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Ni(II)-catalyzed mono-selective *ortho*-arylation of unactivated aryl C–H bonds utilizing amino acids as a directing group†

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The nickel(II)-catalyzed *ortho*-arylation of unactivated C–H bonds utilizing amino acids as directing groups with aryl iodides or bromides as coupling electrophiles is described. This protocol features excellent mono-selectivity, good regioselectivity, and wide functional group tolerance. Additionally, the obtained products bearing a biaryl motif and an amino acid represent bioactive molecules with wide bioactivities.

Introduction

Biaryls are privileged π-conjugated structural units, and are widely found in pharmaceuticals, agrochemicals, and materials science (Fig. 1).[1] Despite the significant progress made in achieving biaryl scaffolds *via* transition metal-catalyzed cross-coupling between aryl halides and organometallic reagents,[2] these reliable methods suffer from harsh conditions, pre-functionalization of substrates, and the extra generation of metal halides. Therefore, there remains the need to develop efficient and environmental-friendly synthetic methods to furnish biaryl derivatives.

Over the past few decades, transition metal-catalyzed direct C(sp^2)–H arylation has been extensively studied as an attractive and complementary access to construct biaryl derivatives.[3] In this context, chelation-assisted strategy has been demonstrated as one of the most powerful methods for regioselective transforming C–H bonds.[4] A wide variety of monodentate or bidentate directing groups have been evaluated to achieve transition metal-mediated regioselective C–H activation, thus, compatible with broad substrates. However, these methodologies mostly rely on the use of expensive and toxic second- or third-row transition metals, such as palladium, ruthenium, and rhodium (Scheme 1a). Recent attention has been shifted on earth-abundant 3d transition metals.[5] Among them, nickel is emerging as a robust and versatile catalyst for C–H activation, owing to its unique activity and low-cost.[6] Pioneered by Chatani's work,[7] the combination of nickel catalysis and *N*-heterocyclic bidentate directing groups, specifically referring to 8-aminoquinoline (AQ)[8] and (pyridin-2-yl)isopropyl (PIP),[9] has shown superior activity for the construction of aromatic C–C bonds. But in most cases, the selectivity for monoarylation *versus* diarylation was not ideal with the aid of AQ or PIP (Scheme 1b).[8h,i,9b,c] Very recently, environmental-friendly and inexpensive amino acids have been employed as novel bidentate directing groups, which have been well demonstrated in palladium-catalyzed C–H functionalization and showed extraordinary reactivity.[10] In continuation of our recent effort on direct C–H functionalization,[11] we proposed the construction of biaryl derivatives *via* Ni(II)-catalyzed amino acid directed C–H cleavage in a mono-selective manner. It is worth notice that amino acids act as not only directing groups, but also a crucial part of the final products with wide potential bioactivities.[12] Herein, we reported the nickel-catalyzed highly mono-selective *ortho*-arylation of unactivated aryl C–H bonds utilizing amino acid as a directing group (Scheme 1c).

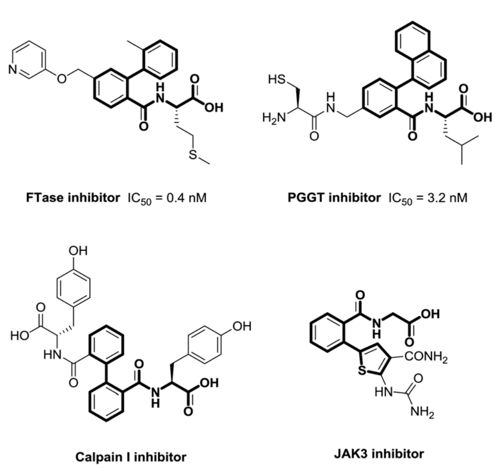

Fig. 1 Representative bioactive molecules.

