ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 4701–4703

www.rsc.org/chemcomm

COMMUNICATION

Iridium catalysed chemoselective alkylation of 2′-aminoacetophenone with primary benzyl type alcohols under microwave conditions†

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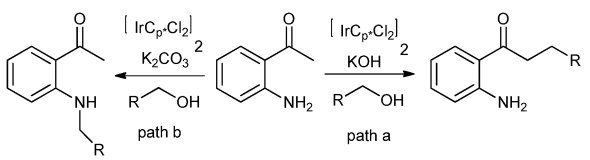
Received 13th February 2012, Accepted 19th March 2012
DOI: 10.1039/c2cc31055d

2′-Aminoacetophenone was chemoselectively alkylated with a range of substituted benzyl, heteroaryl alcohols to afford either the corresponding *C*- or *N*- alkylated products in good yield.

To increase the molecular complexity of a simple organic substrate using efficient (high atom economy), selective, high-yielding, and environmentally benign methods is one of the contemporary challenges for synthetic organic chemists.[1] C–C and C–N bond formations are pivotal methods for achieving this goal. Indirect functionalisation of alcohols using catalytic amounts of a metal complex and base which generates only water as a by-product is an attractive green alternative to standard C–C and C–N bond forming reactions. These cascades are termed as redox-neutral, hydrogen autotransfer or borrowing hydrogen processes. We and others have been involved in alkylation of amines and active methylene compounds with alcohols catalysed by iridium, rhodium and ruthenium complexes to form new C–N and C–C bonds.[1,2] Cho *et al.* reported the direct α-alkylation of ketones with alcohols, using a Ru catalyst, to afford saturated alcohols *via* α-alkylated ketones.[3] The same reaction can be performed in the presence of a sacrificial hydrogen acceptor, such as 1-dodecene, when α-alkylated ketones are obtained.[3] Alternative catalysts for the α-alkylation of ketones with alcohols have been reported including the use of phosphine free catalyst $Ru(DMSO)_4Cl_4$[4] and palladium nanoparticles.[5] Ishii *et al.* reported the direct α-alkylation of ketones with alcohols using an Ir catalyst.[6] As part of a continuing interest in exploring regioselective alkylation reactions we report iridium catalysed chemoselective alkylation of 2′-aminoacetophenone with alcohols to form either new C–C or C–N bonds under microwave irradiation (Scheme 1 path a, path b respectively).



Scheme 1

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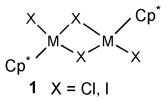
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc31055d

To best of our knowledge this is the first example of iridium catalysed chemoselective alkylation of bifunctional compounds with alcohols.

We initially surveyed a range of catalysts and identified the iridium chloro-bridged compound **1** [X = Cl, M = Ir(III)] as an effective catalyst for this transformation (Scheme 1).



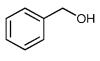
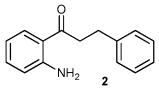
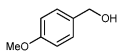
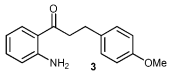
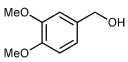
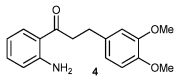
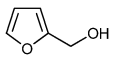
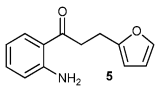
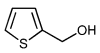
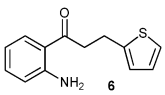
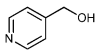
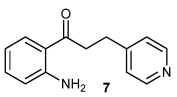
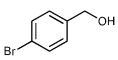
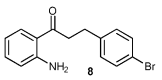
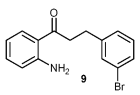
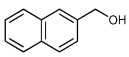
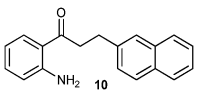
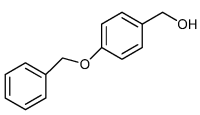
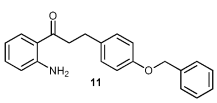
1 X = Cl, I
M = Ir, Rh,Ru

Microwave irradiation is reported to dramatically accelerate a number of metal catalysed reactions.[7] Further optimisation showed that the reaction could be achieved under microwave conditions (220 psi/300 W) and identified potassium hydroxide as the base of choice (Scheme 1 path a). Initially we carried out the alkylation reaction of 2′-aminoacetophenone (1 mmol) with benzyl alcohol (2 mmol), KOH (20 mol%) and $[Cp^*IrCl_2]_2$ (2.5 mol%) in toluene (3 mL) at 110 °C for 30 min in the microwave which afforded cleanly the mono *C*-alkylated product **2** in 60% yield (Table 1, entry 1). In the above process the *N*-alkylated product, *N*-, *C*-dialkylated product, C–C dialkylated product or dihydroquinolone derivative was not detected. No reaction took place in the presence of KOH alone, indicating that the combination of the iridium complex and a base is necessary for the reaction.

