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DOI: 10.1039/C7CC07457C

Journal Name

COMMUNICATION

Ni-Catalyzed Cross-Coupling Reactions of *N*-Acylpyrrole-Type Amides with Organoboron Reagents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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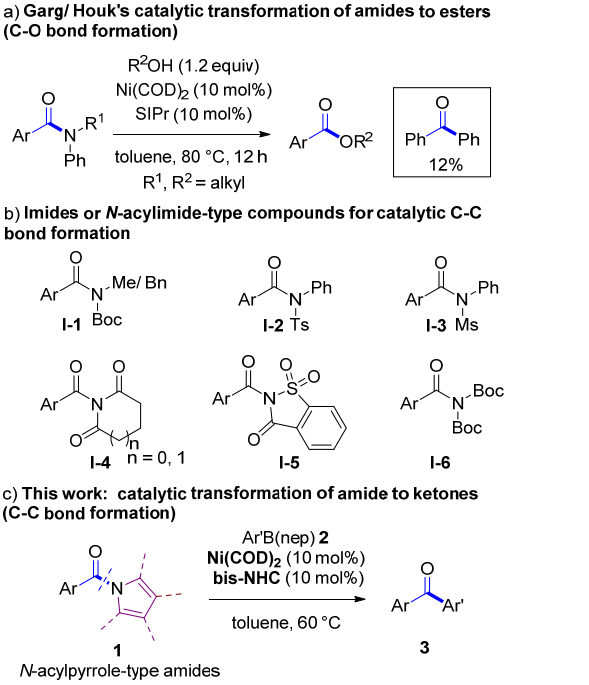
The catalytic conversion of amides to ketones is highly desirable yet challenging in organic synthesis. We report herein the first Ni/bis-NHC-catalyzed cross-coupling of *N*-acylpyrrole-type amides with arylboronic esters to deliver diarylketones. This method is enabled by a new chelating bis-NHC ligand. The reaction tolerates diverse functional groups on both arylamides and arylboronic esters partners including sensitive ester and ketone groups.

Amide (*N*-mono acylamines) is a ubiquitous functional group in chemistry, biology, and material science.[1] Through the amide bond, different α-amino acids are linked to form proteins, the cornerstone of life. In organic synthesis, amides are easily available[2] and serve as versatile starting materials and intermediates.[3] Moreover, amidyl groups serve as protecting groups of amines and directing groups for C–H functionalization.[4] The above-mentioned chemical and biochemical functions of amides rely on their high stability. The latter is due to the strong resonance effects between the vicinal nitrogen lone pair and the vacant $\pi^*_{C=O}$ orbital. The carbon-nitrogen bond of amides thus possesses partial double bond character and displays high C–N bond dissociation energy. Thus common unactivated amides are poor electrophiles reluctant to nucleophilic addition. As a result, the chemoselective and catalytic transformation of amides with C-C bon formation is underdeveloped despite it being in high demanding.

Although many chemoselective methods for the direct transformation of amides with C–C bond formation have appeared in recent years,[5-7] catalytic functionalization of amides are rare. In this context, Dixon reported the first partially catalytic reductive nitro-Mannich cyclization.[7a] Subsequently, catalytic reductive functionalizations of amides, including fully catalytic ones, have been reported by groups of Chida and Sato,[7b,c] Huang,[7d] Adolfsson,[7e,g,h] and Dixon.[7f]



Scheme 1. Catalytic transformations of amides, imides, acylimides, and sulfonamide analogues via metal-catalyzed C–N activation

On the other hand, in 2015, Garg and Houk[8] pioneered the nickel-catalyzed activation of amide C–N bonds for the conversion of amides to esters (Scheme 1a). However, attempted extension of this methodology to convert amides to ketones using carbon nucleophiles afforded disappointing results (cf. Scheme 1a).[9] To tackle the problem of low reactivity of amides, indirect tactics were instead developed. Those methods convert the amides to imide- or to *N*-acylimide-type compounds **I-1** – **I-6** (Scheme 1b)[9,10] before executing the metal-catalyzed coupling reactions.