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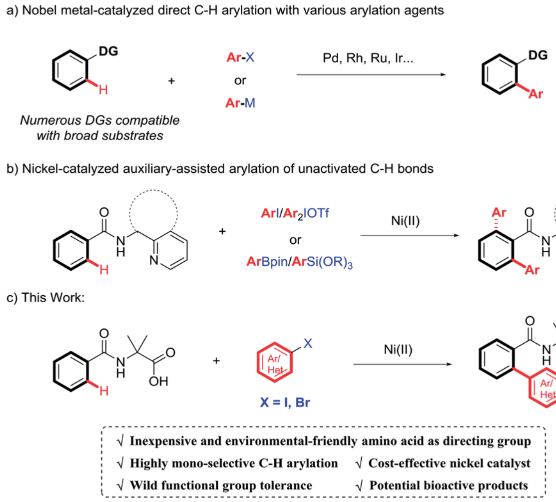


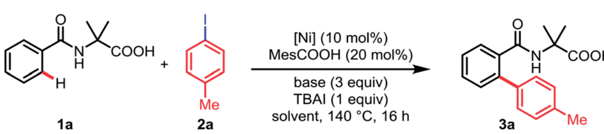
Scheme 1 Transition metal-catalyzed arylation of unactivated C–H Bonds.

Results and discussion

We initiated our studies by investigating the reaction parameters of the coupling between *N*-benzoyl α-amino acid **1a** with 1-iodo-4-methylbenzene **2a** using commercially available nickel(II) salts (Table 1). All of the nickel complexes showed catalytic activity and $Ni(OTf)_2$ was proved to be the most effective catalyst, affording the desired mono-arylation product **3a** in 82% yield (entries 1–4). The efficiency of the reaction was significantly affected by different solvents with DMSO being identified as optimal and no desired product was obtained in nonpolar solvent (entries 5–8). Further optimization of bases revealed that Na_2CO_3 was crucial for the conversion (entries 9–11). Additionally, the yield was decreased without MesCOOH (entry 12). The absence of TBAI also led to a slight decrease of yield (entry 13). By contrast, the reaction gave no conversion when nickel(II) catalyst was omitted (entry 14).

With the optimized reaction conditions in hand, we investigated the substrate scope of *N*-benzoyl α-amino acid derivatives. Generally, various substituents on the aromatic ring were tolerated in this reaction and generated the corresponding products in moderate to high yields without diarylation products being detected (Table 2). The aromatic ring bearing a substituent at

Table 1 Optimization of reaction conditions[a]

