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

Zhanqing Cong,‡abc Feng Gao‡ab and Hong Liu ** **abc

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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 monoselectivity, 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 crosscoupling between aryl halides and organometallic reagents,² these reliable methods suffer from harsh conditions, prefunctionalization 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(sp²)-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

Calpain I inhibitor

Fig. 1 Representative bioactive molecules.

Chatani's work,7 the combination of nickel catalysis and Nheterocyclic 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).

[&]quot;State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai, 201203, China. E-mail: hliu@simm.ac.cn

^bUniversity of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, China

^{&#}x27;School of Life Science and Technology, ShanghaiTech University, 100 Haike Road, Shanghai 201210, China

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[‡] These authors contributed equally.

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a) Nobel metal-catalyzed direct C-H arylation with various arylation agents

PG
Ar-X
Pd, Rh, Ru, Ir...

Numerous DGs compatible with broad substrates

b) Nickel-catalyzed auxiliary-assisted arylation of unactivated C-H bonds

Ar/Mar₂(OTf
or
ArBpin/ArSi(OR)₃

Ni(II)

X = I, Br

Scheme 1 Transition metal-catalyzed arylation of unactivated C-H Ronds

√ Cost-effective nickel catalys

√ Potential bioactive products

Results and discussion

√ Highly mono-selective C-H arylation

Wild functional group tolerance

We initiated our studies by investigating the reaction parameters of the coupling between N-benzoyl α -amino acid $\mathbf{1a}$ with 1-iodo-4-methylbenzene $\mathbf{2a}$ using commercially available nickel(π) 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 $\mathbf{3a}$ 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 Na₂CO₃ was crucial for the

Table 1 Optimization of reaction conditions^a

Entry	[Ni]	Base	Solvent	$Yield^{b}$ (%)
1	Ni(acac) ₂	Na ₂ CO ₃	DMF	13
2	NiCl ₂	Na_2CO_3	DMF	21
3	NiI_2	Na_2CO_3	DMF	12
4	Ni(OTf) ₂	Na ₂ CO 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 $^{\circ}$ 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.

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 2 Scope of N-benzoyl α -amino acid derivatives^a

^a Reaction conditions: 1 (0.2 mmol), 2a (0.6 mmol), Ni(OTf)₂ (10 mol%), MesCOOH (20 mol%), Na₂CO₃ (0.6 mmol), and TBAI (0.2 mmol) in DMSO (2 mL) at 140 $^{\circ}$ C for 16 h. All listed yields are isolated ones.

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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 30). 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 monoarylation 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 (40). 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 singleelectron 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) process14 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

4t. 72%

^a Reaction conditions: 1a (0.2 mmol), 2 (0.6 mmol), Ni(OTf)₂ (10 mol%), MesCOOH (20 mol%), Na₂CO₃ (0.6 mmol), and TBAI (0.2 mmol) in DMSO (2 mL) at 140 °C for 16 h. All listed yields are isolated ones.

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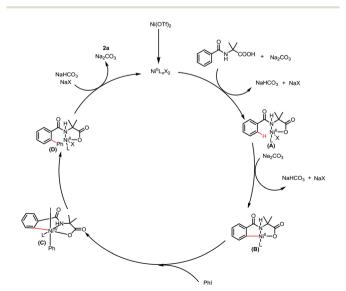
Scheme 2 Gram-scale synthesis and removal of the directing group.

| Ni(OTf)₂ (10 mol%) | Na₂CO₃ (3 equiv) | Na₂CO₃ (10 equiv) | Na₂CO₃ (

3a-d₄

Scheme 3 Mechanistic investigations

A) H/D exchange experiment



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 monoselectivity, 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.

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