Green alcohol couplings without transition metal catalysts: base-mediated β-alkylation of alcohols in aerobic conditions†

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Benzylic secondary alcohols can be alkylated in good yields at the β-position with primary alcohols promoted by KOH and NaOH, eliminating the need for toxic and expensive transition metal catalysts.

Avoidance of mutagenic and waste-forming reagents is a fundamental strategy for green transformations.[1] With this in mind, modern processes are emerging to replace conventional routes to common synthetic building blocks. For example, the traditional route to β-alkylated alcohols from a secondary alcohol requires a three-step procedure that involves stoichiometric oxidation, alkylation with an alkyl halide, and finally, stoichiometric reduction (Scheme 1).[2–5]
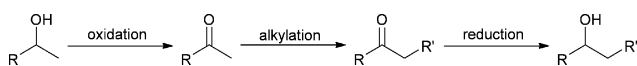
Scheme 1 Classic route to β-alkylated products.

As latent electrophiles, alcohols can replace the mutagenic halide because carbonyl derivatives are produced upon oxidation. One of the first reports of one-pot β-alkylation reactions of secondary alcohols involved $RuCl_2(PPh_3)_3$ as a catalyst; however, the reaction was not atom-economical due to the super-stoichiometric use of base (potassium hydroxide), H_2 acceptor (1-dodecene), and H_2 donor (dioxane) required for H_2 transfer to and from the metal.[6] A subsequent study revealed [Cp*IrCl$_2$]$_2$, along with stoichiometric base, as an active catalyst for the reaction.[4] Efficient β-alkylation was seen in our group with ruthenium and iridium catalysts under nitrogen (N_2) atmosphere or even in air (Scheme 2).[7,8] This strategy significantly decreased the reaction time (to as little as 30 min) over previous systems, which required between 8–24 h.[3,4,6,9,10]
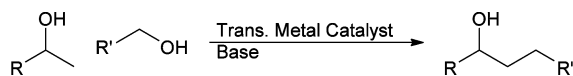
Scheme 2 One-pot β-alkylation.

These systems are examples of green reactions because they minimize waste formation, avoid the use of protecting groups, and maximize atom economy, leaving only water as a by-product.[1] Nevertheless, this system could be improved further by lowering the base to sub-stoichiometric amounts,[3,7,11] lowering the reaction temperature, and using less toxic metals. The only previous reports on homogeneous catalysts for β-alkylation of secondary alcohols involve complexes of ruthenium and iridium, which are considered to be metals with safety concerns.[12–14]

Important recent studies have shown the use of alkali metal bases for oxidation of alcohols to the corresponding carbonyl through an Oppenauer pathway and reduction of aldehydes and ketones to alcohols through a Meerwein–Ponndorf–Verley (MPV) type mechanism.[15–17] We now show that alkali metal bases can also mediate the β-alkylation of secondary alcohols with primary alcohols in good yield.

All of the previous reported systems for β-alkylation have relied on a transition metal catalyst together with a base, such as potassium hydroxide, for product formation. From control reactions in our transition metal studies, we have found that the metal catalyst is not required – simple alkali metal bases are sufficient. In view of the much lower cost of bases, such as KOH, over the majority of transition metal catalysts, the new procedure has been studied in detail. Because many of the previous systems relied on KOH, we started our optimization with this alkali metal hydroxide (Table 1). KOH shows complete conversion of 1-phenylethanol and benzyl alcohol to the corresponding β-alkylated products within 4 h (78% alcohol, 21% ketone, entry 2) in aerobic and solventless conditions. Other bases examined include NaOH, K_2CO_3, Cs_2CO_3, K_3PO_4, KO^{t}Bu, and Ba(OH)$_2$. NaOH took longer than KOH for complete consumption of

Table 1 Comparison of bases for β-alkylation[a]

Entry	Base	Time (h)	Conversion (%)[b]	Yield (%)[c]	Alcohol : ketone
1	Cs_2CO_3	26	55	6	83 : 17
2[d]	KOH	4	99	99	78 : 21
3	KOH[e]	4	99	76	83 : 17
4	NaOH	4	95	69	93 : 7
5	NaOH[e]	5	85	75	99 : 1
6	NaOH[e]	25[f]	100	81	37 : 63
7	KO^{t}Bu	4	90	72	86 : 14
8	K_2CO_3	20	5	2.5	1 : 1
9	K_3PO_4	20	0	0	—
10	Ba(OH)$_2$	20	43	24	42 : 58
11[g]	KOH	20	18	15	100 : 0

[a] Conditions: 2.0 mmol 1-phenylethanol and benzyl alcohol, 100 mol% base, 0.75 mL toluene (reflux), open to air. [b] Conversions were determined by consumption of the 1° alcohol. [c] Yields were determined by ^{1}H NMR using an internal standard (1,3,5-trimethoxybenzene). [d] Reaction completed in solventless conditions. [e] Denotes use of semiconductor-grade metal hydroxide. [f] Continuation of entry 5 for an additional 20 h. [g] N_2 atmosphere.