Benzyl alcohols substituted with electron-withdrawing or donating groups were readily alkylated to afford the corresponding *C*-alkylated products **3–11** in good yield (63–80%) (Table 1, entries 2–10). The reaction was not significantly affected by either the location or the electronic nature of the substituent on the aryl ring. The heteroaromatic furfuryl alcohol, thiophene-2-methanol and 4-pyridyl methanol were alkylated to the corresponding *C*-alkylated products (Table 1 entries 4–6) in good yield. During all these reactions clean *C*-regioselectivity was observed with none of the *N*-alkylated derivatives.

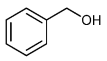
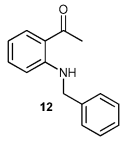
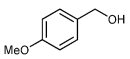
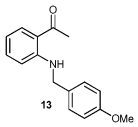
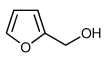
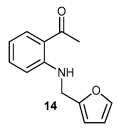
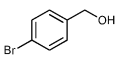
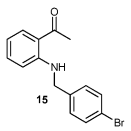
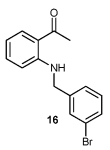
Next we explored the *N*-alkylation of 2′-aminoacetophenone with alcohols using microwave irradiation (Table 2, entries 1–5). Optimisation showed that the reaction could be achieved under microwave conditions (220 psi/300 W) and identified potassium carbonate as the base of choice (Scheme 1, path b) and the temperature was 140 °C. Initially we carried out the alkylation reaction of 2′-aminoacetophenone (1 mmol) with benzyl alcohol (3 mmol), K_2CO_3 (20 mol%) and

Table 1 Ir catalysed *C*-alkylation of 2′-aminoacetophenone[a]

Entry	Alcohol	Product	Yield[b] (%)
1			60
2			76
3			63
4			80
5			74
6			75
7			71
8			73
9			66
10			70

[a] 2′-Aminoacetophenone (1 mmol), alcohol (2 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), KOH (20 mol%), 110 °C, 30–40 min in the microwave. [b] Isolated yield.

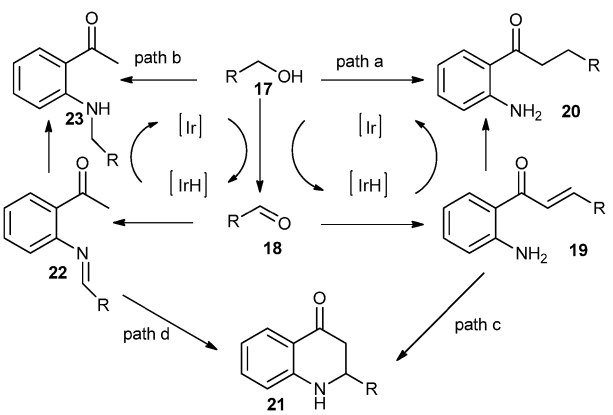
Table 2 Ir catalysed *N*-alkylation of 2′-aminoacetophenone[a]

Entry	Alcohol	Product	Yield[b] (%)
1			73
2			56
3			50
4			92
5			63

[a] 2′-Aminoacetophenone (1 mmol), alcohol (3 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), K_2CO_3 (20 mol%), 140 °C, 60 min in the microwave. [b] Isolated yield.

$[Cp^*IrCl_2]_2$ (2.5 mol%) in xylene (3mL) at 140 °C for 60 min in the microwave which afforded the mono *N*-alkylated product **12** in 73% yield (Table 2, entry 1). Neither the *C*-alkylated product nor the dihydroquinolone derivative was detected in the process. Furfuryl alcohol and 4-methoxy benzyl alcohol were also alkylated to the corresponding *N*-alkylated products (Table 2 entries 3 and 4) in good yield. A trace amount of reduction of ketone was also observed in these examples. In the presence of electron-withdrawing benzyl alcohols the reaction took a little longer in the microwave (2 h) to go to completion (Table 2, entries 4 and 5). During all these reactions clean *N*-regioselectivity was observed with none of the *C*-alkylated derivatives.

The proposed mechanism for this transformation involves dehydrogenation of the primary alcohol (**17**) to generate an aldehyde (**18**) and metal hydride species. Aldol condensation occurs (**19**) followed by hydrogenation of the double bond by the *in situ* formed metal hydride to give the *C*-alkylated product (**20**) (Scheme 2, path a). However there is potential for a competing Michael addition process leading to a dihydroquinolone derivative (**21**) (Scheme 2, path c). Alternatively imine (**22**) formation occurs followed by hydrogenation of the imine by the *in situ* formed metal hydride to give the *N*-alkylated product (**23**) (Scheme 2, path b). In this case there is also potential for a competing Mannich process leading to the same dihydroquinolone derivative (**21**) (Scheme 2, path d). Normally Brønsted or Lewis acid catalysis is the preferred option to make dihydroquinolone derivatives (**21**) *via* path c or path d.



