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Iridium-Catalyzed Selective α-Alkylation of Unactivated Amides with Primary Alcohols

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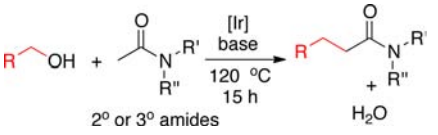
ABSTRACT



The first α-alkylation of unactivated amides with primary alcohols is described. An effective and robust iridium pincer complex has been developed for selective α-alkylation of tertiary and secondary acetamides involving a "borrowing hydrogen" methodology. The method is compatible with alcohols bearing various functional groups. This presents a convenient and environmentally benign protocol for α-alkylation of amides.

The α-alkylation of amides is an important transformation for carbon−carbon bond formation and has found widespread application in the synthesis of natural products and biologically active compounds and in peptide modification.[1] The uncatalyzed reaction of amide enolate with alkyl halides is a traditional transformation for α-alkylation of amides.[1,2] However, this method suffers from the use of mutagenic alkyl halides and the formation of waste salts. In addition, prior to coupling, superbases (e.g., organolithium, alkali metal amides) are required to generate the alkali metal enolate under very low temperature conditions.

In chemical and pharmaceutical industries, alcohols are preferred alkylating reagents because they are less expensive and more environmentally friendly than alkyl halides, and their alkylation produces water as the only waste product. In the past decade, alkylation with alcohols employing the so-called "borrowing hydrogen" or "hydrogen autotransfer" methodology has emerged as a powerful and green process for new bond formations.[3] For example, *N*-alkylation of amines,[3f,h] *β*-alkylation of alcohols,[3b,c,g] alkylation of methyl-*N*-heteroaromatics,[4] and α-alkylation of carbonyl and related compounds[5] have been achieved using primary alcohols as the alkylating reagents. Recently, Ishii et al. reported a remarkable example of α-alkylation of *tert*-butyl acetate with primary alcohols.[6] The reaction occurred at 100 °C in the presence of $[Ir(COD)Cl]_2$ (10 mol % Ir), PPh_3 (15 mol %), and KO*t*Bu (2 equiv) in *t*BuOH, giving the corresponding *tert*-butyl esters in good yields. The substrate scope is limited to *tert*-butyl acetate, and a large excess of this acetate (10 equiv) is required.[6]

The aforementioned α-alkylation of carbonyl occurred by an aldol reaction with aldehydes, which were derived

(1) Challis, B. C.; Challis, J. In *The Chemistry of Amides*; Zabicky, J., Ed.; John Wiley & Sons: London, 1970; pp 731−857.

(2) For examples, see: (a) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269. (b) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070. (c) Seebach, D.; Beck, A. K.; Bossler, H. G.; Gerber, C.; Ko, S. Y.; Murtiashaw, C. W.; Naef, R.; Shoda, S.-I.; Thaler, A.; Krieger, M.; Wenger, R. *Helv. Chim. Acta* **1993**, *76*, 1564.

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(4) (a) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924. (b) Obora, Y.; Ogawa, S.; Yamamoto, N. *J. Org. Chem.* **2012**, *77*, 9429.

(5) For examples, see: (a) Grigg, R.; Löfberg, C.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 849. (b) Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413. (c) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850. (d) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *126*, 72.

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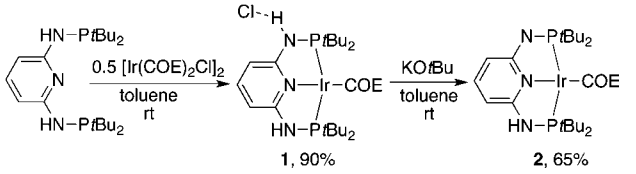
Scheme 1. Synthesis of Complexes **1** and **2**



from primary alcohols via dehydrogenative activation. Among carbonyl compounds, the α-hydrogens of amides are the least acidic[7] and therefore the aldol condensation of amides with aldehydes itself has remained elusive.[7a,8] Thus the α-alkylation of amides with alcohols is a significant challenge. The few known examples of α-alkylation of amides are limited to reactions of oxindoles[9] and 4-hydroxy-quinolones[10] containing activated α-CH. To date, the α-alkylation of readily available unactivated amides with primary alcohols has remained unknown.