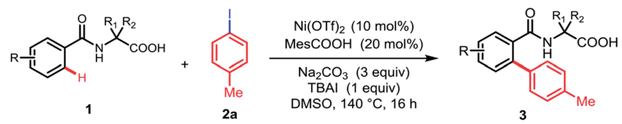


1a 2a 3a

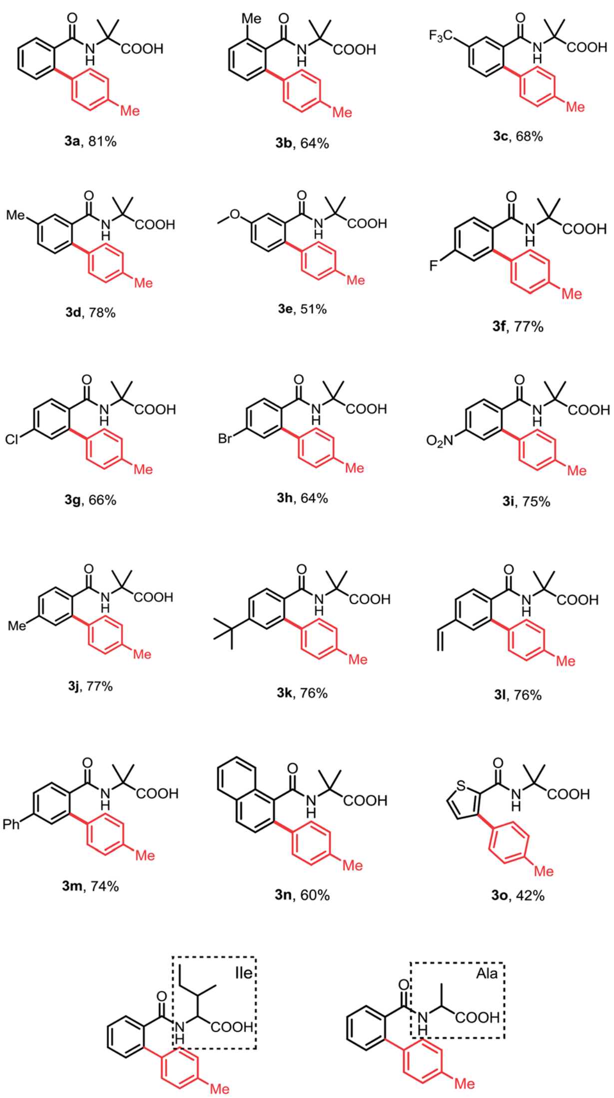
Entry	[Ni]	Base	Solvent	Yield[b] (%)
1	$Ni(acac)_2$	Na_2CO_3	DMF	13
2	$NiCl_2$	Na_2CO_3	DMF	21
3	NiI_2	Na_2CO_3	DMF	12
4	$Ni(OTf)_2$	Na_2CO_3	DMF	82
5	$Ni(OTf)_2$	Na_2CO_3	NMP	25
6	$Ni(OTf)_2$	Na_2CO_3	DMSO	88 (81)
7	$Ni(OTf)_2$	Na_2CO_3	Toluene	N.R.
8	$Ni(OTf)_2$	Na_2CO_3	Dioxane	Trace
9	$Ni(OTf)_2$	KOAc	DMSO	N.R.
10	$Ni(OTf)_2$	K_3PO_4	DMSO	Trace
11	$Ni(OTf)_2$	$NaHCO_3$	DMSO	Trace
12[c]	$Ni(OTf)_2$	Na_2CO_3	DMSO	73
13[d]	$Ni(OTf)_2$	Na_2CO_3	DMSO	62
14	—	Na_2CO_3	DMSO	N.R.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (10 mol%), MesCOOH (20 mol%), base (0.6 mmol), TBAI (0.2 mmol), solvent (2 mL), 140 °C, air, 16 h. [b] NMR yield. Values in parentheses are the isolated yields of **3a**. [c] In absence of MesCOOH. [d] In absence of TBAI.

Table 2 Scope of *N*-benzoyl α-amino acid derivatives[a]



1 2a 3



3a, 81% **3b**, 64% **3c**, 68%

3d, 78% **3e**, 51% **3f**, 77%

3g, 66% **3h**, 64% **3i**, 75%

3j, 77% **3k**, 76% **3l**, 76%

3m, 74% **3n**, 60% **3o**, 42%

3p, 30% 3q, 20%

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Ni(OTf)_2$ (10 mol%), MesCOOH (20 mol%), Na_2CO_3 (0.6 mmol), and TBAI (0.2 mmol) in DMSO (2 mL) at 140 °C for 16 h. All listed yields are isolated ones.

ortho-position, such as methyl, could afford the desired products in moderate yield, probably due to the steric hindrance (**3b**). When *meta*-substituted substrates were employed, the C–H bond arylation took place at the less sterically hindered position in good yields (**3c–3e**). To our delight, the substrates bearing either electron-donating or -withdrawing groups at *para*-position furnished the mono-arylation products selectively in satisfactory yields, irrespective of the electronic nature of the substituents (**3f–3m**). Halogens were also well tolerated under standard conditions, revealing the protocol may have more potential applications (**3f–3h**). Furthermore, the naphthyl and thienyl substrates afforded the desired products in moderate yields (**3n** and **3o**). The other natural amino acid directing groups have showed less activity in this reaction, probably due to the absence of the Thorpe–Ingold effect (**3p** and **3q**).

