ChemPubSoc Europe

DOI: 10.1002/ejoc.201901211

EurJOC European Journal of Organic Chemistry

Communication

Check for updates

C–H Activation

Nickel-Catalyzed *Ortho* C–H Methylation of Aromatic Amides with Di-*tert*-butyl Peroxide as Methylation Reagent

Da Liu,[a,b] Lin Yu,[a] Yongqi Yu,[a] Zhen Xia,[a] Zenan Song,[a] Lihong Liao,[b] Ze Tan,*[a] and Xiang Chen*[a]

Abstract: A new efficient protocol for the *ortho*-methylation of benzamides with DTBP has been developed via Ni(II)-catalyzed C–H activation directed by 8-aminoquinoline. This method is performed under base-free, ligand-free conditions and utilizes cheap and commercially available reagents. Moreover, the by-product acetone derived from DTBP does not affect the purification of the product.

Introduction

Methyl group is one of the most appealing functionalities in pharmaceutical molecules,[1] and it can significantly regulate the biological and physical properties of drugs, which is called "magic methyl effect".[1a] Omeprazole (Losec), a pyridinyl-benzoimidazole derivative with two methyl groups, was the first selective antiulcer proton pump inhibitors (Abbreviation PPIs).[2] Simvastatin (Zocor), a methyl derivative of lovastatin, was developed by Merck and has a longer half-life as the ester hydrolysis is blocked by additional methyl group.[3] Besides, there are also many other drugs containing methyl substituent, which are selectively illustrated in Figure 1.[1a] In addition, the methyl group can serve as an important intermediate to generate aldehydes, carboxylic acids, alcohols and halogenated hydrocarbons.[4] It is worthwhile to note that aryl methyl group has also found applications in C–N coupling reactions.[5] Therefore, development of efficient strategies for the introduction of methyl group is one of the central research topics in medicinal and synthetic organic chemistry. Traditionally, the introduction of methyl group has largely relied on the reaction of aryl metal species with electrophilic reagents, such as iodomethane,[6] dimethyl

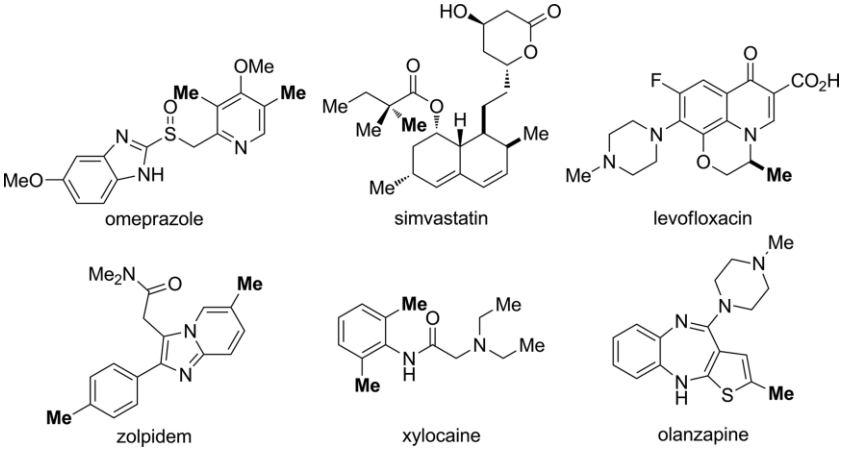


Figure 1. A selection of methylated drugs.

sulfate[7] and $PhMe_3NI$.[8] These methods, although still broadly utilized in industry as well as in academic study, tend to suffer from the use of hazardous and toxic methylation reagents. Therefore, it is highly desirable to develop a new methylation method that can overcome above-mentioned drawbacks.