In view of the importance and challenging of the catalytic conversion of amides to ketones in organic synthesis, and in connection with our interest in the direct transformation of amides,[3d,6a,d,g-i,7d] we decided to investigate the catalytic transformation of *N*-acylpyrroles[11] (Scheme 1c). The latter are

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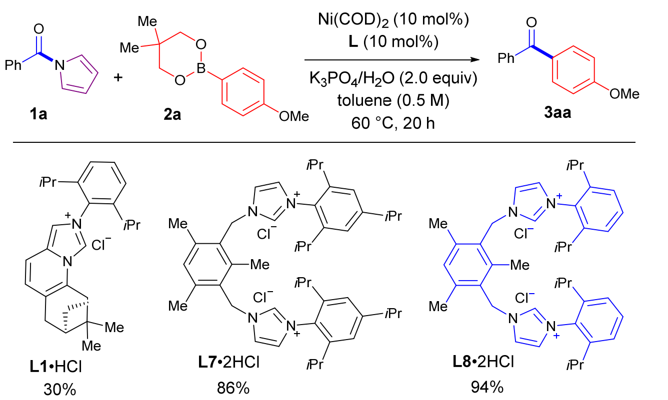
† Dedicated to Professor Li-He Zhang on the occasion of his 80th birthday.

‡ Electronic Supplementary Information (ESI) available: experimental procedures compounds characterization data, screened ligands, ^{1}H and ^{13}C NMR spectra of obtained compounds. See DOI: 10.1039/x0xx00000x

advantageous alternatives[11a] to the well-known Weinreb amides[12] because of the enhanced electrophilicity, ease availability, and increased synthetic potential.[11] Regarding the catalyst, while palladium-catalysis has gained tremendous attention in the past half-century for cross-coupling reactions including the Suzuki-coupling,[13] the use of earth abundant first-row transition metals such as nickel in catalysis has emerged as a new frontier.[14] We reasoned that a combination of the employment of more reactive *N*-acylpyrroles as the carbonyl donor with the use of novel Ni/bis-dentate NHC complex[14c,d,15b,c] as the catalyst would overcome the problem (Scheme 1c). An investigation along this line has been undertaken and the results are reported herein.[16]

We chose the coupling of *N*-benzoylpyrrole **1a** with 4-methoxyphenylboronic acid neopentylglycol ester [4-MeOPhB(nep)] **2a** as a prototype reaction for reaction optimization. At the outset of our investigation, phosphines (Table S1, entries 5–7) and bi-pyridine (Table S1, entry 8) were examined as ligands (For the structures of ligands **L2**–**L6** and **L9** see: Table S1 in ESI). The failure lead us to turn our attention to NHC[15b,c] ligands. Chiral NHC precursor **L1**·HCl (10 mol %), prepared previously in our laboratory,[17] was used in combination with $Ni(COD)_2$ (10 mol %) as the catalyst. To our delight, the reaction proceeded under mild conditions [K_3PO_4, H_2O (2.0 equiv), toluene, 60 °C, 20 h] to deliver diarylketone **3aa** in 30% yield (Table 1). After screening several NHC precursors (Table S1, entries 11–15), we focused on the chelating bis-NHC ligands **L7**–**L8** (Table 1). Pleasantly, the employment of the known ligand **L7**[18] furnished ketone **3aa** in 86% yield. In searching for an optimal NHC ligand, the hitherto unknown **L8**·2HCl was discovered and synthesized in gram-scale by a three-step procedure. The use of **L8**·2HCl as a ligand precursor in the reaction boosted the yield of **3aa** to 94%.

