Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 55

www.rsc.org/greenchem

COMMUNICATION

Effective synthesis of 2,5-disubstituted tetrahydrofurans from glycerol by catalytic alkylation of ketones†

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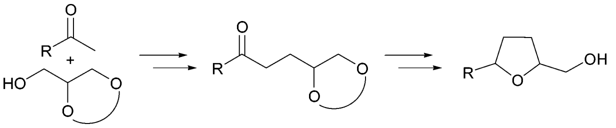
Received 28th June 2011, Accepted 22nd September 2011
DOI: 10.1039/c1gc15764g

The $[IrCl(cod)]_2$ catalyzed α-alkylation of substituted acetophenones with solketal followed by reduction and iron mediated cyclization provides 2,5-disubstituted tetrahydrofurans.

The development of improved protocols and strategies for the efficient construction of carbon-carbon bonds continues to be a challenge in organic synthesis. Among the vast array of established transformations, the α-alkylation of carbonyl compounds emerged as a powerful method for C–C bond formation.[1] Typically classical methods make use of electrophilic alkylating agents like alkyl halides and result in the formation of undesired salts as by-products.[2] As a greener and more economical alternative, the metal catalyzed α-alkylation of carbonyl, and its related compounds, with primary alcohols is attracting attention.[3] This method possesses significant advantages over conventional α-alkylation methods as it proceeds through a hydrogen autotransfer process ("borrowing hydrogen") in which water is the only generated waste product.[3] The overall process is a domino reaction based on the alcohol dehydrogenation which yields an aldehyde that undergoes aldol condensation with the existing carbonyl compound – commonly a methyl ketone – to afford an α,β-unsaturated carbonyl which is subsequently regioselectively reduced at the C–C double bond. Full reduction may also take place, affording a saturated secondary alcohol as the product. In this context, Cho *et al.* described the ruthenium catalyzed α-alkylation of ketones with primary alcohols leading to saturated secondary alcohols as major products.[4] In order to suppress the reduction of the carbonyl group, the same reaction was performed in the presence of 1-dodecene serving as a hydrogen acceptor.[5] Yus *et al.* reported the α-alkylation of ketones with benzylic alcohols using $[Ru(DMSO)_4Cl_2]$ as a phosphine free catalyst.[6] Heterogeneous palladium catalysts, such as palladium on carbon,[7] and palladium nanoparticles on a polymer[8] or entrapped in aluminium hydroxide [Pd/AlO(OH)][9] have also been applied in these processes.[10]

A catalytic system based on a $[Ir(cod)Cl]_2$–PPh_3–KOH combination was reported to be effective for the alkylation of ketones with primary alcohols and diols in the absence of solvent.[11] Iridium was also found to be an efficient catalyst for the α-alkylation of other functional groups such as nitriles or acetates.[12–14]

Given the features of the described transformations, we decided to investigate the possibility of integrating such a process into a more elaborate sequential protocol which would allow the synthesis of more complex structures in a sustainable manner. Herein, we report our designed strategy and its successful application in the diastereoselective synthesis of 2,5-disubstituted tetrahydrofurans (Scheme 1).[15]



Scheme 1 Proposed sequential strategy for the synthesis of tetrahydrofuran derivatives.

Due to its latent functionalization, solketal (**2**), which is readily available through the protection of glycerol with acetone,[16] was chosen as a hydrogen donor for the α-alkylation of acetophenone. A large range of bases was evaluated in the reaction of acetophenone (**1a**) with solketal (**2**) and the results are summarized in Table 1.

In the presence of K_2CO_3, the reaction of acetophenone with solketal proceeded with less than 10% conversion (Table 1, entry 1). Stronger bases like CsOH, NaOH and $Ba(OH)_2$ afforded the product in moderate yields (Table 1, entries 2–4). $LiOH·H_2O$ (40 mol%) proved to be the most successful base affording the desired product in 82% yield (Table 1, entry 7). In the presence of triethylamine no alkylation product could be detected (Table 1, entry 8). The same result was observed when the reaction was performed in the absence of a base.