The C–C bonds formation via transition-metal-catalyzed C–H activation is emerging as a research hotspot and has aroused wide concern recently.[9] Therefore, chemists have paid much attention to the development of transition-metal-catalyzed

[a] *State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China*
E-mail: ztanze@gmail.com
lucasphe@163.com
http://cc.hnu.edu.cn/
[b] *Kamp Pharmaceuticals CO., LTD. Changde 415900, P. R. China*

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901211.

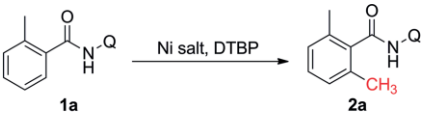
C–H methylation with active nucleophilic reagents such as MeMgX,[10] $AlMe_3$[11] and methylboron reagents.[12] However, one major problem in these reactions is that they are needed to be run under air and moisture free conditions. For this reason, other methylation reagents, such as DMSO,[13] peroxide reagents such as dicumyl peroxide (DCP)[14] and *tert*-butyl peracetate,[15] have been applied in transition-metal-catalyzed C–H bond methylations. Along this line, Li and Lu group revealed a cobalt-catalyzed direct methylation of a $C(sp^2)$–H bond using DCP as methylation reagent.[14a] Despite the usefulness of these reactions, however, an equivalent of acetophenone is always produced as by-product, and this could make the separation of products more difficult. In view of this situation and also in continuation of our recent interest in base metal promoted C–H bond functionalization,[16] we wonder whether DTBP, a common and cheap commercial material, can be used as methylation reagent to achieve the same methylation because the boiling point of by-product acetone derived from DTBP is rather low. Thus, it can be easily removed, facilitating the isolation of the desired product. In light of this and recent plethora of reports on nickel catalyzed C–H bond functionalizations,[17] we embarked on a study aiming to achieve a selective methylation with DTBP and suitable Ni-catalyst. Herein we report that *ortho*-methylation of aromatic amides can be indeed efficiently performed with DTBP via Ni(II)-catalyzed C–H activation directed by 8-aminoquinoline (Scheme 1).

Scheme 1. Di-*tert*-butyl peroxide as methylation reagent in Ni-catalyzed C–H bond functionalization of aromatic amides.

Results and Discussion

Our original plan was to install an acetonitrile group on the aromatic ring through transition-metal-catalyzed $C(sp^2)$–H activation assisted by 8-aminoquinoline because the nitrile group plays an important role in bioactive molecules[18] and pharmaceuticals.[19] However, preliminary experimental results showed that a methylation product was actually obtained when 2-methyl-*N*-(quinolin-8-yl)benzamide **1a** was treated with 2.0 equiv. of DTBP, 0.2 equiv. of $Ni(OAc)_2{\cdot}4H_2O$ in CH_3CN at 140 °C for 12 hours under a nitrogen atmosphere (Table 1, entry 1). In order to optimize the reaction conditions, various solvents, reaction time, nickel salts as well as the amount of DTBP, were screened (Table 1). When CH_3CN was replaced with 1,4-dioxane, DMF, THF, DCE, *t*Bu-benzene or DMSO, no target product **2a** was obtained (Table 1, entries 2–7). Prolonging the reaction time to 24 hours slightly improved the yield to 41 % (Table 1, entry 8). Pleasingly, the product **2a** was isolated in 79 % yield when the amount of DTBP was increased to 4.0 equiv. and all of the starting material **1a** was consumed (Table 1, entry 9). When the reaction was carried out at 120 °C, the yield was decreased to 40 % (Table entry 10). In order to further increase the yield, we investigated other nickel salts such as $Ni(OAc)_2$, $NiCl_2$, NiF_2, $NiBr_2$, $Ni(OTf)_2$, $Ni(dppp)Cl_2$ and $Ni(Ph_3P)_2Cl_2$. Unfortunately, we did not see any improvement with all the above nickel salts tested (Table 1, entries 11–17). In addition, no reaction took place in the absence of Ni salts, suggesting that the nickel catalyst is necessary for the reaction to proceed (Table 1, entry 18). Based on the above results, we decided to set reacting **1a** with 20 mol-%. of $Ni(OAc)_2{\cdot}4H_2O$, 4 equiv. of DTBP in CH_3CN at 140 °C under N_2 for 12 h as our standard conditions. It should be noted that we also carried out the model reaction using other oxidants under our standard conditions. No product **2a** was formed with TBPB and TBHP whereas the use of DCP gave **2a** in 35 % yield. In addition, we did place a safety shield in front of our reaction set up for safety reasons though no explosion ever took place throughout our study.