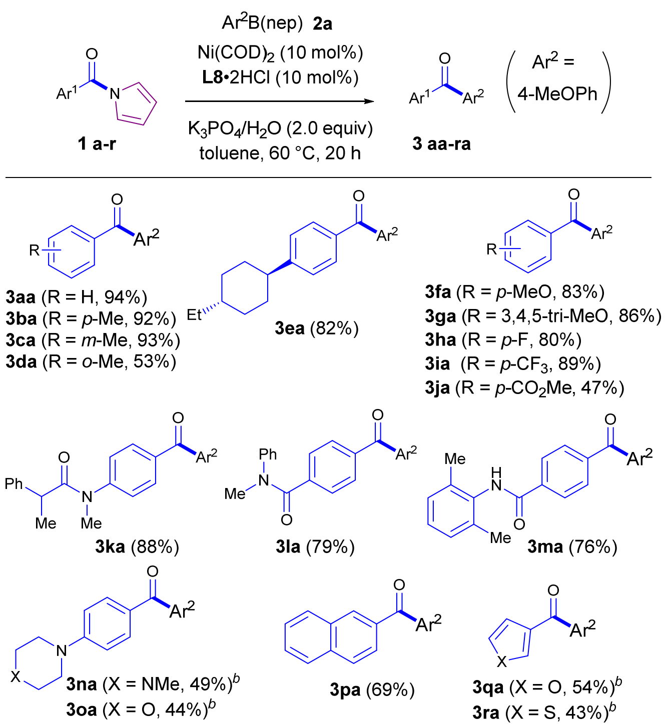
Table 1. Screening of NHC ligands[a]



[a] Isolated yields. For the structures of ligands **L2–L6** and **L9**, see: Table S1 in ESI.

With the optimal catalytic system defined, the scope of *N*-acylpyrrole **1** was surveyed (Table 2). The coupling reaction of *para*-, *meta*-, and *ortho*-toluamides produced the corresponding ketones **3ba**, **3ca**, and **3da** in 92%, 93%, and 53% yield, respectively. The reduced yield from *ortho*-toluamide compared with those from *para*- and *meta*-toluamides suggested that the reaction was sensitive to steric hindrance. The reaction tolerated both electron-donating (**3ba–3ga**) and electron-withdrawing groups (**3ha–3ma**). Moreover, in the presence of other tertiary (**3ka** and **3la**) and acidic hydrogen-containing secondary (**3ma**) amidyl groups, the reactions proceeded chemoselectively at the *N*-acylpyrrole. The reaction also tolerated basic amino groups (**3na** and **3oa**) although the yields are only modest. 2-Naphthamide, furan-3-carboxamide and thiophene-3-carboxamide also reacted to yield the corresponding coupling products **3pa**, **3qa** and **3ra** in 69%, 54% and 43% yield, respectively.

Table 2. *N*-acylpyrrole substrate scope[a]



[a] Reaction conditions: **1a–r** (0.24 mmol), **2a** (0.48 mmol), $Ni(COD)_2$ (10 mol%), **L8**·2HCl (10 mol%), K_3PO_4 (2.0 equiv), H_2O (2.0 equiv), toluene (0.5 M), 60 °C, 20 h. Isolated yields. [b] T = 80 °C.

Next, the scope of arylboronic ester **2** was examined (Table 3). The coupling reaction worked well with phenylboronic ester which gave benzophenone (**3ab**) in 90% yield. Effective nucleophilic partners cover arylboronic esters bearing electron-donating groups such as *p*-Me (**3ac**), *p*-*t*Bu (**3ad**) and *o*-MeO (**3ae**) or electron-withdrawing groups including F (**3af**), CF_3 (**3ag**), ester (**3ah**) and ketone (**3ai**) at the *para*-position of the aryl moiety. The beneficial effect of the electron-donating group at the *para*-position can be attributed to the enhanced nucleophilicity of the corresponding arylboronic esters. The compatibility of coupling reaction with esters and ketones is noteworthy. The reaction also tolerated 2-naphthyl (**3aj**) and 3-furyl (**3ak**) groups, as well as basic heterocycle such as 1-methyl-1*H*-pyrazole (**3al**) and 2-methoxypyridine (**3am**).