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starting materials, but showed greater selectivity for the alcohol product. Because reagent-grade KOH and NaOH are known to have transition metal contaminants, semiconductor-grade KOH and NaOH, 99.99% pure based on trace metal analysis (Sigma-Aldrich), were also examined (entries 3, 5, 6). As seen in Table 1, the use of semiconductor-grade NaOH and KOH did not dramatically change the product distribution or yield *versus* the reagent-grade base. The product of alcohol to ketone does, however, change dramatically over time, most likely due to aerobic oxidation (entry 6). When the reaction was run under nitrogen atmosphere, we found only 18% conversion of the starting material and only the alcohol alkylation product in 15% yield (entry 11).

With the success of the general reaction with 1-phenylethanol and benzyl alcohol, the substrate scope was examined. KOH shows moderate to good yields with various derivatives of benzyl alcohol and 1-phenylethanol; however, some substrates required longer reaction times (Table 2). With aliphatic alcohols, KOH mediates the reaction of primary alcohols with 1-phenylethanol (entries 13 and 14) but not the reaction of secondary alcohols with benzyl alcohol (entries 15 and 16).

In many cases the conversion was quantitative but the product yields were somewhat lower. We noted that an insoluble, unidentifiable polymer was formed for the majority of the reactions. As shown in Tables 1 and 2, the ratio of alcohol to ketone was generally high. Even on prolonged reaction in air, the alcohol was never completely oxidized to the ketone (Table 1, entry 6). The role of the alkali metal was probed by addition of a sequestering agent. When 18-crown-6, a known potassium chelator, was added, no reaction was seen, suggesting direct potassium involvement in the mechanism.

The mechanism for transition-metal-catalyzed β-alkylation has previously been attributed to a "hydrogen-borrowing" process in which both alcohols are oxidized, followed by an aldol condensation with loss of water, and finally reduction to give alcohol product.[18] Because no transition metal is included

in our reaction mixtures, another pathway must be responsible for product formation. We propose that air oxidation of the secondary alcohol produces some ketone that is required for an Oppenauer mechanism to operate, followed by a base-assisted aldol reaction to give the enone, and then an MPV reduction and isomerization to give the observed products (Scheme 3). Both *trans*-chalcone and (*E*)-1,3-diphenylprop-2-en-1-ol are converted to the alcohol and ketone products under KOH conditions with either primary or secondary alcohol as reductant, supporting the proposed pathway.
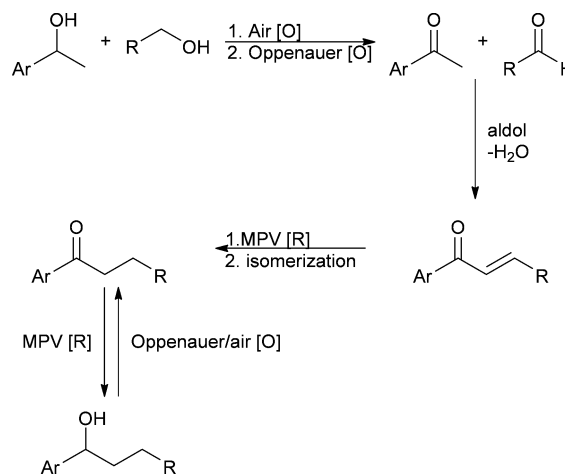
Scheme 3 Possible route for β-alkylation.

In conclusion, the atom-economical one-pot β-alkylation of secondary alcohols with primary alcohols has been demonstrated to proceed without requiring transition metal catalysts. Inexpensive alkali metal hydroxides (NaOH or KOH, 1.0 eq.) promote the reaction in air with various 1-phenylethanol derivatives and primary alcohols to give the β-alkylated product in good yields. Further mechanistic studies are underway to

Table 2 β-alkylation of secondary alcohols with primary alcohols catalyzed by alkali metal hydroxides

Entry[a]	R	R′	Base	Time (h)	Conversion (%)[b]	Yield (%)[c]	Alcohol : ketone
1	Ph	Ph	KOH, neat	4	99	99	78 : 21
2	Ph	p-BrC$_6$H$_4$	KOH, neat	4	97	93	89 : 11
3	Ph	p-BrC$_6$H$_4$	NaOH	23	100	76	63 : 37
4	Ph	p-ClC$_6$H$_4$	KOH	4	100	79 (63)[d]	87 : 13
5	Ph	p-ClC$_6$H$_4$	NaOH	25	100	66	42 : 58
6	Ph	p-^{t}BuC$_6$H$_4$	KOH	4	91	85 (62)[d]	90 : 10
7	Ph	p-^{t}BuC$_6$H$_4$	NaOH	4	90	92	87 : 13
8	Ph	p-MeC$_6$H$_4$	KOH	4	97	94	66 : 34
9	p-ClC$_6$H$_4$	Ph	KOH	4	98	68	95 : 5
10	p-MeC$_6$H$_4$	Ph	KOH	4	86	71	90 : 10
11	Ph	p-^{n}BuOC$_6$H$_4$	KOH	4	100	100 (80)[d]	90 : 10
12	Ph	PhCH$_2$	KOH	22	0	0	—
13	Ph	^{n}Pentyl	KOH	20	59	28	100 : 0
14	Ph	^{n}Pr	KOH	20	13	10	100 : 0
15	^{n}Pr	Ph	KOH	20	0	0	—
16	Et	Ph	KOH	20	0	0	—

[a] Conditions: 2.0 mmol 1° and 2° alcohol, 100 mol% base, 0.75 mL toluene (reflux), open to air. [b] Conversions were determined by consumption of the 1° alcohol. [c] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] Isolated yields.

determine the role of base in the reaction. These data indicate that base-only control reactions are needed for transition-metal-catalyzed versions, and that some previous conclusions in aerobic systems may need to be re-examined in light of this work.

