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Catalytic Alkylation of Methyl-*N*-Heteroaromatics with Alcohols

Benoît Blank and Rhett Kempe*

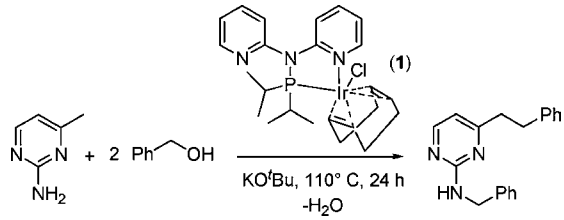
Anorganische Chemie II, Universität Bayreuth, Universitätsstrasse 30, 95440 Bayreuth, Germany

Received November 17, 2009; E-mail: kempe@uni-bayreuth.de

The so-called "borrowing hydrogen" methodology (Williams et al.[1]) or "hydrogen autotransfer" reaction (Yus et al.[2]) has aroused great interest in recent years and provides excellent protocols for the (selective[3]) alkylation of amines using simple, nontoxic alcohols[4,5] (also under mild conditions).[3b] Similar (but much less intensively investigated) methodologies have been used to accomplish C−C bond formations[1] such as β-alkylation of secondary alcohols[6] and alkylation of methylketones.[2,7] We herein report a novel iridium-based C−C bond formation reaction, namely, the catalytic alkylation of methyl-*N*-heteroaromatics using simple alcohols.

In the course of amine alkylation studies[3] with the P,N-ligand-stabilized[8] iridium catalyst **1** (Scheme 1), we observed C-alkylation of a methyl group as a side reaction.

Scheme 1. Observed N- and C-Alkylation with Alcohols



N-Benzylated 4-methylpyrimidin-2-ylamine (**2**) was employed to optimize several reaction parameters for this C-alkylation step (see the Supporting Information). The results showed that diglyme is the best solvent and that a reaction temperature of 110 °C is necessary. Screening of several organic and inorganic bases showed that the reaction works best with KO^{t}Bu, but it can also be performed with KOH or NaO^{t}Bu, albeit with ∼20% lower yields of the corresponding products. Ligand screening (Table 1) revealed that the P,N-ligand $Py_2NP(i\text{-}Pr)_2$ (Py = pyridinyl, Pr = propyl) affords the best results but that the reaction can interestingly also be performed with $[IrCl(cod)]_2$ (cod = cycloocta-1,5-diene), although slightly lower product yields are obtained.

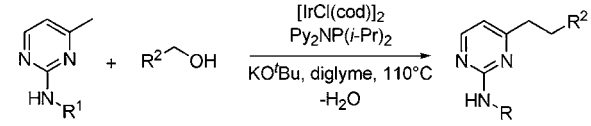
Table 1. Ligand Screening[a]

Entry	Ligand	TON	Yield[b]
1	PPh_3	137	41
2	$Py_2NP(i\text{-}Pr)_2$	243	73
3	$Ph_2PC_3H_6PPh_2$	97	29
4	2,2′-bipyridine	200	60
5	1,3-bis(2,6-dimethylphenyl)-4,5-dihydroimidazole	0	0
6	1,3-bis(2,6-diisopropylphenyl)imidazole	0	0
7	none (COD)	227	68

[a] Reaction conditions: 1.0 mmol of **2**, 1.1 mmol of benzyl alcohol, 0.0015 mmol of $[IrCl(cod)]_2$, 0.003 mmol of ligand, 300 μL of diglyme, 1.1 mmol of KO^{t}Bu, 24 h, 110 °C. [b] Determined by GC analysis with dodecane as internal standard.

It is possible that the substrate in a deprotonated form could itself act as an aminopyridinate, a class of ligands that has been extensively studied in our group.[9] To show the general applicability of this novel C-alkylation methodology, several alcohols were used (Table 2).

Table 2. General Application of Several Substituted Benzylic and Aliphatic Alcohols[a]



R^1= H, Bn (**2**) R^2 = aryl, alkyl R = Bn (**3**) / -(CH$_2$)-R^2 (**4**)

Entry	R^1	R^2	Product	TON	Yield[b]
1	Bn	Ph	**3a**	49	98 (87)
2	Bn	4-OMe-C_6H_4	**3b**	48	95 (78)
3	Bn	4-Me-C_6H_4	**3c**	45	90 (77)
4	Bn	3-Me-C_6H_4	**3d**	46	91
5	Bn	2-Me-C_6H_4	**3e**	46	92
6	Bn	2,4,6-Me_3-C_6H_2	**3f**	47	94
7	Bn	4-*t*-Bu-C_6H_4	**3g**	46	91
8	Bn	4-SMe-C_6H_4	**3h**	37	73
9	Bn	3-Cl-C_6H_4	**3i**	39	78
10	Bn	2-CF_3-C_6H_4	**3j**	31	62[c]
11	Bn	alcohol = 1-octanol	**3k**	37	74
12	Bn	alcohol = 1-butanol	**3l**	43	86
13	H	Ph	**3a**	43	85[d]
14	H	4-OMe-C_6H_4	**4a**	42	83[d]
15	H	3-Me-C_6H_4	**4b**	41	81[d]
16	H	alcohol = 1-butanol	**4c**	31	62[e]