With the optimized conditions for the alkylation reaction in hand, the reaction of various acetophenones with solketal was investigated using catalytic amounts of $[Ir(cod)Cl]_2$ (Table 2). Subsequent reduction with $NaBH_4$ afforded the corresponding secondary alcohols **4** in good to high yields. Acetal deprotection and cyclization mediated by $FeCl_3$ afforded 2,5-disubstituted

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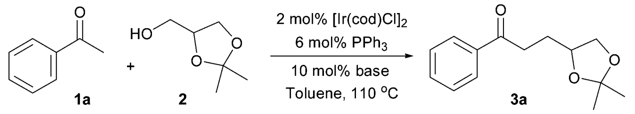
† Electronic supplementary information (ESI) available: General procedures, characterization data, and copies of the NMR spectra of the products are provided. See DOI: 10.1039/c1gc15764g

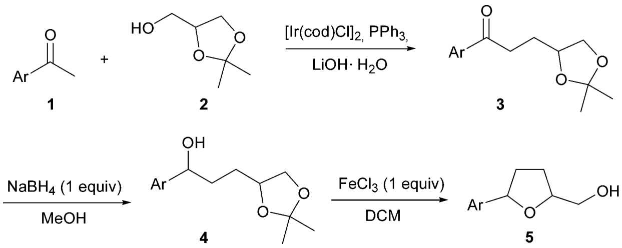
Table 1 Catalytic α-alkylation of acetophenone with solketal using $[Ir(cod)Cl]_2$ and different bases[a]

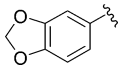
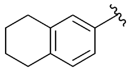
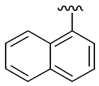
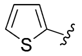


Entry	Base	Yield (%)[b]
1	K_2CO_3	8
2	CsOH	25
3	NaOH	48 (36 + 12)
4	$Ba(OH)_2$	53 (46 + 7)
5	KOH	61 (55 + 6)
6	$LiOH·H_2O$	68 (60 + 8)
7[c]	$LiOH·H_2O$	82 (73 + 9)
8	Et_3N	0
9	—	0

[a] **1a** (1 mmol) was reacted with solketal (**2**, 1.8 mmol) in the presence of Ir complex (2 mol%) and base (10 mol%) in toluene (0.2 mL) at 110 °C for 17 h. [b] Yield – numbers in the brackets represent the mixture of α-alkylated ketone (major) and alcohol. [c] $LiOH·H_2O$ (40 mol%) was used.

Table 2 Synthesis of 2,5-disubstituted tetrahydrofurans

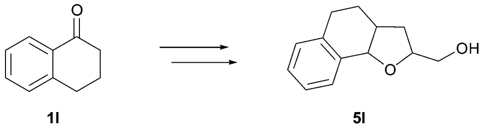


Entry	**1**, Ar	**4**, Yield (%)[a,b]	**5**, Yield (%)[c] (*trans* : *cis*)[d,e]
1	Ph	80	**5a**, 86 (1.8 : 1)
2	$4\text{-F–}C_6H_4$	87	**5b**, 88 (2.0 : 1)
3	$3\text{-}CF_3\text{–}C_6H_4$	82	**5c**, 81 (1.4 : 1)
4	$4\text{-}C_6H_5\text{–}C_6H_4$	93	**5d**, 89 (6.3 : 1)
5	4-*t*-Bu–C_6H_4	85	**5e**, 91 (3.8 : 1)
6	$3,4\text{-}CH_3\text{–}C_6H_3$	88	**5f**, 92 (3.3 : 1)
7	$4\text{-MeO–}C_6H_4$	86	**5g**, 90 (1.8 : 1)
8		91	**5h**, 89 (1.7 : 1)
9		86	**5i**, 88 (4.3 : 1)
10		84	**5j**, 83 (5.9 : 1)
11		77	**5k**, 74 (1 : 1)

[a] The reactions were carried out with **1** (1 mmol), solketal (**2**, 1.8 mmol) in the presence of $[Ir(cod)Cl]_2$ (2 mol%), PPh_3 (6 mol%) and $LiOH·H_2O$ (40 mol%) in toluene (0.2 mL) at 110 °C; solvent was removed and **3** was treated with 1 equiv. of $NaBH_4$ in methanol at 10 °C for 2 h. [b] Yield over two steps. [c] Alcohol **4** was treated with 1 equiv. of anhydrous $FeCl_3$ in DCM at room temperature for 45 min. [d] Diastereomeric ratio was determined by ^1H NMR spectroscopy. [e] The *trans* stereochemistry for the major diastereomer has been assigned according to the literature.[17e,f,h]

tetrahydrofurans **5** bearing a primary alcohol functional group in very good yields.[17]