Table 1. Screening of reaction conditions.[a]



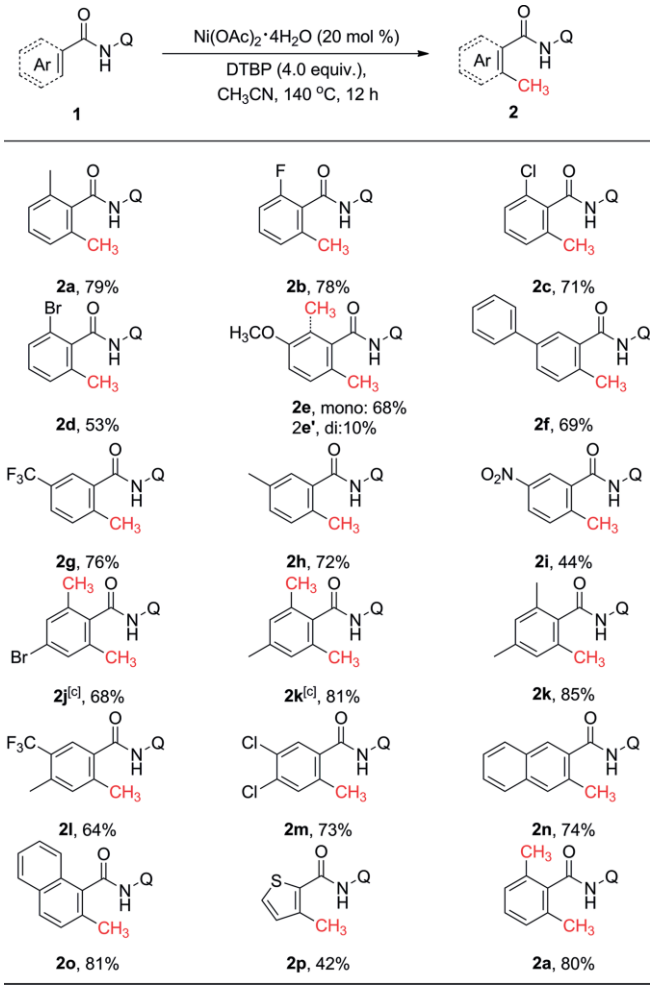
Entry	Ni salt	Solvent	Yield[b] (%)
1[c]	$Ni(OAc)_2{\cdot}4H_2O$	MeCN	29
2[c]	$Ni(OAc)_2{\cdot}4H_2O$	1,4-dioxane	ND
3[c]	$Ni(OAc)_2{\cdot}4H_2O$	DMF	ND
4[c]	$Ni(OAc)_2{\cdot}4H_2O$	THF	ND
5[c]	$Ni(OAc)_2{\cdot}4H_2O$	DCE	ND
6[c]	$Ni(OAc)_2{\cdot}4H_2O$	*t*Bubenzene	ND
7[c]	$Ni(OAc)_2{\cdot}4H_2O$	DMSO	ND
8[d]	$Ni(OAc)_2{\cdot}4H_2O$	MeCN	41
9	**$Ni(OAc)_2{\cdot}4H_2O$**	**MeCN**	**79**
10[e]	$Ni(OAc)_2{\cdot}4H_2O$	MeCN	40
11	$Ni(OAc)_2$	MeCN	77
12	$NiCl_2$	MeCN	60
13	NiF_2	MeCN	55
14	$NiBr_2$	MeCN	67
15	$Ni(OTf)_2$	MeCN	42
16	$Ni(dppp)Cl_2$	MeCN	65
17	$Ni(Ph_3P)_2Cl_2$	MeCN	69
18[f]	—	MeCN	ND

