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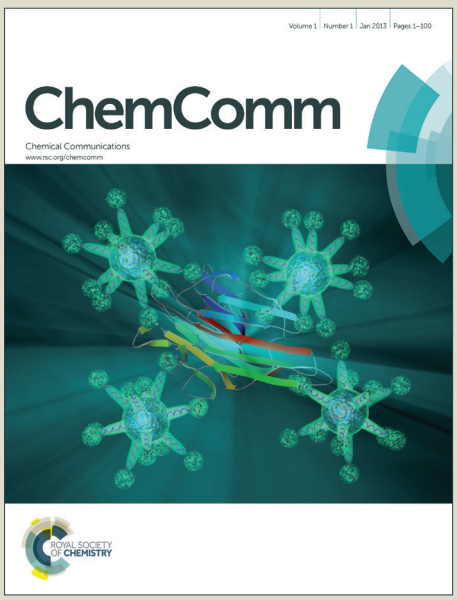

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Direct synthesis of *N*-alkylated amides *via* tandem hydration/*N*-alkylation reaction from nitriles, aldoximes and alcohols†

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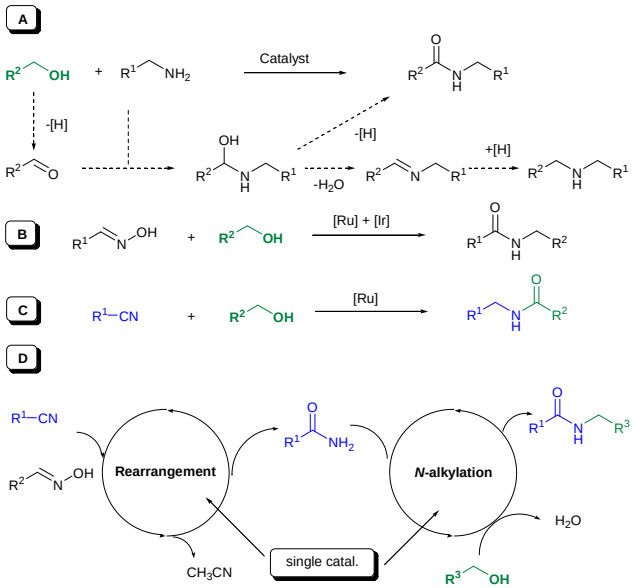
The novel strategy for direct synthesis of *N*-alkylated amides from nitriles, aldoximes and alcohols was proposed and accomplished in the presence of Cp*Ir complex.

The *N*-alkylated amides represent an important class of chemical compounds that have ubiquitous application in natural products, pharmaceuticals, fine chemicals and polymers, etc.[1] Traditional procedures for the synthesis of *N*-alkylated amides are couplings of carboxylic acids or their derivatives, such as acid chlorides, anhydrides and esters, with *N*-alkylated amines.[2] However, these procedures suffer from the use of the stoichiometric amount of hazardous and/or expensive reagents and the generation of a large amount of harmful by-products.

In recent several years, much attention has been paid to the development of catalytic strategies for the synthesis of *N*-alkylated amides using alcohols as starting materials because alcohols are less toxic, abundant and renewable feedstock reagents. Several groups have developed direct couplings of amines and primary alcohols for the preparation of *N*-alkylated amides using transition metal catalysts, such as PNN-type ruthenium complex,[3] the combination of *N*-heterocyclic carbene (NHC) precursor, and $[Ru(cod)Cl]_2$,[4] $[Ru(p\text{-cymene})Cl_2]_2$, $[Ru(benzene)Cl_2]_2$[5] or $[RuH_2(PPh_3)_4]$ systems,[6] *N*-heterocyclic carbene based ruthenium complexes,[7] ruthenium diphosphine diamine complexes.[8] However, it is still extreme challenge to control the selectivity of reaction and reduce the generation of by-products *N*-alkylated amines (Scheme 1, **A**). In 2013, we demonstrated the direct synthesis of *N*-alkylated amides from aldoximes and alcohols *via* tandem rearrangement/*N*-alkylation reaction catalyzed by Ru/Ir dual catalyst system, which exhibited excellent selectivity for target products (Scheme 1, **B**).[9] However, most of aldoximes are not commercially available and must be synthesized *via* the condensation of corresponding aldehydes with hydroxylamine hydrochloride in the presence of base, and the single catalyst (ruthenium or iridium complex) is not efficient for such tandem transformation. More recently, Hong and co-workers reported a catalytic strategy for the synthesis of *N*-alkylated amides from nitriles and alcohols with complete atom economy based on "hydrogen transfer" (Scheme 1, **C**),[10] exhibiting significant advantages over traditional Ritter reaction (Amidation of