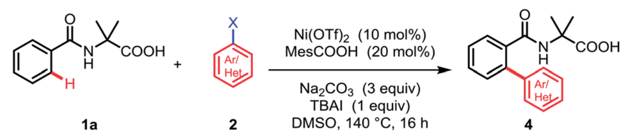
Subsequently, a wide range of aryl halides were examined under standard conditions. As illustrated in Table 3, various aryl iodides could be tolerated in this reaction and gave mono-arylation products in moderate to high yields. The aryl iodides bearing either electron-donating or -withdrawing groups at *para*- and *meta*-position proceeded smoothly to afford the corresponding arylation products in good to high yields (**4a–4i**). Additionally, multisubstituted aryl iodides and heterocyclic iodide provided the desired products in good yields (**4j–4k**). The introduction of a substituent at *ortho*-position of aryl iodides afforded no desired products, probably because of interference with the oxidative addition process (**4m** and **4n**). To broaden the usability and enhance the practicality of this method, we tried to apply this reaction with less reactive aryl bromides. Fortunately, 4-bromobenzonitrile was found feasible in the reaction (**4o**). Furthermore, the thiophene bromides showed great compatibility in this reaction and various functional groups were well tolerated under standard conditions, such as halides and carbonyl, guaranteeing further transformation (**4p–4t**).

Importantly, the *ortho*-arylation could be carried out on a gram scale to afford **3a** in 80% yield. Moreover, the amino acid group could be easily removed and afforded the corresponding ester **5** in nearly quantitative yield (Scheme 2).

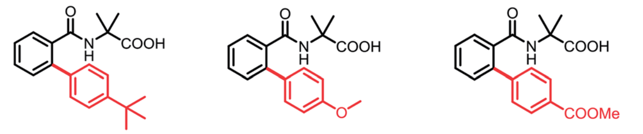
To understand the reaction mechanism, a series of mechanistic experiments were carried out. The H/D exchange experiment demonstrated that the cleavage of the C–H bond was an irreversible process (Scheme 3A). Furthermore, the radical scavenger experiments were performed by the addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). The reaction efficiency was not affected, indicating that a single-electron transfer (SET) process was probably not involved (Scheme 3B). By employing **1a**-d_5 as the substrate, the kinetic isotope effect (KIE) was observed to be 1.2, suggesting that the C–H bond cleavage was not the rate-limiting step.[13]

Based on the preliminary results and reported literatures,[8b,8d,8f,8g] a plausible mechanism was proposed. First, the coordination of **1a** to the nickel catalyst generated a nickel intermediate **A**, followed by a concerted metalation–deprotonation (CMD) process[14] to produce the nickel complexes **B** irreversibly. Then the oxidative addition of PhI to intermediate **B** led to a high-valent Ni intermediate **C**, which underwent reductive elimination to release the catalyst and give the final product **3a** (Scheme 4).

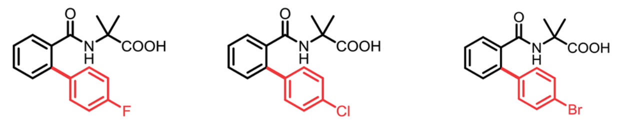
Table 3 Scope of aryl halides[a]