[a] Reaction conditions: amide **1a** (0.15 mmol), DTBP (0.60 mmol), Ni salt (0.03 mmol), solvent (1.0 mL), 140 °C under N_2 for 12 h. [b] Isolated yield. [c] DTBP (0.30 mmol). [d] DTBP (0.30 mmol), reaction time 24 h. [e] At 120 °C. [f] Without Ni salt.

With the optimized conditions in hand, the scope and limitation of the reaction was explored and the results were summarized in Table 2. From the table we could find that the reaction worked well for various substituted benzamides to obtain the desired *ortho*-methylation products in moderate to good yields, and functional groups on the aromatic ring of benzamides including electron-donating (methoxyl, methyl) and -withdrawing (fluoro, chloro, bromo, nitro, phenyl as well as trifluoromethyl) substituents are well tolerated.

The *ortho*-substituted substrates underwent the desired methylation reaction smoothly in 53–79 % yields (Table 2, **2a**–**2d**). For the *meta*-substituted substrates, methylation tended to take place on the less hindered site because of the steric hindrance effect (Table 2, **2e**–**2i**). However, a *meta*-methoxyl-substituted substrate produced mono-methylation product **2e** with simultaneous generation of a small amount of di-methylation product **2e′**, which is most possibly owing to the extra-chela-

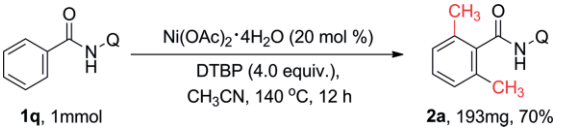
Table 2. Ni salt-catalyzed methylation of benzamides with di-*tert*-butyl peroxide.[a,b]



[a] Reaction conditions: amide **1** (0.15 mmol), DTBP (0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.03 mmol), CH_3CN (1.0 mL), 140 °C under N_2 for 12 h. [b] Isolated yield. [c] Reaction time 19 h.

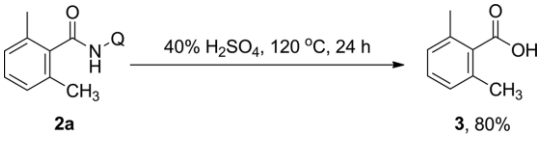
tion from the oxygen atom, which could help stabilize the nickelacycle intermediate once C–H activation takes place. The reaction of *para*-substituted benzamides delivered a mixture of mono- and di-methylation products when it was subjected to the optimized reaction conditions (not shown in Table 2), but after prolonging the reaction time to 19 hours, the reaction delivered the di-methylation product exclusively (Table 2, **2j**–**2k**). The substrate bearing 2,4-dimethyl group also produced the **2k** in 85 % yield. We were also glad to see that both 2-naphthoic acid and 1-naphthoic acid derived amide could participate in the reaction as well, producing the desired products **2n** and **2o** in 74 % and 81 % yields, respectively (Table 2, **2n** and **2o**). It should be noted that a thiophene derived amide was also found to be a viable coupling partner, giving **2p** in 42 % yield (Table 2, **2p**). The parent substrate, i.e., *N*-(quinolin-8-yl)benzamide, also produced the **2a** in 80 % yield. We were disappointed to find that methacrylic acid derived amide failed to react when it was subjected to the optimized conditions (not shown in Table 2).

To demonstrate the practical applicability of the method, a larger-scale reaction was performed to give 193 mg of **2a** in 70 % yield starting from **1q** (see Scheme 2 and the Supporting Information).