Scheme 2

Crabtree *et al.* have reported a DFT study on iridium catalysed alkylation of amines with alcohols and shown that the amine dissociation is the rate determining step in this process.[8] The ancillary carbonate ligand on iridium is shown to be involved in the hydrogen transfer. As a result, higher temperatures are required to achieve good rates for *N*-alkylation. Complementary to these results we found that optimum yields of *N*-alkylated products were achieved using elevated temperatures and potassium carbonate as base. Furthermore, no *C*-alkylation was observed under optimized *N*-alkylation conditions.

In summary 2′-aminoacetophenone was successfully alkylated with a range of substituted benzyl, heteroaryl alcohols to afford either the corresponding *C*- or *N*- alkylated products in good yield. Further studies to expand the application of the synthetic strategy using diols are currently underway.

We thank Prof Chris Rayner, Dr Andrew Wilson and Leeds University for support.

Notes and references

1 Review articles on redox-neutral process: (*a*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (*c*) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358; (*d*) S. Baehn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853.

2 Reports using Ir catalysts: (*a*) K. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2002, **4**, 2691; (*b*) K. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 2687; (*c*) K. Fujita, T. Fujii and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 3525; (*d*) G. Cami-Kobeci and J. M. J. Williams, *Chem. Commun.*, 2004, 1072; (*e*) K. Fujita and R. Yamaguchi, *Synlett*, 2005, 560; (*f*) S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299; (*g*) C. T. Eary and D. Clausen, *Tetrahedron Lett.*, 2006, **47**, 6899; (*h*) L. U. Nordstrøm and R. Madsen, *Chem. Commun.*, 2007, 5034; (*i*) R. Yamaguchi, S. Kawagoe, C. Asai and K. Fujita, *Org. Lett.*, 2008, **10**, 181; (*j*) K. Fujita, Y. Enoki and R. Yamaguchi, *Tetrahedron*, 2008, **64**, 1943; (*k*) G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 535; (*l*) A. Prades, R. Corber, M. Poyatos and E. Peris, *Chem.–Eur. J.*, 2008, **14**, 11474; (*m*) A. Pontes da Costa, M. Viciano, M. Sanaú, S. Merino, J. Tejeda, E. Peris and B. Royo, *Organometallics*, 2008, **27**, 1305; (*n*) H. Aramoto, Y. Obara and Y. Ishii, *J. Org. Chem.*, 2009, **74**, 628; (*o*) S. Liu, M. Rebros, G. Stephens and A. C. Marr, *Chem. Commun.*, 2009, 2308; (*p*) K. Fujita, A. Komatsubara and R. Yamaguchi, *Tetrahedron*, 2009, **65**, 3624; (*q*) L. Miao, S. C. DiMaggio, H. Shu and M. L. Trudell, *Org. Lett.*, 2009, **11**, 1579; (*r*) R. Grigg, C. Lofberg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 849; (*s*) R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 4375; (*t*) R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 7468; (*u*) I. Cumpstey, S. Agrwal, K. E. Borbas and M. B. Matute, *Chem. Commun.*, 2011, **47**, 7827; (*v*) K. Fujita, Y. Tetsuyga, I. Yoichira and Y. Ryohei, *Org. Lett.*, 2011, **13**, 2278; (*w*) F. Li, H. Shan, L. Chen, Q. Kang and P. Zou, *Chem. Commun.*, 2012, **48**, 603.

3 (*a*) C. S. Cho, T. Kim, T. J. Kim and S. C. Shim, *J. Org. Chem.*, 2001, **6**, 9020; (*b*) C. S. Cho, T. J. Kim and S. C. Shim, *Tetrahedron Lett.*, 2002, **43**, 7987.

4 (*a*) R. Martinez, G. J. Brand, D. J. Ramon and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683; (*b*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8982; (*c*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **240**, 8988; (*d*) G. Guillena, D. Ramon and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2.

5 Y. M. A. Yamada and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375.

6 K. Tauchi, H. Nakagawa, T. Hirabayashi, S. Sakauchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72.

7 (*a*) C. Loefberg, R. Grigg, M. A. Whittaker, A. Keep and A. Derrick, *J. Org. Chem.*, 2006, **71**, 8023; (*b*) A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328.

8 D. Balcells, A. Nova, E. Clot, D. Gnanamgari, R. H. Crabtree and O. Eisentein, *Organometallics*, 2008, **27**, 2529.