[a] Reaction conditions: 1.0 mmol of **2**, 1.1 mmol of alcohol, 1 mol % $[IrCl(cod)]_2$, 2 mol % $Py_2NP(i\text{-}Pr)_2$, diglyme, 1.1 mmol of KO^{t}Bu, 24 h, 110°C. [b] Isolated yield; yields in parentheses correspond to the reaction with neat $[IrCl(cod)]_2$. [c] Using 8 mol % **1**. [d] Using 2.2 mmol of alcohol and KO^{t}Bu. [e] Using 3.0 mmol of 1-butanol and a reaction time of 48 h.

The presented results show that a multitude of functional groups are tolerated and that benzylic (entries 1−10) and aliphatic alcohols (entries 11 and 12) can be employed. The reaction works especially well with electron-donating substituents in the ortho, meta, and para positions and even with rather bulky substrates such as 2,4,6-trimethylbenzylic alcohol. The reaction with electron-withdrawing substituents is slightly more difficult, and higher catalyst loadings are necessary in order to obtain high conversions (entry 10). This is somehow a contradiction to literature results for the condensation of aldehydes with methylheteroaromatics, where a higher efficiency was observed for electron-poor aldehydes.[10] This implies that the successive hydrogenation of the formed olefin rather than the condensation step is hampered by electron-withdrawing substituents. As determined above, the reaction can also be performed using neat $[IrCl(cod)]_2$ without the addition of the P,N-ligand, but as shown for entries 1−3 (the values in parentheses), the expected products are obtained in 10−20% lower yields in comparison to those using **1**. The simultaneous N- and C-alkylation of 2-amino-4-methylpyrimidine with alcohols (entries 13−16) can, however, only be performed with **1**, affording products **3a** and **4a**−**c**.

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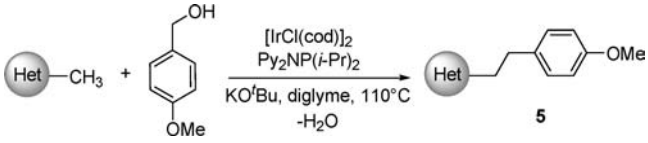
A range of different methyl-substituted heteroaromatic substrates was also tested in order to show the general applicability of this novel method (Table 3).

Table 3. Variation of the Heteroaromatic (Het) Substrate[a]



Entry	Cat. Load. [mol% Ir]	(Hetero)arom. educt	Prod.	TON	Yield[b]
1	5.0		**5a**	14	71
2	5.0		**5b**	15	74
3	5.0		**5c**	8	38
4	5.0		**5d**	7	33
5	5.0		**5e**	9	45
6	5.0		---	0	0

[a] Reaction conditions: 3.0 mmol of heteroaromatic substrate, 1.0 mmol of alcohol, 2.5 mol % $[IrCl(cod)]_2$, 5 mol % $Py_2NP(i\text{-}Pr)_2$, diglyme, 1.1 mmol of KO'Bu, 48 h, 110°C. [b] Isolated yield.

As shown in entries 1−5, not only methyl-substituted pyrimidines but also pyrazines, pyridazines, and even pyridines can be used as substrates. As expected, with decreasing acidity of the methyl protons[11] from 4-methylpyrimidine and 2-methylpyrazine toward the chemically similar substrates 3-methylpyridazine[12] and 2-picoline, the reaction proceeds less efficiently and affords lower yields of the C-alkylated products. However, it is interesting that the alkylation of 2- and 4-picoline with alcohols is still possible, even though the latter are only poorly activated substrates. Furthermore, the presence and position of the N atom in the heterocylic ring plays an important role, since only substrates with N in the 2- or 4-position can be efficiently alkylated, whereas 3-picoline, toluene, and pentafluorotoluene do not react. A tautomerization of the heteroaromatic educt into the corresponding enamine seems to be crucial for the reaction, which is possible neither for 3-picoline nor toluene derivatives. These findings support our theory that a "borrowing hydrogen" or "hydrogen autotransfer" mechanism is operating here, including dehydrogenation of the alcohol and subsequent condensation of the formed aldehyde with the heteroaromatic substrate, which has beforehand been deprotonated by the strong base (using a stoichiometric amount of the base). This should lead to the corresponding aldol product, which rapidly eliminates H_2O at elevated temperatures to form an olefinic substrate, onto which the "borrowed" hydrogen equivalents can be retransmitted to yield the final alkylation product (see the Supporting Information).

In conclusion, we have developed a protocol allowing the alkylation of methyl groups in N-heteroaromatic substrates using simple alcohols in a novel catalytic C−C bond formation reaction. This protocol extends the application scope of the "borrowing hydrogen" or "hydrogen autotransfer" methodology toward a new reaction and a new class of substrates. The work indicates the hidden potential of catalytic reactions using alcohols. Mechanistic studies and the development of more efficient catalysts are underway.

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Supporting Information Available: Characterization data and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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