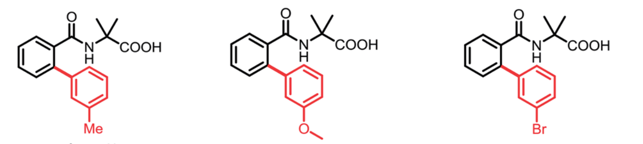
X = I



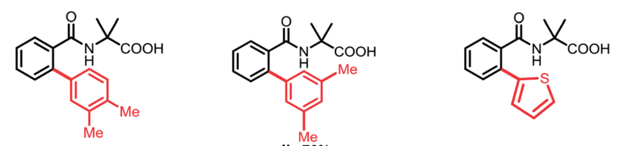
4a, 80% **4b**, 66% **4c**, 76%



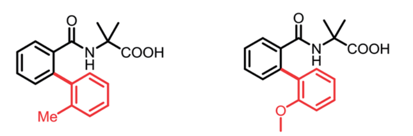
4d, 74% **4e**, 66% **4f**, 69%



4g, 75% **4h**, 68% **4i**, 64%

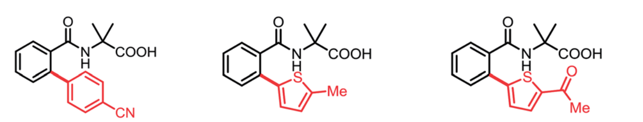


4j, 80% **4k**, 76% **4l**, 79%

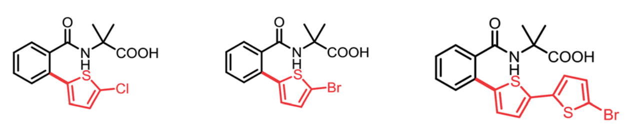


4m, trace **4n**, trace

X = Br

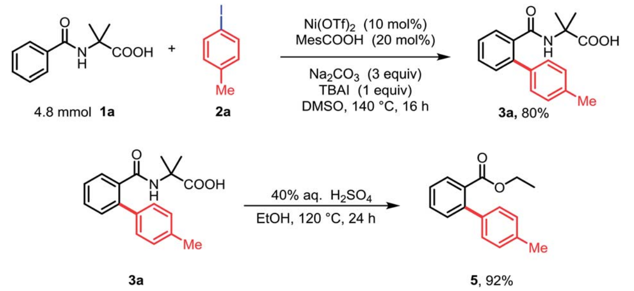


4o, 34% **4p**, 67% **4q**, 73%

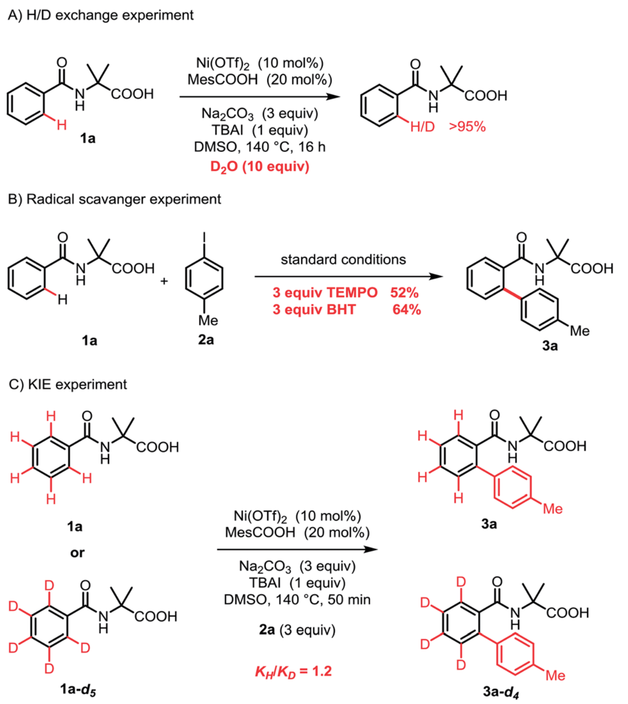


4r, 62% **4s**, 72% **4t**, 72%

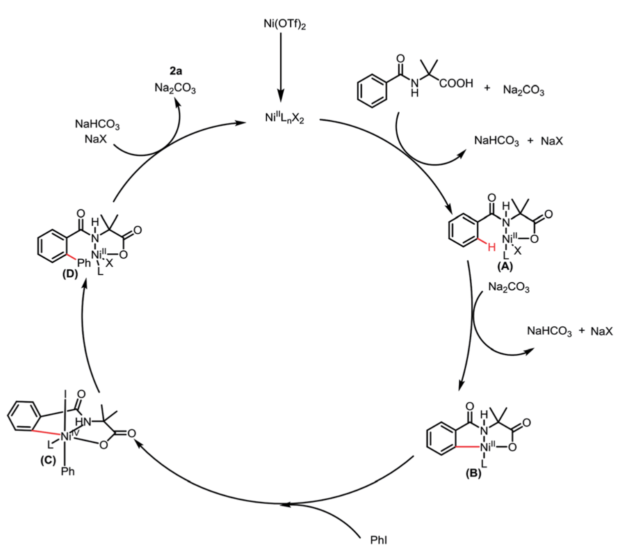
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Ni(OTf)$_2$ (10 mol%), MesCOOH (20 mol%), Na_2CO_3 (0.6 mmol), and TBAI (0.2 mmol) in DMSO (2 mL) at 140 °C for 16 h. All listed yields are isolated ones.