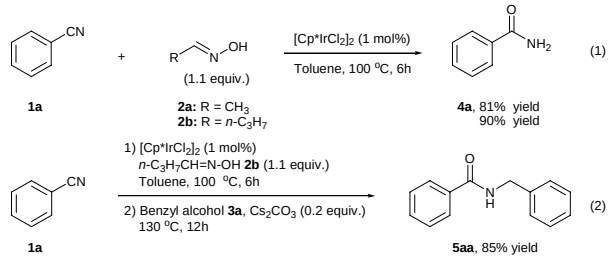
Scheme 1 Strategies for the synthesis of *N*-alkylated amines from alcohols.

nitriles with alcohols or alkenes in the presence of at least stoichiometric amount of concentrated sulfuric acid).[11] This procedure still has some limitations and it required 10 mol% catalyst loading, 10 mol% ligand, 20 mol% strong base (NaH) and long reaction time (48 h).

The selective hydration of nitriles with aldoximes as water surrogates for the synthesis of amides has been developed using transition metal catalysts, such as rhodium,[12a] palladium,[12b] indium,[12c] copper,[12d] nickel[12e] complexes or salts. This methodology is attractive due to mild and neutral reaction conditions that avoid the formation of carboxylic acids and allow functional groups to remain intact. However, these known procedures still suffer from high catalyst loading (5-10 mol%) or/and excess of aldoxime (2-5 equiv.). As part of a continuing interest in developing new reactions with the activation of alcohols,[9,13] herein we wish to explore the direct synthesis of *N*-alkylated amides *via* tandem hydration/*N*-alkylation reaction from nitriles, aldoximes and alcohols. The proposed reaction pathway is as follows: nitriles are first hydrated with aldoximes as water surrogates to form amides,

which are further *N*-alkylated with alcohols as alkylating agents to *N*-alkylated amides (Scheme 1, **D**). Compared with Hong's method, [10] this procedure would provide different *N*-alkylated amides from same starting materials (nitriles and alcohols).

In our previous work,[9] a range of commercially available transition metal complexes, including $[Ru(p\text{-cymene})Cl_2]_2$, $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl), $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadienyl), $[Cp^*IrCl_2]_2$ and $[Ir(cod)Cl]_2$, were assayed for their ability to catalyze the *N*-alkylation of benzamide with benzyl alcohol to the *N*-benzylbenzamide and $[Cp^*IrCl_2]_2$ was found to be the most efficient catalyst. As a result of it, our initial efforts in this work focused on the hydration of benzonitrile **1a** with commercially available aldoxime, such as acetylaldoxime **2a** and *n*-butylaldoxime **2b,** as the water surrogate catalyzed by $[Cp^*IrCl_2]_2$. The reaction of **1a** with **2a** (1.1 equiv.) was carried out in the presence of $[Cp^*IrCl_2]_2$ (1 mol%) at 100 °C for 6h to give benzamide **4a** with 81% yield. To our delight, the product **4a** could be obtained with 90% yield when **2b** was used for this reaction [Equation (1)]. The *n*-butylaldoxime **2b** was chosen as the water surrogate for further research. After the reaction of **1a** with **2b** was carried out at 100 °C for 6h, benzyl alcohol **3a** (1.3 equiv.) and Cs_2CO_3 (0.2 equiv.) were



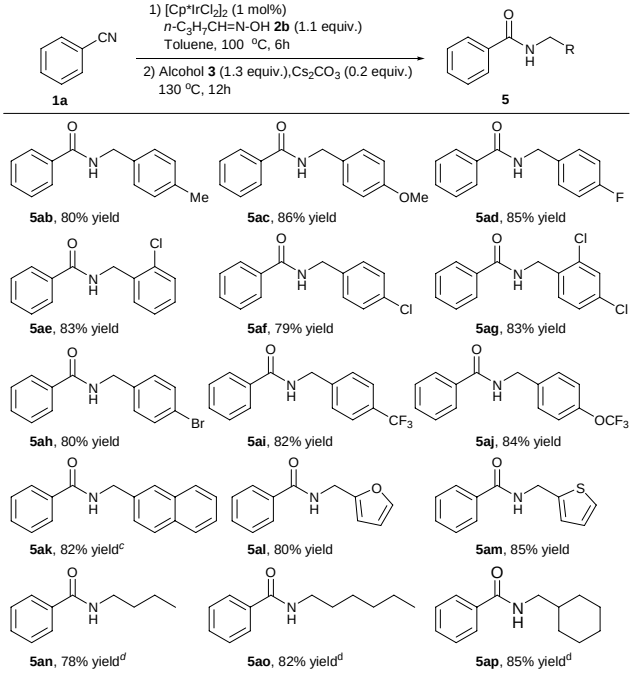
added into above reactor. This reaction continued to proceed at 130 °C for another 12h to afford the desired *N*-alkylated amide **5aa** with 85% yield [Equation (2)].

