: C–H coupling · epoxides · lactones · nickel · stereospecificity

- a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; b) L. Ping, D. S. Chung, J. Bouffard, S. Li, *Chem. Soc. Rev.* **2017**, *46*, 4299; c) M. T. Mihai, G. R. Genov, R. J. Phipps, *Chem. Soc. Rev.* **2018**, *47*, 149; d) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62; *Angew. Chem.* **2018**, *130*, 64. See the Supporting Information for a complete list of references.
- a) Z. Wang, Y. Kuninobu, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 6140. A recent computational study: b) B. Lian, L. Zhang, S.-J. Li, D.-C. Fang, *J. Org. Chem.* **2018**, *83*, 3142.
- G. Cheng, T.-J. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 10950.
- R. Li, G. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 1697; *Angew. Chem.* **2018**, *130*, 1713.
- T. T. Nguyen, L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2018**, *57*, 1688; *Angew. Chem.* **2018**, *130*, 1704.
- Pioneering work: a) V. Z. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154. Selected reviews: b) M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, *52*, 9896; *Angew. Chem.* **2013**, *125*, 10080; c) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; d) L. C. M. Castro, N. Chatani, *Chem. Lett.* **2015**, *44*, 410; e) N. Chatani, *Top. Organomet. Chem.* **2016**, *56*, 19; f) J. Liu, G. Chen, Z. Tan, *Adv. Synth. Catal.* **2016**, *358*, 1174; g) Y. Komagall, N. Chatani, *Coord. Chem. Rev.* **2017**, *350*, 117; h) N. Chatani, *Bull. Chem. Soc. Jpn.* **2018**, *91*, 211.
- a) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 4457; *Angew. Chem.* **2013**, *125*, 4553; b) K. Takamatsu, K. Hirano, M. Miura, *Angew. Chem. Int. Ed.* **2017**, *56*, 5353; *Angew. Chem.* **2017**, *129*, 5437; See the Supporting Information for a complete list of references.
- For seminal work on Ni-catalyzed C–H functionalization with assistance of *N,N*-bidentate coordination, see: a) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952; b) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308; c) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898.
- For limited successful examples of C–H couplings with concomitant removal of bidentate directing groups, see: a) T. Uemura, T. Igarashi, M. Noguchi, K. Shibata, N. Chatani, *Chem. Lett.* **2015**, *44*, 621; b) P. Gandeepan, P. Rajamalli, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2016**, *55*, 4308; *Angew. Chem.* **2016**, *128*, 4380; c) J. Liu, J. Zou, J. Yao, G. Chen, *Adv. Synth. Catal.* **2018**, *360*, 659; and ref 7g, j.
- Selected examples: a) Y. Li, I. Plitzko, J. Zaugg, S. Hering, M. Hamburger, *J. Nat. Prod.* **2010**, *73*, 768; b) R. Haritakun, M. Sappan, R. Suvannakad, K. Tassanathai, M. Isaka, *J. Nat. Prod.* **2010**, *73*, 75; c) L. Xu, Z. He, J. Xue, X. Chen, X. Wei, *J. Nat. Prod.* **2010**, *73*, 885; d) F. Lehmann, E. A. Currier, R. Olsson, J.-N. Ma, E. S. Burstein, U. Hacksell, K. Luthman, *Bioorg. Med. Chem.* **2010**, *18*, 4844.
- Benzamides that bear other bidentate or monodentate directing groups showed no or much lower reactivity. See the Supporting Information for more detailed optimization studies.
- CCDC 1842695 (**3kb**), 1842697 (**3mb**), 1842696 (**3kj**), 1842698 (*cis*-**3kk**), and 1853295 (**3sb**) contains the supplementary crystallographic