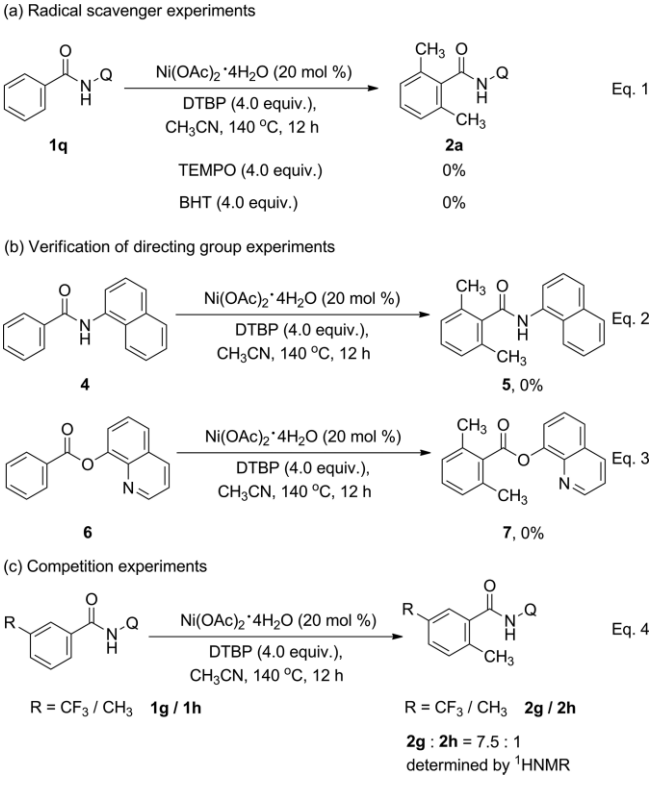
Scheme 2. Larger-scale synthesis of **2a** from **1q**.

In order to highlight the synthetic utility of this protocol, the removal of the 8-aminoquinoline auxiliary was performed. 2,6-dimethylbenzoic acid **3** could be obtained in 80 % yield through acid hydrolysis of **2a** (see Scheme 3 and the Supporting Information).



Scheme 3. Removal of the directing group.

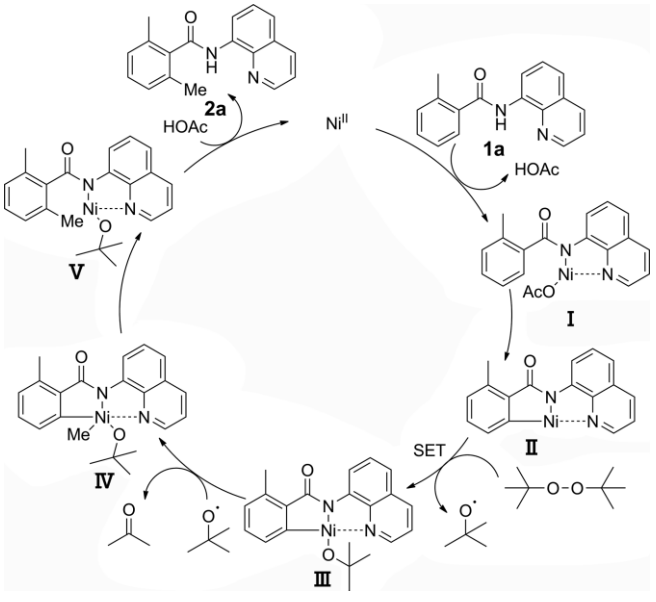
To gain some information on the reaction mechanism, several preliminary mechanistic experiments were performed under the optimized conditions. When 4.0 equiv. of a radical scavenger such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the standard reaction, the desired product was not detected (Scheme 4, Eq. 1). This result suggested that the reaction may involve a



Scheme 4. Preliminary mechanistic studies.

radical pathway. When *N*-(naphthalen-1-yl)benzamide **4** or quinolin-8-yl benzoate **6** was treated under standard conditions, no desired product was obtained, suggesting that 8-aminoquinoline played a key role in the C–H activation (Scheme 4, Eq. 2 and Eq. 3). Moreover, we also carried out an intermolecular competition reaction to investigate the electronic effect of the benzamide. When the reaction was explored using a mixture of equal moles of **1g** and **1h** under the standard conditions (Scheme 4, Eq. 4), ^{1}H NMR analysis of the product mixture (**2g** and **2h**) demonstrated that the ratio of **2g**: **2h** was 7.5: 1, which indicates that an electron-withdrawing group is favored for the reaction.