Scheme 2 Gram-scale synthesis and removal of the directing group.



Scheme 3 Mechanistic investigations.



Scheme 4 Plausible mechanism.

Conclusions

In conclusion, we developed a nickel(II)-catalyzed *ortho*-arylation of unactivated aryl C–H bonds utilizing inexpensive amino acid as a directing group. This protocol features excellent mono-selectivity, good regioselectivity, and wide functional tolerance. Moreover, the resulted productions bearing a biaryl motif and an amino acid represent bioactive molecules with wide bioactivities, especially the natural amino acid molecules, which will be of great importance to medicinal chemists.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) I. Cepanec, *Synthesis of Biaryls*, Elsevier, New York, 2004; (*b*) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384–5427; (*c*) Y. Deng, Y. W. Chin, H. Chai, W. J. Keller and A. D. Kinghorn, *J. Nat. Prod.*, 2007, **70**, 2049–2052; (*d*) Y. J. Wu, J. Guernon, J. Shi, L. Marcin, M. Higgins, R. Rajamani, J. Muckelbauer, H. Lewis, C. Chang, D. Camac, J. H. Toyn, M. K. Ahlijanian, C. F. Albright, J. E. Macor and L. A. Thompson, *J. Med. Chem.*, 2016, **59**, 8593–8600.

2 (*a*) P. Leowanawat, N. Zhang, A. M. Resmerita, B. M. Rosen and V. Percec, *J. Org. Chem.*, 2011, **76**, 9946–9955; (*b*) X. C. Cambeiro, N. Ahlsten and I. Larrosa, *J. Am. Chem. Soc.*, 2015, **137**, 15636–15639; (*c*) I. Hussain, J. Capricho and M. A. Yawer, *Adv. Synth. Catal.*, 2016, **358**, 3320–3349; (*d*) F. Lv and Z.-J. Yao, *Sci. China: Chem.*, 2017, **60**, 701–720; (*e*) S. Mao, Z. Chen, L. Wang, D. B. Khadka, M. Xin, P. Li and S. Q. Zhang, *J. Org. Chem.*, 2019, **84**, 463–471.

3 (*a*) M. E. D. A. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*b*) I. V. Sereginn and V. Gevorgya, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (*c*) B.-J. Li, S.-D. Yang and Z.-J. Shi, *Synlett*, 2008, 949–957; (*d*) J.-W. Park and C.-H. Jun, *ChemCatChem*, 2009, **1**, 69–71; (*e*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (*f*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295; (*g*) P. Y. Choy, S. M. Wong, A. Kapdi and F. Y. Kwong, *Org. Chem. Front.*, 2018, **5**, 288–321; (*h*) R. Das and M. Kapur, *Asian J. Org. Chem.*, 2018, **7**, 1217–1235.

4 (*a*) G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450–2494; (*b*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (*c*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743;

(*d*) F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906–6919.

5 (*a*) A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087–4109; (*b*) S. Bezzenine-Lafollee, R. Gil, D. Prim and J. Hannedouche, *Molecules*, 2017, **22**, 1901/1–1901/29; (*c*) J. Chen and Z. Lu, *Org. Chem. Front.*, 2018, **5**, 260–272; (*d*) F. Kallmeier and R. Kempe, *Angew. Chem., Int. Ed.*, 2018, **57**, 46–60.

6 (*a*) Y. Tamaru, *Modern Organonickel Chemistry*, Wiley-VCH, 2005; (*b*) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299–309; (*c*) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898–901; (*d*) J.-P. Wan, Y. Li and Y. Liu, *Org. Chem. Front.*, 2016, **3**, 768–772.

7 (*a*) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952–14955; (*b*) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2013, **135**, 5308–5311.