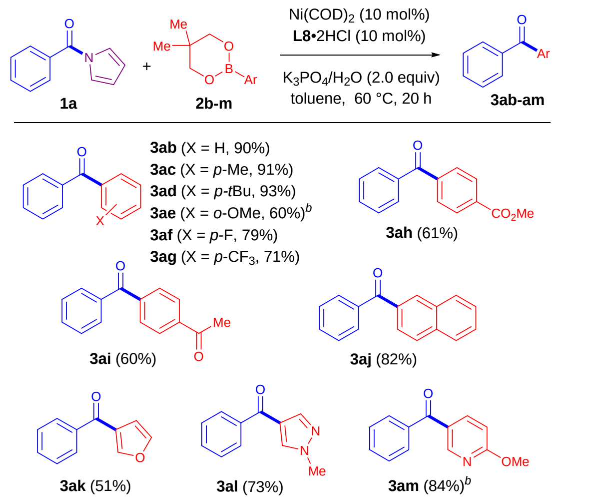
The good functional group tolerance is important for applications in organic synthesis, while the ability to incorporate F, CF_3 and heterocycles are significant for developing medicinal agents.[19]

As a further demonstrate synthetic utility of the reaction, gram-scale synthesis was examined. The gram-scale reactions of **1a** with **2n**, and **1h** with **2f** proceeded smoothly to give **3an** and **3hf** in 70% and 71% yield, respectively (Scheme 2). Moreover, the high-yielding coupling of **1g** with **2n** to yield a potent microtubule inhibitor **3gn**[20] revealed the potential of the method in medicinal chemistry.

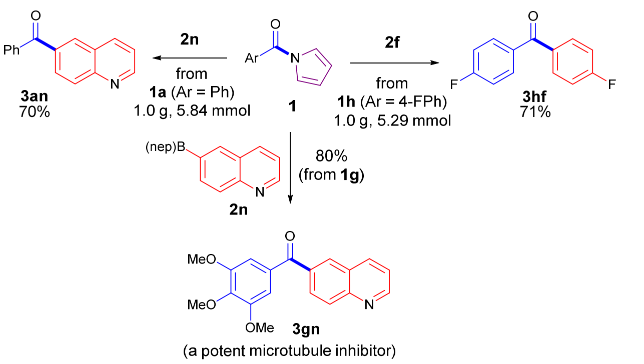
N-Acylpyrroles are accessible by several methods.[11] Among them, Evan's method starting from 1,1'-carbonyldipyrrole (**4**) is flexible and versatile.[11g] Merging Evan's synthesis of *N*-acylpyrroles with our

coupling reaction provided a convenient and convergent synthetic approach to diarylketones from the "C_1" source **4** (Scheme 3).

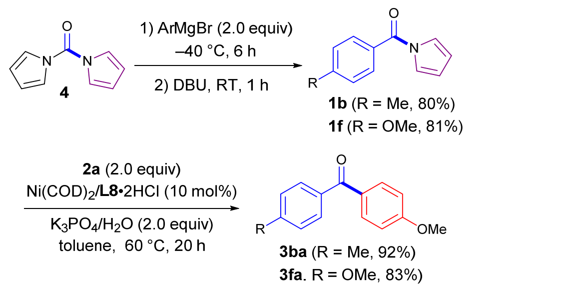
Table 3. Scope of arylboronic ester[a]



[a] Reaction conditions: **1a** (0.24 mmol), **2b–m** (0.48 mmol), $Ni(COD)_2$ (10 mol%), **L8**·2HCl (10 mol%), K_3PO_4 (2.0 equiv), H_2O (2.0 equiv), toluene (0.5 M), 60 °C, 20 h. Isolated yields. [b] Based on recovered starting material. [c] T = 80 °C.

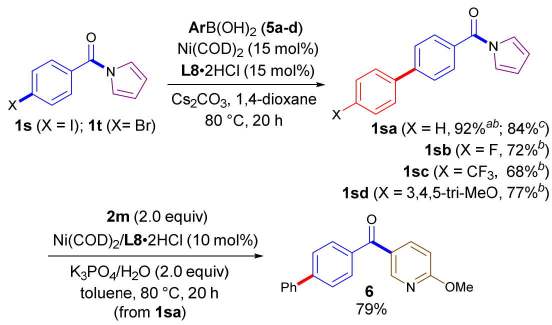


Scheme 2. Gram-scale synthesis and synthetic application.



Scheme 3. Convergent synthesis of diarylketones.