Having established the catalyst system and reaction conditions, a variety of alcohols **3** were used as substrates instead of benzyl alcohol **3a** for the investigation and the results are summarized in Table 1. Similar to the case of **3a**, reactions with benzylic alcohols bearing an electron-donating group, such as methyl **3b** and methoxy **3c**, afforded the corresponding products **5ab** and **5ac** with 80% and 86% yields, respectively. Benzylic alcohols bearing one or two halide atoms, such as fluoro **3d**, chloro **3e-f**, dichloro **3g** and bromo **3h**, were successfully converted into the desired products **5ad-5ah** with 79-85% yields. Furthermore, transformations of benzylic alcohols bearing a strong electron-withdrawing group, such as trifluoromethyl **3i** and trifluoromethoxy **3j,** gave the corresponding products **5ai** and **5aj** with 82% and 84% yields, respectively. When 2-naphthalenemethanol **3k**, furan-2-ylmethanol **3l** and thiophen-2-ylmethanol **3m** were tested, the desired products **5ak-5am** were obtained with 80%-85% yields, respectively. Apart from benzyl-type alcohols, aliphatic alcohols, including liner *n*-butanol **3n** and *n*-hexanol **3o**, and cyclohexylmethanol **3p**, were proven to be suitable substrates and reactions gave the corresponding products **5an-5ap** with 78-85% yields.

To expand further the scope of reaction, a series of nitriles **1** were used as substrates for the examination. As shown in Table 2, reactions of benzonitriles bearing one or two electron-donating substituents, such as methyl **1b** and methoxy **1c**, gave the corresponding products **5ba-5ca** with 81% and 76% yields, respectively. Transformation of benzonitriles bearing one or two halogen atoms, such as fluoro **1d**, chloro **1e**, dichloro **1f** and bromo **1g**, gave the desired products **5da-5ga** with 81-90% yields. In the case of benzonitriles bearing a strong electron-withdrawing substituent, such as trifluoromethyl **1h** and trifluoromethoxy **1i**, the corresponding products **5ha** and **5ia** were obtained with 80% and 82% yields, respectively. Reactions of heterocyclic nitriles, such as furan-2-carbonitrile **1j** and thiophene-2-carbonitrile **1k**, gave the desired products **5ja** and **5ka** with 84% and 86% yields, respectively. This tandem reaction was also applied to aliphatic nitriles, such as 2-phenylacetonitrile **1l** and *n*-butyronitrile **1m** (**2a** was used as the water surrogate), affording the corresponding products **5la** and **5ma** with 76% and 78% yields, respectively.

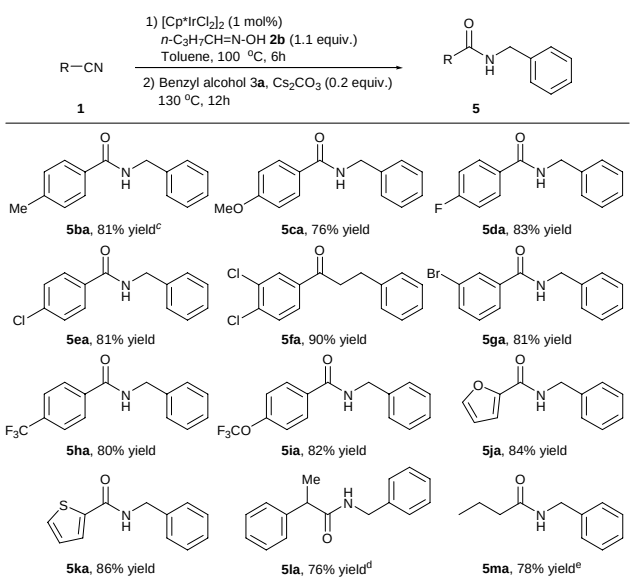
A plausible mechanism is proposed to account for this present reaction (Scheme 2). The initial step involves the formation of iridium-nitrile species **A**, followed by the resulting species **A** were subsequently attacked by one molecular of aldoximes to afford five-membered cyclic species **B**, which decomposed to release amides and nitriles, and to regenerate the catalytic active iridium species. Finally, the resulting amides were further *N*-alkylated with alcohols to