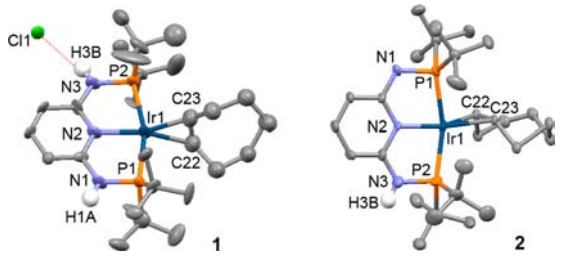


Figure 1. ORTEP diagrams of complexes **1** (left) and **2** (right).

Since several iridium catalysts are known for dehydrogenation of alcohols, we sought to develop a highly active and robust iridium catalyst for α-alkylation of amides with primary alcohols. Pincer iridium complexes exhibit high thermal stability and are versatile in terms of alcohol,[11] amine,[12] and alkane dehydrogenation.[13] Herein, we report a new PN^3P-type iridium pincer catalyst for the first α-alkylation of tertiary and secondary acetamides with primary alcohols. This reaction provides a convenient and environmentally benign route to a diverse library of amides from very simple substrates.

The synthesis of the PN^3P iridium complex **1** is outlined in Scheme 1. Treatment of *N*,*N*-bis(di-*tert*-butylphosphino)-2,6-diaminopyridine with 0.5 equiv of $[Ir(COE)_2Cl]_2$ in toluene afforded complex **1** in 90% yield. The spectroscopic features of **1** show two broad signals for the NH groups at 9.13 and 7.93 ppm in the ^1H NMR spectrum. The ^{31}P NMR spectrum of **1** exhibits an AB pattern at 100.7 and 90.0 ppm. The NMR data imply the formation of an asymmetric cationic iridium PNP complex with an outer-sphere chloride anion. The single-crystal X-ray structure of **1** confirms a pseudosquare coordination geometry of the Ir(I) site with the NH group participating in a N−H···Cl hydrogen bonding interaction with the chloride anion (see Figure 1). Complex **1** is air stable for at least several weeks in the solid state and several days in solution.

The α-alkylation of *N*,*N*-dimethylacetamide **4a** with benzyl alcohol **3a** employing complex **1** as the precatalyst was selected as the model reaction. The reactions were carried out under various conditions, and the results are summarized in Table 1. Using 2 mol % **1**, the reaction of **3a** (1 mmol) with **4a** (2 mmol) in the presence of KO*t*Bu (1 equiv) in toluene (1 mL) at 120 °C gave the desired product, *N*,*N*-dimethyl-3-phenylpropionamide **5a**, in 62% yield after 15 h (entry 1). The efficiency of this transformation increased with increasing amounts of KO*t*Bu. The reaction with 2 equiv of KO*t*Bu provided an 88% yield of **5a** (81% isolated yield),[14] while decreasing the loading of the base to 0.5 equiv gave **5a** in 46% yield (entries 2 and 3). Similarly, a high loading of KO*t*Bu was also required in the alkylation of *tert*-butyl acetate[6] and methyl-*N*-heteroaromatics.[4a] The reactions in THF, 1,4-dioxane, digyme, and DMF generated **5a**, but in lower yields compared to the reaction in toluene (entries 4−7 vs entry 2). The reaction in neat *N*,*N*-dimethylacetamide (10 equiv relative to **3a**) gave the product **5a** in 82% yield (entry 8). The concentration of the reaction mixture has a minimal effect on the productivity. Using the otherwise same reaction conditions as those for entry 2, the reaction in a dilute solution (15 mL toluene) afforded **5a** in 81% yield (entry 9). The efficiency of the reaction with NaO*t*Bu (87%, entry 10) is similar to the reaction efficiency with KO*t*Bu, but using KOH as the base gave the product **5a** in a much lower yield (25%, entry 11). No product was formed in reactions with relatively weak bases such as Cs_2CO_3 and K_2CO_3 (entries 12 and 13).

We also evaluated the effectiveness of the known iridium pincer complexes for α-alkylation of *N*,*N*-dimethylacetamide **4a** with benzyl alcohol **3a**. With KO*t*Bu (2 equiv) as the base, the reaction in toluene using PONOP-Ir (**6**) afforded the product **5a** in 65% yield at 120 °C after 15 h (entry 14), while using POCOP-Ir (**7**) and PCP-Ir (**8**)

(7) pK_a's of amides, esters, aldehydes, and ketones in DMSO are ~35, ~31, ~27, and ~27, respectively; also see: (a) Foo, S. W.; Oishi, S.; Saito, S. *Tetrahedron Lett.* **2012**, *53*, 5445. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (c) Fersner, A.; Karty, J. M.; Mo, Y. *J. Org. Chem.* **2009**, *74*, 7245.