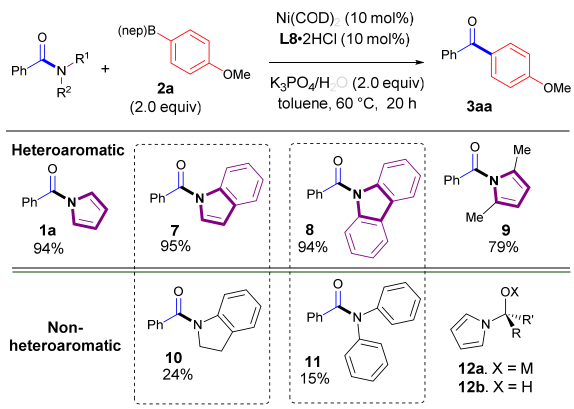
To further expand the entrance to functionalized *N*-acylpyrroles, the orthogonal Suzuki-coupling and amide-coupling using *N*-acylpyrrole **1s/1t** containing a C(aryl)–I/Br bond was investigated. Pleasingly, under modified reaction conditions, our newly developed catalytic system Ni/**L8** was able to catalyze the Suzuki-coupling reaction of **1s/1t** with various phenyl boronic acids without affecting the amide moiety (Scheme 4). This chemoselective Suzuki-coupling provides a versatile avenue to functionalized *N*-acylpyrroles and further to biarylketones through subsequent amide coupling. For example, the coupling of the amide **1sa**, which was obtained from **1s/1t** through Suzuki coupling, with functionalized heteroarylboronic ester **2m** afforded biarylketones **6** in good overall yield (Scheme 4).



Scheme 4. Synthesis of birayl ketones through orthogonal Suzuki coupling and amide activation. [a] $Ni(COD)_2$ (10 mol%), **L8**·2HCl (10 mol%). [b] from **1s**. [c] from **1t**.

The higher reactivity of *N*-acylpyrroles toward Ni-catalyzed C–N activation compared with common amides can be attributed to the heteroaromaticity effect. The lone pair of the amidyl nitrogen in *N*-acylpyrroles is engaged in the formation of the pyrrole aromatic ring system, which reduces its participation in the interaction with $\pi^*_{C=O}$ orbital. Without this delocalization, *N*-acylpyrroles display comparable electrophilic reactivity as ketones. This can be seen from the remarkable stability of tetrahedral intermediates **12a** from nucleophilic additions to *N*-acylpyrroles and the corresponding carbinol **12b**.[11g] To confirm that this heteroaromaticity effect is responsible for the observed high reactivity of *N*-acylpyrroles, the coupling reactions of the relevant *N*-acylpyrrole-type amides[11,4c] **7**, **8**, **9**, **10** and **11** were investigated (Table 4). Indeed, the reactions of heteroaromatic *N*-acylindole **7** and *N*-acylcarbazole **8** produced ketone **3aa** in 95% and 94% yield, respectively. In contrast, low yields (24% and 15%) were obtained from non-heteroaromatic *N*-benzoylindoline **10** and *N,N*-diphenylbenzamide **11**. Sterically hindered heteroaromatic *N*-benzoyl(2,5-dimethyl)pyrrole **9** also served as an effective coupling partner providing the **3aa** in 79% yield.

Table 4. Ni-Catalyzed cross-coupling reactions of different type of amides.



In summary, we have achieved the first Ni-catalyzed coupling reaction of *N*-acylpyrrole-type amides (*N*-acylpyrroles, *N*-acylindole, *N*-acylcarbazole and *N*-acyl-2,5-dimethylpyrrole) with arylboronic esters. The success of this method relies on the discovery of a new chelating bis-NHC ligand. The Ni/bis-

NHC catalytic system enables the activation of *N*-acylpyrrole-type amides under mild conditions with high chemoselectivity and functional group tolerance allowing access to biraylketones bearing unprotected functional groups such as ketones and esters, which are not compatible with traditional conditions involving reactive Grignard or organolithium reagents.

The authors are grateful for financial support from the National Key R&D Program of China (grant No. 2017YFA0207302), the National Natural Science Foundation of China (21332007 and 21672176) and the Program for Changjiang Scholars and Innovative Research Team in University of Ministry of Education, China.

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DOI: 10.1039/C7CC07457C

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