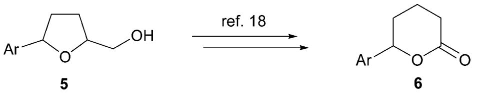
Moderate *trans*/*cis* isomeric ratios were observed with ketones bearing electron-withdrawing (Table 2, entries 2, 3) and electron-donating groups (Table 2, entries 7, 8) on the aryl substituent. Slightly better *trans*/*cis* selectivities were observed with substrates bearing *t*-Bu and Me groups (Table 2, entries 5, 6). Improved diastereomeric ratios were obtained for the substrates bearing biphenyl and naphthyl residues. (Table 2, entries 4, 10). The heteroaryl derivative **1k** afforded the desired product **5k** as a 1 : 1 diastereomeric mixture in good yields (Table 2, entry 11). Cyclic ketone **1l** worked well in the alkylation and reduction steps (**4l** 73% yield), however, the yield of the final step was moderate and the product was obtained as a 1 : 1 ratio of isomers (Scheme 2, **5l** 46% yield).



Scheme 2 Conversion of cyclic ketone **1l**.

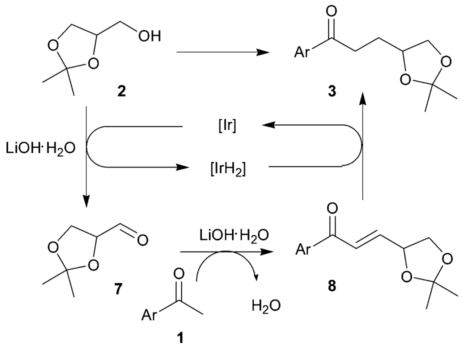
Furthermore, a one-pot three-step procedure that does not require chromatographic purification of any of the intermediates, proved to be feasible and the product **5a** has been obtained in an overall yield of 59%.

Subsequent derivatisation of the products is possible through oxidation of the primary alcohol to afford 5-phenyltetrahydrofuran-2-carbaldehydes which can easily be converted into the corresponding six-membered ring lactones **6** (Scheme 3).[18]



Scheme 3 Functionalization of the tetrahydrofuran derivatives **5**.

Regarding the reaction mechanism, it is assumed that the alkylation reaction follows the same pathway as the previously reported related transformations (Scheme 4).[3] In the first step, hydrogen transfer oxidation of the alcohol **2** gives aldehyde **7** and an iridium hydride. Base-catalyzed aldol condensation between aldehyde **7** and ketone **1** gives α,β-unsaturated ketone **8** which is hydrogenated by the Ir-hydride complex generated in the course of the reaction, to form the α-alkylated ketone **3**.



Scheme 4 Proposed mechanism for the α-alkylation of solketal.

In conclusion, a convenient and highly effective Ir-catalyzed α-alkylation of ketones with subsequent reduction and deprotection/cyclization methodology for the synthesis of valuable 2,5-disubstituted tetrahydrofurans was developed. Notably, commercially available substituted acetophenones as well as solketal a readily available derivative of the bulk chemical glycerol are used in the atom-economic transfer hydrogen reaction, whereby water is the only by-product. The subsequent reduction and deprotection/cyclization proceed under mild reaction conditions and afford 2,5-disubstituted tetrahydrofurans in good to high overall yields. In addition, a more practical, one-pot three-step procedure has been developed.

Acknowledgements

V.B.P. thanks the Alexander von Humboldt foundation for a post-doctoral research fellowship.

Notes and references

1 (*a*) D. Caine, in *Comprehensive Organic Synthesis*, vol. 3, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, pp. 1–63; (*b*) S. Carrettin, J. Guzman and A. Corma, *Angew. Chem., Int. Ed.*, 2005, **44**, 2242–2245; (*c*) *Modern Carbonyl Chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, 2000.

2 *Handbook of Green Chemistry and Technology*, ed. J. H. Clark and D. J. Macquarrie, Blackwell, Oxford, 2002.

3 For recent reviews (*a*) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358–2364; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753–762; (*c*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (*d*) F. Alonso, F. Foubelo, J. C. Gonzáles-Gómez, R Martínez, D. J. Ramón, P. Riente and M. Yus, *Mol. Diversity*, 2010, **14**, 411–424.

4 (*a*) C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *J. Org. Chem.*, 2001, **66**, 9020–9022. For a combined Ir–Ru catalytic system applied in the asymmetric alkylation of ketones with alcohols affording chiral secondary alcohols in good yields and excellent selectivities, see: (*b*) G. Onodera, Y. Nishibayashi and S. Uemura, *Angew. Chem., Int. Ed.*, 2006, **45**, 3819–3822.