On the basis of the above investigations and previous reports,[14,15,17c,17d] a plausible mechanism is proposed in Scheme 5. Initially, the amide-coordinated Ni(II) intermediate **I** is generated by the reaction of amide **1a** with $Ni(OAc)_2{\cdot}4H_2O$. Subsequently the intermediate **I** undergoes cleavage of the *ortho* C–H bonds and forms the intermediate **II**. Next the **II** undergoes a single electron transfer (SET) with DTBP, which gives the Ni(III) species **III** and *tert*-butoxyl radical, The *tert*-butoxyl radical undergoes C–C bond scission to give a molecule of acetone and a methyl radical, which immediately adds to the Ni(III) species **III** to give the Ni(IV) intermediate **IV**. After reductive elimination and protonation, the product **2a** and Ni(II) are released, thus completing the catalytic cycle.



Scheme 5. Plausible mechanism.

Conclusions

In summary, we have developed a novel and efficient process for the *ortho*-methylation of benzamides with DTBP via Ni(II)-catalyzed C–H activation assisted by 8-aminoquinoline. Our method features simple reaction conditions, broad substrate scope, and use of cheap and commercially available reagents. Another notable feature is that the reaction is performed under base-free, and ligand-free conditions. In addition, compared with other known methods, the acetone by-product generated from DTBP can be easily removed since it is a low boiling compound. Therefore, it has no negative effect on the separation of the desired products. Further investigations on the reaction mechanism as well as synthetic application of this method are currently underway, and the results will be reported in due course.

Experimental Section

General Procedure for Introduction of Methyl Group: Benzamide **1** (0.15 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (8 mg, 0.03 mmol), DTBP(88 mg, 0.60 mmol), and anhydrous CH_3CN (1 mL) were added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed under N_2 and stirred at 140 °C for 12–19 h. After the completion of the reaction, It was then cooled to room temperature. The solvent was evaporated under reduced pressure, and the product was isolated by silica gel column purification with petroleum ether/ethyl acetate eluent to give the desired products product **2**.

Keywords: Ni-catalysis · Di-*tert*-butyl peroxide · Methylation · Base-free conditions · Ligand-free conditions

[1] a) H. Schönherr, T. Cernak, *Angew. Chem. Int. Ed.* **2013**, *52*, 12256–12267; *Angew. Chem.* **2013**, *125*, 12480; b) C. S. Leung, S. S. F. Leung, J. Tirado-Rives, W. L. Jorgensen, *J. Med. Chem.* **2012**, *55*, 4489–4500; c) S. Sun, J. Fu, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3283–3289; d) E. J. Barreiro, A. E. Kümmerle, C. A. M. Fraga, *Chem. Rev.* **2011**, *111*, 5215–5246.

[2] a) R. P. Walt, M. D. F. A. Gomes, E. C. Wood, L. H. Logan, R. E. Pounder, *Br. Med. J.* **1983**, *287*, 12–14; b) B. Wallmark, A. Brändström, H. Larsson, *Biochim. Biophys. Acta* **1984**, *778*, 549–558; c) H. Larsson, E. Carlsson, U. Junggren, L. Olbe, S. E. Sjöstrand, I. Skänberg, G. Sundell, *Gastroenterology* **1983**, *85*, 900–907.