Table 1 Reaction of benzonitrile **1a**, *n*-butylaldoxime **2b** and a variety of alcohols **3** [a,b]

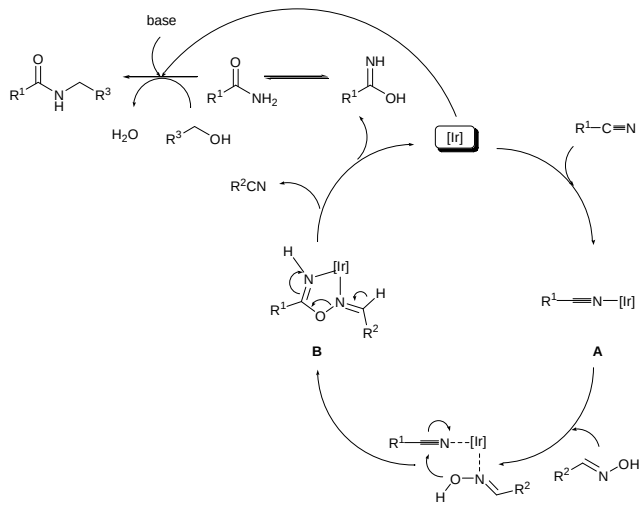


[a] Reaction conditions: 1) **1a** (1 mmol), **2b** (1.1 mmol), $[Cp^*IrCl_2]_2$ (1 mol%), toluene (1 ml), 100 °C, 6h; 2) **3** (1.3 mmol) and Cs_2CO_3 (0.2 equiv.) were added into the reactor, 130 °C, 12h. [b] Isolated yield. [c] **3k** (1.5 mmol). [d] **3** (2 mmol), KO*t*Bu (0.2 equiv.).

Table 2 Reaction of a series of nitriles **1**, *n*-butylaldoxime **2b** and benzyl alcohol **3a** [a,b]



[a] Reaction conditions: 1) **1** (1 mmol), **2b** (1.1 mmol), $[Cp^*IrCl_2]_2$ (1 mol%), toluene (1 ml), 100 °C, 6h; 2) **3a** (1.3 mmol) and Cs_2CO_3 (0.2 equiv.) were added into the reactor, 130 °C, 12h. [b] Isolated yield. [c] **2b** (1.3 mmol), **3a** (1.5 mmol). [d] **2b** (1.3 mmol), **3a** (2 mmol), $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (0.4 equiv.), 150 °C. [e] **2a** (1.3 mmol), **3a** (2 mmol), $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (0.4 equiv.), 150 °C.



Scheme 2 Plausible mechanism

afford *N*-alkylated amides catalyzed by iridium/base system.

It should be pointed that aromatic nitriles and benzyl-type alcohols bearing different elctronic substituents could be converted into desired products with high yields and thus none of electronic properties to influence on reactions was found. In the process of catalytic hydration of aromatic nitriles with *n*-butylaldoxime, a small amount of *n*-butyramide wasgenerated due to the competing hydration of *n*-butyranitrile derivated from the hydration of *n*-butylaldoxime. However, only trace amount of *N*-alkylated butyramides were detected when tandem reactions were finished, indicating that more strong reaction conditions are necessary for the *N*-alkylation of aliphatic amides with alcohols. To transform aliphatic nitriles (**1l-1m**) into the corresponding *N*-alkylated amides (**5la-5ma**), $[Cp^*IrCl_2]_2$ (2 mol%) and 1.3 equiv. of aldoxime in the step of hydration, and 2 equiv. of alcohol and 0.4 equiv. of KO*t*Bu in the step of *N*-alkylation were required. In this process, *N*-benzyl butyramide or *N*-benzyl acetamide were also generated as by-products.

In summary, we have demonstrated a novel strategy for the direct synthesis of *N*-alkylated amides *via* tandem hydration/*N*-alkylation from nitriles, aldoximes and alcohols. The protocol is highly attractive due to the use of single catalyst with low loading, high yields and operational convenience.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data for products. See DOI: 10.1039/b000000x/

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