8 (*a*) M. Corbet and F. De Campo, *Angew. Chem., Int. Ed.*, 2013, **52**, 9896–9898; (*b*) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 15509–15512; (*c*) M. Iyanaga, Y. Aihara and N. Chatani, *J. Org. Chem.*, 2014, **79**, 11933–11939; (*d*) L. C. M. Castro and N. Chatani, *Chem. Lett.*, 2015, **44**, 410–421; (*e*) N. Lv, Z. Chen, Y. Liu, Z. Liu and Y. Zhang, *Org. Lett.*, 2018, **20**, 5845–5848; (*f*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155; (*g*) A. P. Honeycutt and J. M. Hoover, *ACS Catal.*, 2017, **7**, 4597–4601; (*h*) Y. Cheng, Y. Wu, G. Tan and J. You, *Angew. Chem., Int. Ed.*, 2016, **55**, 12275–12279; (*i*) A. Yokota, Y. Aihara and N. Chatani, *J. Org. Chem.*, 2014, **79**, 11922–11932.

9 (*a*) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187–4192; (*b*) Y. J. Liu, Y. H. Liu, S. Y. Yan and B. F. Shi, *Chem. Commun.*, 2015, **51**, 6388–6391; (*c*) S. Y. Yan, Y. J. Liu, B. Liu, Y. H. Liu and B. F. Shi, *Chem. Commun.*, 2015, **51**, 4069–4072.

10 (*a*) X. M. Zhou, Q. Wang, W. H. Zhao, S. S. Xu, W. Zhang and J. M. Chen, *Tetrahedron Lett.*, 2015, **56**, 851–855; (*b*) G. Chen, T. Shigenari, P. Jain, Z. Zhang, Z. Jin, J. He, S. Li, C. Mapelli, M. M. Millers, M. A. Pos, P. M. Scola, K. S. Yeung and J. Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 3338–3351; (*c*) L. Wei, Y. W. Dong, L. Z. Yong, Y. Fei and M. C. Jun, *Adv. Synth. Catal.*, 2016, **358**, 1968–1974; (*d*) L. C. M. Castro and N. Chatani, *Chem.–Eur. J.*, 2014, **20**, 4548–4553; (*e*) J. Kim, M. Sim, N. Kim and S. Hong, *Chem. Sci.*, 2015, **6**, 3611–3616; (*f*) T. Toba, Y. Hu, A. T. Tran and J. Q. Yu, *Org. Lett.*, 2015, **17**, 5966–5969; (*g*) C. Wang, C.-P. Chen, J.-Y. Zhang, J. Han, Q. Wang, K. Guo, P. Liu, M.-Y. Guan, Y.-M. Yao and Y.-S. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 9884; (*h*) M. Guan, Y. Pang, J. Zhang and Y. Zhao, *Chem. Commun.*, 2016, **52**, 7043; (*i*) J. Han, P. Liu, C. Wang, Q. Wang, J. Zhang, Y. Zhao, D. Shi, Z. Huang and Y. Zhao, *Org. Lett.*, 2014, **16**, 5682.

11 (*a*) W. Zhu, D. Zhang, N. Yang and H. Liu, *Chem. Commun.*, 2014, **50**, 10634–10636; (*b*) F. Gao, W. Zhu, D. Zhang, S. Li, J. Wan and H. Liu, *J. Org. Chem.*, 2016, **81**, 9122–9130; (*c*) S. Li, W. Zhu, F. Gao, C. Li, J. Wang and H. Liu, *J. Org. Chem.*, 2017, **82**, 126–134; (*d*) X. W. Wu, B. Wang, S. B. Zhou, Y. Zhou and H. Liu, *ACS Catal.*, 2017, **7**, 2494–2499.

12 (*a*) J. D. Ochocki and M. D. Distefano, *MedChemComm*, 2013, **4**, 476–492; (*b*) A. Montero, M. Alonso, E. Benito, A. Chana, E. Mann, J. M. Navas and B. Herradon, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2753–2757.

13 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072.

14 (*a*) G. Ercolano, F. Farina, S. Cavaliere, D. Jones and J. Roziere, *Nanomaterials*, 2016, **6**, 236/1–236/12; (*b*) S. J. Freakley, J. Ruiz-Esquius and D. J. Morgan, *Surf. Interface Anal.*, 2017, **49**, 794–799.