Experimental

All reagents were received from commercial sources and used without further purification. Toluene and dichloromethane were dried with a solvent purification system using a 1 m column containing activated alumina. ^{1}H NMR spectra were obtained at room temperature using CDCl₃ as solvent on 400 and 500 MHz Bruker spectrometers.

General procedure

Secondary alcohol (2.0 mmol), primary alcohol (2.0 mmol), and base (2.0 mmol) were combined in a 5 mL round-bottomed flask equipped with a micro stir-bar, toluene (0.75 mL) and a reflux condenser. The reaction was refluxed for the appropriate amount of time and then cooled to room temperature. The reaction mixture was then quenched with 0.5 M citric acid, diluted with ethyl acetate, washed with distilled water and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give the crude product, which was further purified by flash column chromatography.

1-Phenyl-3-*p*-tolylpropan-1-ol. ^{1}H NMR: (400 MHz, CDCl₃) 7.36 (4 H, d, *J* 4.3), 7.30 (1 H, dt, *J* 4.4, 9.0), 7.10 (4 H, s), 4.69 (1 H, m), 2.77–2.59 (2 H, m), 2.33 (3 H, s), 2.19–1.96 (2 H, m). ^{13}C NMR: (126 MHz, CDCl₃) 144.70, 138.75, 135.26, 129.11, 128.49, 128.37, 127.57, 126.01, 73.82, 40.59, 31.61, 21.05.

3-(4-*tert*-Butylphenyl)-1-phenylpropan-1-one. ^{1}H NMR: (400 MHz, CDCl₃) 7.95 (2 H, dd, *J* 1.2, 8.4), 7.57 (1 H, dd, *J* 4.2 10.5), 7.47 (2 H, t, *J* 7.6), 7.36 (2 H, d, *J* 8.3), 7.22 (2 H, d, *J* 8.1), 3.38–3.26 (2 H, m), 3.13–2.99 (2 H, m), 1.33 (9 H, s). ^{13}C NMR: (101 MHz, CDCl₃) 199.53, 149.10, 138.33, 137.02, 133.16, 128.73, 128.22, 125.55, 40.62, 34.52, 31.53, 29.71.

References

1 P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*, Oxford University Press, Oxford/New York, 1998.
2 K. Sawatari, Y. Nakanishi and T. Matsushima, *Ind. Health*, 2001, **39**, 341–345.
3 H. W. Cheung, T. Y. Lee, H. Y. Lui, C. H. Yeung and C. P. Lau, *Adv. Synth. Catal.*, 2008, **350**, 2975–2983.
4 K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, **7**, 4017–4019.
5 B. M. Trost and I. Fleming, *Comprehensive organic synthesis: selectivity, strategy, and efficiency in modern organic chemistry*, Pergamon Press, Oxford/New York, 1991.
6 C. S. Cho, B. T. Kim, H. S. Kim, T. J. Kim and S. C. Shim, *Organometallics*, 2003, **22**, 3608–3610.
7 D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton and R. H. Crabtree, *Org. Biomol. Chem.*, 2008, **6**, 4442–4445.
8 D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito and R. H. Crabtree, *Organometallics*, 2009, **28**, 321–325.
9 R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8982–8987.
10 A. Prades, M. Viciano, M. Sanau and E. Peris, *Organometallics*, 2008, **27**, 4254–4259.
11 K. Shimizu, R. Sato and A. Satsuma, *Angew. Chem., Int. Ed.*, 2009, **48**, 3982–3986.
12 *Guideline on the specification limits for residues of metal catalysts or metal reagents*, European Medicines Agency: Committee for medicinal products for human use. Doc. ref: EMEA/CHMPSWP/4446/2000. London, 2008, http://www.ema.europa.eu/pdfs/human/swp/444600enfin.pdf (34 pp).
13 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.
14 Shimizu, *et al.* (ref. 11) report a heterogeneous catalyst for β-alkylation of secondary alcohols with primary alcohols to give the ketone product using alumina-supported silver subnanoclusters.
15 V. Polshettiwar and R. S. Varma, *Green Chem.*, 2009, **11**, 1313–1316.
16 A. Ouali, J.-P. Majoral, A.-M. Caminade and M. Taillefer, *ChemCatChem*, 2009, **1**, 504–509.
17 J. R. Miecznikowski and R. H. Crabtree, *Organometallics*, 2004, **23**, 629–631.
18 M. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575.