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A novel, solventless reductive coupling of carbonyl compounds by alkali metals, catalysed by bromobenzene

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Catalysed by bromobenzene, alkali metals including Li, Na, and K can mediate the reductive coupling of carbonyl compounds under mild, solventless conditions to furnish the corresponding pinacol products.

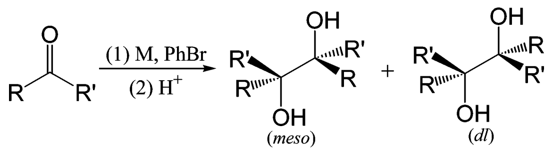
Reductive coupling of carbonyl compounds is one of the most important reactions for the formation of carbon–carbon bonds.[1] Its mechanism and applications have been intensively studied for many years.[2] Recently the reductive coupling of carbonyl compounds have been used in the synthesis of HIV-protease inhibitors[3] and some natural products such as taxol.[4]

Metals including Na,[5] Zn,[6] Mg,[7] Mn,[8] In,[2] Ti,[9] Sm,[2] Al,[10] and Ce[11] have been found to be able to mediate the reductive coupling of carbonyl compounds. Organic solvents such as dichloromethane,[6] tetrahydrofuran,[12] and dimethoxyethane (DME)[13] are generally used in these reactions. For economic and ecological reasons the use of aqueous media to conduct reductive carbonyl couplings has recently attracted considerable interest.[6,14]

We sought to find the conditions for a cleaner reductive carbonyl coupling. Therefore, we attempted to conduct carbonyl coupling in a solventless and catalytic fashion. Interestingly, we found that catalysed by bromobenzene, alkali metals including Li, Na, and K can mediate the reductive coupling of carbonyl compounds under mild, solventless conditions. Using this method, the yield as well as the diastereoselectivity of the coupling is quite high.

Typical procedures for the reductive coupling are as follows: to a mixture of 3.5 ml of benzophenone (30 mmol) and a catalytic amount of bromobenzene (3 mmol) is added 0.9 g of small pieces of sodium (39 mmol). The reaction mixture is stirred at ambient temperature for 5 h. Inert gas (N_2 or Ar) protection is not necessary in the reaction. After the reaction is completed, 1 ml of ethanol was added into the mixture to quench the remaining sodium. The mixture is neutralized with 2 M hydrochloric acid (Scheme 1). The products are separated using flash column chromatography over silica gel. The detailed results for the reductive couplings of different substrates are summarized in Table 1.

According to Table 1, it can be seen that in the absence of bromobenzene, the yield of the coupling is very low (14%). In comparison, when bromobenzene is added the yield of the coupling improves. In addition, the added bromobenzene could be fully recovered after the reaction. Therefore, bromobenzene is a catalyst for the coupling. Because of the catalytic effect of bromobenzene, the coupling can be conducted under very mild conditions (solventless, room temperature, no inert gas protection). Such reaction conditions should be compared to the previously reported reductive coupling of acetone mediated by sodium or lithium metal, which is conducted in liquid ammonia or THF.[5]



M = Li, Na, K; R = aryl, alkyl; R' = H, alkyl

Scheme 1

The required reaction time decreases in the order Li > Na > K. This order is consistent with the order of reactivity of each alkali metal. Nevertheless, because of the high reactivity, use of K usually leads to lower yield of the desired products. The yields for the use of Li and Na are similar. The diastereoselectivity of the catalytic reductive coupling is mostly quite high. Comparing entries 2, 3, and 4 of Table 1, we can see that a faster reaction is favourable for the *dl* products. For aromatic ketones and aldehydes, electron-withdrawing substituents on the phenyl ring are favourable for the *dl* products, whereas electron-donating substituents are favourable for the *meso* products (entry 5–11). Cyclohexanone shows less reactivity than the aromatic ketones in the reductive coupling.

Interestingly, although the reductive coupling can be conducted without any inert gas protection, use of nitrogen protection significantly increases diastereoselectivity of the coupling (entry 12 and 13). The cause of this observation remains to be clarified.

Use of organic solvents does not favour the coupling. In fact, when the coupling is conducted in tetrahydrofuran or in *N,N*-dimethylformamide, the yield of the coupling of $PhCOCH_3$ decreases to 8% or 2%.