(8) For examples of aldol condensation of amides: (a) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 7346. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2001**, *124*, 392.

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(10) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468.

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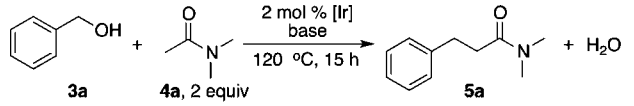
(12) (a) Gu, X.-Q.; Chen, W.; Morales-Morales, D.; Jensen, C. M. *J. Mol. Catal. A: Chem.* **2002**, *189*, 119. (b) Bernskoetter, W. H.; Brookhart, M. *Organometallics* **2008**, *27*, 2036.

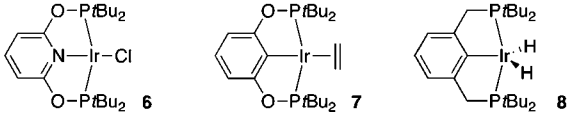
(13) For reviews, see: (a) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761. (b) *The Chemistry of Pincer Compounds*; Morales-Morales, D., Jensen, C., Eds.; Elsevier: Amsterdam, 2007.

(14) Under otherwise identical conditions, the reaction using 1 equiv of amide gave **5a** in only 45% yield. Thus, all the reactions were conducted with 2 equiv of amide.

Table 1. Iridium-Catalyzed α-Alkylation of *N*,*N*-Dimethylacetamide **4a** with Benzyl Alcohol **3a**[a]

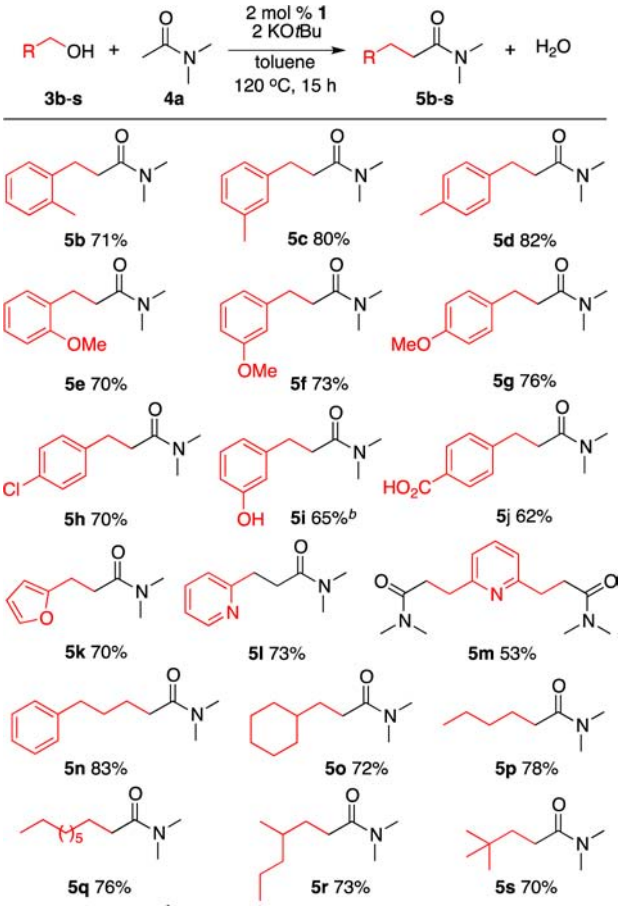


entry	catalyst	solvent	base (equiv)	% yield of **5a**[b]
1	**1**	toluene	KO*t*Bu (1)	62
2	**1**	toluene	KO*t*Bu (2)	88 (81)
3	**1**	toluene	KO*t*Bu (0.5)	46
4	**1**	THF	KO*t*Bu (2)	58
5	**1**	1,4-dioxane	KO*t*Bu (2)	66
6	**1**	diglyme	KO*t*Bu (2)	70
7	**1**	DMF	KO*t*Bu (2)	61
8	**1**	neat	KO*t*Bu (2)	70
9	**1**	toluene[c]	KO*t*Bu (2)	61
10	**1**	toluene	NaO*t*Bu (2)	87
11	**1**	1,4-dioxane	KOH (2)	25
12	**1**	1,4-dioxane	Cs_2CO_3 (2)	3
13	**1**	1,4-dioxane	K_2CO_3 (2)	0
14	**6**	toluene	KO*t*Bu (2)	65
15	**7**	toluene	KO*t*Bu (2)	74
16	**8**	toluene	KO*t*Bu (2)	69



[a] Reaction conditions: iridium complex (0.02 mmol) in 1.0 mL of solvent with **3a** (1 mmol), **4a** (2 mmol), and base (0.5–2 mmol) at 120 °C for 15 h. [b] Yields were determined by ^{1}H NMR with mesitylene as an internal standard. Value in parentheses is isolated yield. [c] Using 15 mL of toluene.