[3] W. F. Hoffman, A. W. Alberts, P. S. Anderson, J. S. Chen, R. L. Smith, A. K. Willard, *J. Med. Chem.* **1986**, *29*, 849–852.

[4] a) M. Mahyari, M. S. Laeini, A. Shaabani, *Chem. Commun.* **2014**, *50*, 7855–7857; b) P. K. Chaurasia, S. L. Bharati, S. K. Singh, S. Yadava, *Russ. J. Gen. Chem.* **2015**, *85*, 173–175; c) N. Hirai, N. Sawatari, N. Nakamura, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2003**, *68*, 6587–6590; d) T. Nakai, T. Iwai, M. Mihara, T. Ito, T. Mizuno, *Tetrahedron Lett.* **2010**, *51*, 2225–2227; e) J. Park, Y.-M. Lee, W. Nam, S. Fukuzumi, *J. Am. Chem. Soc.* **2013**, *135*, 5052–5061; f) K. Shimada, T. Nanae, S. Aoyagi, Y. Takikawa, C. Kabuto, *Tetrahedron Lett.* **2001**, *42*, 6167–6169.

[5] C. Yamamoto, K. Takamatsu, K. Hirano, M. Miura, *J. Org. Chem.* **2016**, *81*, 7675–7684.

[6] a) K. Chen, F. Hu, S.-Q. Zhang, B.-F. Shi, *Chem. Sci.* **2013**, *4*, 3906–3911; b) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124–2127; c) C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647–650; d) R.-Y. Zhu, J. He, X.-C. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 13194–13197.

[7] A. Basak, M. K. Nayaka, A. K. Chakraborti, *Tetrahedron Lett.* **1998**, *39*, 4883–4886.

[8] T. Uemura, M. Yamaguchi, N. Chatani, *Angew. Chem. Int. Ed.* **2016**, *55*, 3162–3165; *Angew. Chem.* **2016**, *128*, 3214.

[9] a) L.-B. Zhang, X.-Q. Hao, Z.-J. Liu, X.-X. Zheng, S.-K. Zhang, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 10012–10015; *Angew. Chem.* **2015**, *127*, 10150; b) Z. Xie, S. Luo, Q. Zhu, *Chem. Commun.* **2016**, *52*, 12873–12876; c) D. Liang, Y. He, Q. Zhu, *Org. Lett.* **2014**, *16*, 2748–2751; d) M. Sattar, S. Kumar, *Org. Lett.* **2017**, *19*, 5960–5963; e) M. Sattar, Praveen, C. D. Prasad, A. Verma, S. Kumar, S. Kumar, *Adv. Synth. Catal.* **2016**, *358*, 240–253; f) Q. Li, W. Hu, R. Hu, H. Lu, G. Li, *Org. Lett.* **2017**, *19*, 4676–4679; g) X. Dong, Q. Li, G. Li, H. Lu, *J. Org. Chem.* **2018**, *83*, 13402–13413.

[10] a) Q. Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232–3234; b) K. Graczyk, T. Haven, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 8812–

8815; c) L. Ilies, S. Ichikawa, S. Asako, T. Matsubara, E. Nakamura, *Adv. Synth. Catal.* **2015**, *357*, 2175–2179; d) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 1109–1113; *Angew. Chem.* **2011**, *123*, 1141; e) Q. Sun, N. Yoshikai, *Org. Chem. Front.* **2018**, *5*, 2214–2218.

[11] R. Shang, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7660–7663.

[12] a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511; b) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302–2305; c) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 7317–7320; *Angew. Chem.* **2013**, *125*, 7458.

[13] B. Yao, R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, M.-K. Wang, R.-Y. Tang, X.-G. Zhang, C.-L. Deng, *Adv. Synth. Catal.* **2012**, *354*, 1890–1896.