Other metals such as Mg powder or pieces, which could also be used in the reductive coupling of carbonyl compounds, do not provide any product under the present reaction condition

Table 1 Products and yields of the reductive coupling of aldehydes or ketones

Entry	Carbonyl compounds	Metal[a]	Yield (%)[b]	*dl*:*meso*[c]
1	$PhCOCH_3$	Li[d]	14	69:31
2	$PhCOCH_3$	Li	87	74:26
3	$PhCOCH_3$	Na	93	77:23
4	$PhCOCH_3$	K	47	84:16
5	p-$CH_3C_6H_4COCH_3$	Li	77	25:75
6	p-$CH_3OC_6H_4COCH_3$	Na	86	*meso* only
7	2,4-$Cl_2C_6H_3CHO$	Li	90	*dl* only
8	o-ClC_4H_4CHO	Li	81	*dl* only
9	$PhCH{=}CHCOCH_3$	Li	75	*dl* only
10	p-$ClC_6H_4COCH_3$	Na	84	96:4
11	p-$BrC_6H_4COCH_3$	Na	84	99:1
12	PhCHO	Li	75	65:35
13	PhCHO	Li[e]	84	99:1
14	Cyclohexanone	Li	54	—
15	Cyclohexanone	Na	52	—
16	Cyclohexanone	K	34	—

[a] The reaction time is 6–8 hours for Li, 2–4 hours for Na, and 1 hour for K, respectively. [b] Isolated yield. [c] Ratios were determined from ^1H NMR (400 MHz) and GC-MS analyses of the isolated products. [d] Reaction performed in the absence of bromobenzene. [e] Reaction performed under nitrogen protection.

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even after prolonged reaction time (48 h). This may be due to the fact that the alkali metals are much more electropositive than other metals. Magnesium oxide on the surface of magnesium metal may also obstruct the reaction.

Chlorobenzene and iodobenzene can also catalyse the reductive coupling, but their efficiency is slightly worse than that of bromobenzene. For example, for the coupling of $PhCOCH_3$ the yields associated with chlorobenzene, iodobenzene, and bromobenzene are 76%, 74%, and 87%, respectively. Another catalyst we found for the reductive coupling is naphthalene. However, for the coupling of $PhCOCH_3$ using naphthalene as the catalyst can only give a yield of 24%.

Addition of *p*-dinitrobenzene completely inhibits the coupling, as it can capture the electron and turn into a radical anion as indicated by the electron paramagnetic resonance (ESR) spectrum (Fig. 1).[15] Interestingly, this ESR signal does not appear if either bromobenzene or the metal is not added to the reaction mixture. We could not observe the ESR spectrum of bromobenzene radical anion in the reaction, possibly because this radical anion is too reactive. However, as long as both metal and bromobenzene are added, the ESR signal appears in the absence of the carbonyl compound. All these observations indicate that *p*-nitrobenzene inhibits the reaction because it captures the electron carried by the bromobenzene radical anion.[16] (Scheme 2).

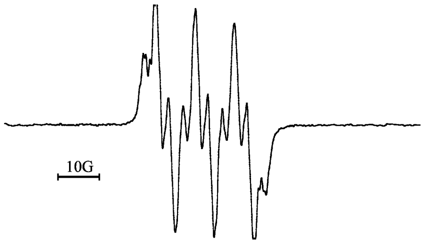
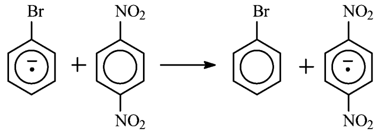
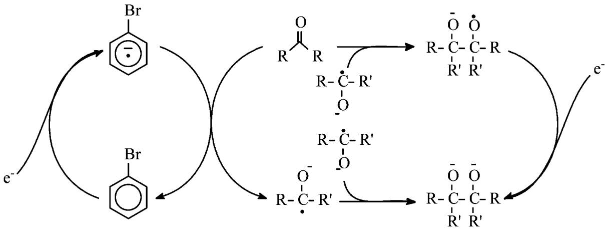


Fig. 1 EPR spectrum of *p*-dinitrobenzene radical anion.



Scheme 2

On the basis of the above observations, we propose a mechanism for the catalytic reductive coupling (Scheme 3). According to this mechanism, bromobenzene obtains one electron from the alkali metal and becomes a radical anion. Then bromobenzene radical anion transfers an electron to the carbonyl compound, which is consequently turned into the coupling products as discussed before.[16] Bromobenzene makes the reaction more efficient because the electron transfer rate is higher between the alkali metal and bromobenzene than between the alkali metal and carbonyl compound.



Scheme 3

In summary, we found a novel bromobenzene-catalysed reductive coupling reaction of carbonyl compounds. The reaction can be conducted under very mild conditions. The yields are usually good. The diastereoselectivity is mostly high. A single electron transfer mechanism is proposed for the coupling.

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