Scheme 2. α-Alkylation of **4a** with Various Primary Alcohols (**3b**–**s**)[a]



[a] Isolated yields. [b] Reaction performed with 3 equiv of KO*t*Bu.

supported by anionic pincer ligands gave the product in 74% and 69% yields, respectively (entries 15 and 16). By comparison, complex **1**, PN^{3}P–Ir, is most efficient (entry 2) among the pincer Ir complexes for this transformation.

Complex **1** catalyzed α-alkylation of *N*,*N*-dimethylacetamide **4a** with numerous primary alcohols was carried out using the same reaction conditions as those for entry 2 in Table 1. The results are summarized Scheme 2. The developed methodology worked efficiently for benzylic alcohols bearing both electron-donating and -withdrawing groups. Methyl and methoxy substitution in all the positions on the aromatic ring was well tolerated, giving the alkylated amides in 70–82% isolated yields (Scheme 2, **5b**–**g**). The reaction of 4-chlorobenzyl alcohol with **4a** gave **5h** in 70% isolated yield. Notably, 3-hydroxybenzyl alcohol (**5i**, 65%) was compatible under the reaction conditions. The alkylation of **4a** with 4-(methoxycarbonyl)benzyl alcohol occurred, but it gave 4-[3-(dimethylamino)3-oxopropyl] benzoic acid (**5j**, 62%) due to hydrolysis of the ester. Product **5j** was also obtained by the reaction of 4-carboxybenzyl alcohol with **4a**, albeit in relatively low yield (48%). Additionally, heterocyclic alcohols, such as 2-furanmethanol (**5k**, 70%) and 2-pyridinemethanol (**5l**, 73%), underwent alkylation in useful yields. Treatment of 2,6-pyridinedimethanol with **4a** afforded 2,6-bis(*N*,*N*-dimethylpropionamide)pyridine (**5m**, 53%),[15] which is a potential liquid–liquid extractant for lanthanide and actinide metals.[16] Alkylation of **4a** with 3-phenyl-1-propanol and aliphatic alcohols such as cyclohexylmethanol, *n*-butanol, and *n*-octanol gave the corresponding *N*,*N*-dimethyl amides **5n**–**q** in 72–83% yields. α-Alkylation of amide with alcohols bearing secondary and tertiary *β*-carbons proceeded smoothly. The reactions with 2-methyl-1-pentanol **4r** and 2,2-dimethyl-1-propanol **4s** gave the desired products **5r** and **5s** in 73 and 70% isolated yields, respectively.

A range of *N*,*N*-disubstituted acetamides underwent alkylation with a primary alcohol in high yields by this method. The results are summarized Scheme 3. The reaction of *N*,*N*-diethylacetamide with benzyl alcohol **3a** gave *N*,*N*-diethyl-3-phenylpropionamide (**9b**) in 78% isolated yield. *N*-Acetylpiperidine was also efficiently alkylated with benzyl alcohol (**9c**, 74%). Treatment of 4-acetylmorpholine with **3a** formed 4-(3-phenylpropanoyl)morpholine (**9d**) in 76% isolated yield.

(15) The single alkylation product, 3-(6-(hydroxymethyl)pyridin-2-yl)-*N*,*N*-dimethylpropanamide, was also observed (15%).