5 C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *Tetrahedron Lett.*, 2002, **43**, 7987–7989.

6 (*a*) R. Martínez, G. J. Brand, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683–3686; (*b*) R. Martínez, D. J. Ramón and M. Yus, *Tetrahedron*, 2006, **62**, 8988–9001.

7 C. S. Cho, *J. Mol. Catal. A: Chem.*, 2005, **240**, 55–60.

8 Y. M. A. Yamada and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375–1378.

9 M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem., Int. Ed.*, 2005, **44**, 6913–6915.

10 For the alkylation of methyl ketones with primary alcohols promoted by Nickel nanoparticles (1 equiv), see: F. Alonso, P. Riente and M. Yus, *Synlett*, 2007, 1877–1880.

11 (*a*) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72–73. For the reaction of ketones with diols leading to diketones, see; (*b*) K. Maeda, Y. Obora, S. Sakaguchi and Y. Ishii, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 689–696.

12 Iridium catalyzed alkylation of nitriles: (*a*) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep and A. Derrick, *J. Org. Chem.*, 2006, **71**, 8023–8027. Rhodium catalyzed alkylation of nitriles; (*b*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *Tetrahedron Lett.*, 1981, **22**, 4107–4110. Ruthenium catalyzed alkylation of nitriles; (*c*) K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2004, **126**, 5662–5663.

13 Iridium catalyzed alkylation of acetates: Y. Iuchi, Y. Obora and Y. Ishii, *J. Am. Chem. Soc.*, 2010, **132**, 2536–2537.

14 For the Ir catalyzed alkylation of other substrates with alcohols (C–C bond formation): (*a*) M. G. Edwards and J. M. J. Williams, *Angew. Chem., Int. Ed.*, 2002, **41**, 4740–4743; (*b*) C. Löfberg, R. Grigg, A. Keep, A. Derrick, V. Sridharan and C. Kilner, *Chem. Commun.*, 2006, 5000–5002; (*c*) P. J. Black, G. Cami-Kobeci, M. G. Edwards, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Org. Biomol. Chem.*, 2006, **4**, 116–125; (*d*) M. Morita, Y. Obora and Y. Ishii, *Chem. Commun.*, 2007, 2850–2852; (*e*) S. Whitney, R. Grigg, A. Derrick and A. Kepp, *Org. Lett.*, 2007, **9**, 3299–3302; (*f*) K.-I. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, **7**, 4017–4019; (*g*) D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton and R. H. Crabtree, *Org. Biomol. Chem.*, 2008, **6**, 4442–4445.

15 For a recent review on the diastereoselective synthesis of 2,5-disubstituted tetrahydrofuranes, see: G. Jalce, X. Franck and B. Figadère, *Tetrahedron: Asymmetry*, 2009, **20**, 2537–2581.

16 (*a*) C. X. A. da Silva, V. L. C. Goncalves and C. J. A. Mota, *Green Chem.*, 2009, **11**, 38–41; (*b*) A. Behr, J. Eilting, K. Irawadi, J. Leschinski and F. Lindner, *Green Chem.*, 2008, **10**, 13–30.

17 For alternative protocols, see: (*a*) S. Inoki and T. Mukaiyama, *Chem. Lett.*, 1990, 67–70; (*b*) J. Berninger, U. Koert, C. Eisenberg-Höhl and P. Knochel, *Chem. Ber.*, 1995, **128**, 1021–1028; (*c*) K. Miura, T. Hondo, S. Okajima and A. Hosomi, *Tetrahedron Lett.*, 1996, **37**, 487–490; (*d*) K. Miura, T. Hondo, T. Takahashi and A. Hosomi, *Tetrahedron Lett.*, 2000, **41**, 2129–2132; (*e*) K. Miura, S. Okajima, T. Hondo, T. Nakagawa, T. Takahashi and A. Hosomi, *J. Am. Chem. Soc.*, 2000, **122**, 11348–11357; (*f*) J. Hartung, S. Drees, M. Greb, P. Schmidt, I. Svoboda, H. Fuess, A. Murso and D. Stalke, *Eur. J. Org. Chem.*, 2003, 2388–2408; (*g*) B. M. Pérez, D. Schuch and J. Hartung, *Org. Biomol. Chem.*, 2008, **6**, 3532–3541; (*h*) C. Palmer, N. A. Morra, A. C. Stevens, B. Bajtos, B. P. Machin and B. L. Pagenkopf, *Org. Lett.*, 2009, **11**, 5614–5617.

18 L. Wang, K. Thai and M. Gravel, *Org. Lett.*, 2009, **11**, 891–893.