- data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [13] We performed several control experiments to get the mechanistic insight: 1) the deuterium-labeled benzamide rapidly underwent the H/D exchange reaction, thus indicating the reversible and non-rate-limiting C–H cleavage; 2) in the absence of benzamide, no reaction of epoxide occurred; 3) 2-chlorocyclohexanol was not the intermediate of the reaction. See the Supporting Information for more details.
- [14] See the Supporting Information for more details. In addition, Ohshima recently reported the related Ni(II)-catalyzed alcoholysis of 8-aminoquinoline amides. T. Deguchi, H.-L. Xin, H. Morimoto, T. Ohshima, *ACS Catal.* **2017**, *7*, 3157.
- [15] For seminal studies on the stereoinvertive oxidative addition/reductive elimination of aziridines with Ni, see: a) B. L. Lin, C. R. Clough, G. L. Hillhouse, *J. Am. Chem. Soc.* **2002**, *124*, 2890. Also see related reactions: b) R. J. De Pasquale, *J. Chem. Soc. Chem. Commun.* **1973**, 157; c) A. Miyashita, T. Shimada, A. Sugawara, H. Nohira, *Chem. Lett.* **1986**, 1323; d) J.-E. Bäckvall, F. Bökman, M. R. A. Blomberg, *J. Am. Chem. Soc.* **1992**, *114*, 534; e) M. Mavrikakis, D. J. Doren, M. A. Barteau, *J. Phys. Chem. B* **1998**, *102*, 394; f) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076.
- [16] For recent elegant studies on the stereoretentive oxidative addition of epoxides to Ni via a bimolecular mechanism, see: A. N. Denoyer, E. G. Bowes, B. O. Patrick, J. A. Love, *J. Am. Chem. Soc.* **2015**, *137*, 12748.
- [17] The isolated *cis*-**3ob** underwent no *cis/trans* isomerization under NiCl₂(PEt₃)₂ catalysis even with prolonged reaction periods. Thus, the *trans*-**3ob** might be kinetically formed.
- [18] The NiCl₂(PEt₃)₂ and NiCl₂(PCy₃)₂ salts also catalyzed the reaction of other amides such as the parent **1a** with efficiency comparable to Ni(OAc)₂•4H₂O, but we identified Ni(OAc)₂•4H₂O to be best from the view point of cost (NiCl₂(PEt₃)₂: 4166 JPY/g (ALFA AESAR), NiCl₂(PCy₃)₂: 3940 JPY/g (TCI), Ni(OAc)₂•4H₂O: 13 JPY/g (Aldrich)). Additionally, the stereochemical erosion was unique to the thiophene **1o**: in the reaction of nonheteroaromatic **1k** and cyclohexene oxide (**2b**) Ni(OAc)₂•4H₂O/PPh₃, NiCl₂(PEt₃)₂, and NiCl₂(PCy₃)₂ all afforded **3kb** with high *cis*-selectivity (16:1→20:1). See the Supporting Information for details.
- [19] Several attempts to apply microwave irradiation with aliphatic amides **1p–u** resulted in burst, although we have no explanation for the reason. Thus, we performed the reaction under conventional heating conditions with an oil bath.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

Author(s), Corresponding Author(s)*

Page No. – Page No.

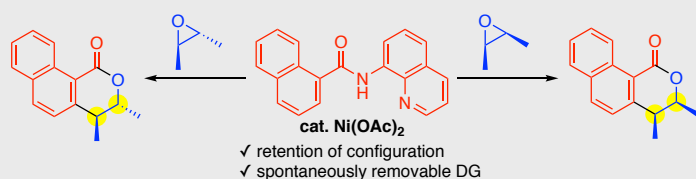
Title

Layout 2:

COMMUNICATION

S. Xu, K. Takamatsu, K. Hirano,* M. Miura*

Page No. – Page No.

Nickel-Catalyzed Stereospecific C–H Coupling of Benzamides with Epoxides

Stop configuration: An Ni(OAc)₂-catalyzed C–H coupling of 8-aminoquinoline-derived benzamides with epoxides has been developed. The reaction proceeds with concomitant removal of 8-aminoquinoline auxiliary to form the corresponding 3,4-dihydroisocoumarins directly. Additionally, the nickel catalysis is stereospecific; both *cis*- and *trans*-epoxides are converted to the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of configuration, which is complementary to the previous palladium catalysis. Moreover, while still preliminary, the C_{sp3}–H functionalization is also achieved in the presence of modified NiCl₂ catalysts.