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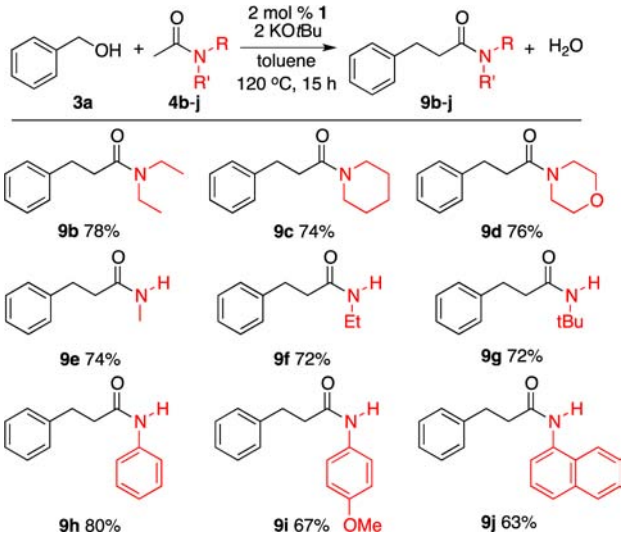
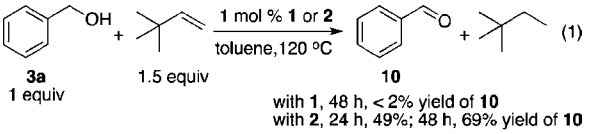
Scheme 3. α-Alkylation of Tertiary and Secondary Acetamides (**4b**–**j**) with Benzyl Alcohol Benzyl Alcohol **3a**[a]



[a] Isolated yields.

More importantly, this method was not limited to reactions of tertiary amides; selective α-alkylation of secondary amides with alcohols occurred using this protocol. Reactions of *N*-methyl acetamide, *N*-ethyl acetamide, and *N*-*tert*-butyl acetamide with benzyl alcohol **3a** selectively formed the corresponding secondary amides **9e**–**g** in 72–80% isolated yields. α-Alkylation of *N*-aryl-substituted secondary amides including *N*-phenyl acetamide, *N*-(4-methoxyphenyl) acetamide, and *N*-1-naphthalenyl acetamide occurred to give the desired products **9h**–**j** in 63–80% isolated yields. Notably, no *N*-alkylation of secondary amides with benzyl alcohol was observed in these reactions. In contrast, α-alkylation of secondary amides under basic conditions using alkyl halides as the alkylating reagents often results in undesired *N*-alkylation.[1]

Having studied the substrate scopes of primary alcohols and acetamides for the α-alkylation transformation, we sought to determine the active species in catalysis. The complex **1** contains two NH groups and may undergo deprotonation in the presence of KO*t*Bu. To assess whether a deprotonated species derived from **1** is the active catalyst for α-alkylation of acetamides with alcohols, we prepared a new Ir complex **2** (65%) by reaction of **1** with 1.5 equiv of KO*t*Bu (Scheme 1). The solid-state structure of **2** contains an anionic PN^3P ligand with no evidence for dearomatization of the pyridine ring (Figure 1; see Supporting Information for key bond distances and angles).[17] Treatment of complex **2** with KO*t*Bu did not lead to further deprotonation of the remaining NH group.



Using the isolated complex **2**, the reaction of acetamide **4a** with benzyl alcohol **3a** in the presence of 2 equiv of KO*t*Bu at 120 °C afforded the alkylated product **5a** in an 86% yield after 15 h. In addition, we tested the catalytic activity of complexes **1** and **2** for the oxidation of benzyl alcohol because the initial step in catalytic alkylation with primary alcohols involves metal-catalyzed dehydrogenation of alcohols to form aldehydes. With *tert*-butylethylene as the hydrogen acceptor, the transfer dehydrogenation of **3a** using **2** (1 mol %) did form 69% of benzaldehyde after 48 h at 120 °C, whereas the reaction using **1** (1 mol %) gave a neglectable amount of benzaldehyde (< 2%) under the same reaction conditions (eq 1). Taken together, the data indicate that complex **2** of the tridentate anionic PN^3P ligand is most likely to be the active catalytic species in the α-alkylation of acetamides with alcohols. Related iridium complexes of anionic bidentate PN ligands have been reported by Kempe et al. for efficient *N*-alkylation of amines.[18]

In summary, we report here an efficient method for the first catalytic α-alkylations of unactivated acetamides with primary alcohols. The simple preparation of the catalyst, readily available and environmentally benign alkylating reagents, formation of water as the only byproduct, and tolerance toward many functional groups render this method a highly attractive route for the α-alkylation of tertiary and secondary amides.

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Supporting Information Available. Experimental procedures and product characterization. X-ray crystallographic data (cif) for **1** and **2** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) In solution, however, the pyridine ring in **2** presumably undergoes dearomatization according to ^{1}H NMR analysis (see Supporting Information). Also see: (a) Ben-Ari, E.; Leitus, G.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2006**, *128*, 15390. (b) He, L.-P.; Chen, T.; Xue, D.-X.; Eddaoudi, M.; Huang, K.-W. *J. Organomet. Chem.* **2012**, *700*, 202.

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