[14] a) Q. Li, Y. Li, W. Hu, R. Hu, G. Li, H. Lu, *Chem. Eur. J.* **2016**, *22*, 12286–12289; b) T. Kubo, N. Chatani, *Org. Lett.* **2016**, *18*, 1698–1701; c) Z. Xu, C. Yan, Z.-Q. Liu, *Org. Lett.* **2014**, *16*, 5670–5673; d) Q. Xia, X. Liu, Y. Zhang, C. Chen, W. Chen, *Org. Lett.* **2013**, *15*, 3326–3329.

[15] D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem. Int. Ed.* **2014**, *53*, 4802–4806; *Angew. Chem.* **2014**, *126*, 4902.

[16] a) L. Yu, H. Huang, X. Chen, L. Hu, Y. Yu, Z. Tan, *Chem. Commun.* **2017**, *53*, 4597–4600; b) L. Hu, X. Chen, L. Yu, Y. Yu, Z. Tan, G. Zhu, Q. Gui, *Org. Chem. Front.* **2018**, *5*, 216–221; c) L. Yu, X. Chen, D. Liu, L. Hu, Y. Yu, H. Huang, Z. Tan, Q. Gui, *Adv. Synth. Catal.* **2018**, *360*, 1346–1351; d) L. Yu, X. Chen, Z.-N. Song, D. Liu, L. Hu, Y. Yu, Z. Tan, Q. Gui, *Org. Lett.* **2018**, *20*, 3206–3210; e) Y. Yu, Q. Wu, D. Liu, L. Hu, L. Yu, Z. Tan, G. Zhu, *J. Org. Chem.* **2019**, *84*, 7449–7458; f) L. Yu, C. Yang, Y. Yu, D. Liu, L. Hu, Y. Xiao, Z.-N. Song, Z. Tan, *Org. Lett.* **2019**, *21*, 5634–5638.

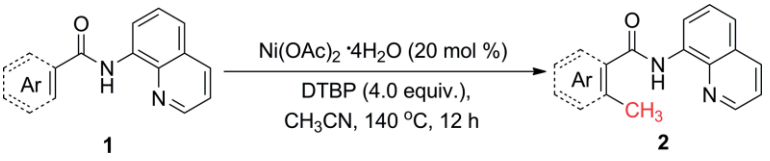
[17] a) Y.-J. Liu, Y.-H. Liu, S.-Y. Yan, B.-F. Shi, *Chem. Commun.* **2015**, *51*, 6388–6391; b) Q. Zhang, B.-F. Shi, *Chin. J. Chem.* **2019**, *37*, 647–656; c) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792; d) K. Yang, Y. Wang, X. Chen, A. A. Kadi, H.-K. Fun, H. Sun, Y. Zhang, H. Lu, *Chem. Commun.* **2015**, *51*, 3582–3585.

[18] a) R. Zhang, S. Jin, Q. Liu, S. Lin, Z. Yan, *J. Org. Chem.* **2018**, *83*, 13030–13035; b) K. R. McGovern-Gooch, N. S. Mahajani, A. Garagozzo, A. J. Schramm, L. G. Hannah, M. A. Sieburg, J. D. Chisholm, J. L. Hougland, *Biochemistry* **2017**, *56*, 919–931.

[19] a) M. Ohtawa, S. Ichikawa, Y. Teishikata, M. Fujimuro, H. Yokosawa, A. Matsuda, *J. Med. Chem.* **2007**, *50*, 2007–2010; b) T. Honda, H. Yoshizawa, C. Sundararajan, E. David, M. J. Lajoie, F. G. Favaloro, T. Janosik, X. Su, Y. Honda, B. D. Roebuck, G. W. Gribble, *J. Med. Chem.* **2011**, *54*, 1762–1778.

Received: August 18, 2019

C–H Activation



1 2

A novel and efficient process for the *orth*-methylation of benzamides with DTBP via Ni(II)-catalyzed C–H activation assisted by 8-aminoquinoline was developed.

DOI: 10.1002/ejoc.201901211