Tert-Butoxide-Mediated Protodeformylation of Tertiary Homobenzaldehydes

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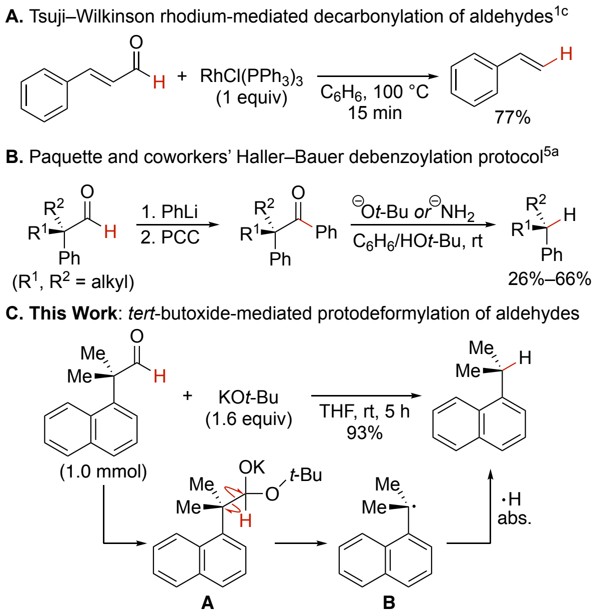
Supporting Information Placeholder

ABSTRACT: *Tert*-butoxide mediates the protodeformylation of tertiary homobenzaldehydes and related compounds at ambient temperature. Both geminal dialkyl and geminal diaryl substituents are tolerated. Monocyclic aromatic homobenzaldehydes require cyclic *gem*-dialkyls or *gem*-diaryls for efficient protodeformylation, whereas *gem*-dimethyls are sufficient for protodeformylation of polycyclic arenyl substrates. Our data suggest a stabilized radical is generated upon attack of the aldehyde by *tert*-butoxide.

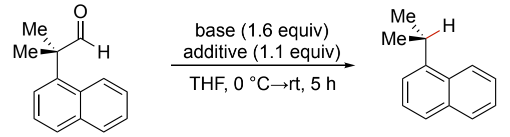
The decarbonylation of aldehydes is an important C–C bond-cleaving reaction. Decarbonylations mediated by stoichiometric rhodium complexes at high temperature like the one shown Scheme 1A were first developed by Tsuji and Wilkinson[1] and are notable for their application in natural products total synthesis;[2] flow-type alternatives have been developed to lower the cost.[3] The Haller–Bauer *tert*-butoxide-mediated protodebenzoylation has been used as the third step of aldehyde protodeformylation sequences (Scheme 1B).[4,5] A few other examples of aldehyde decarbonylation have been reported, but have not been generalized.[6–8] Herein we describe an ambient temperature *tert*-butoxide-mediated protodeformylation of inherently non-enolizable tertiary homobenzaldehydes and related compounds via a putative stabilized tertiary benzylic radical **B** generated from unstable *tert*-butoxide adduct **A** (Scheme 1C). Invoking *tert*-butoxide as a nucleophilic mediator is somewhat uncommon.[9–11]

Scheme 1. Aldehyde Decarbonylation Methods



In the course of developing new alkene functionalization reactions of tertiary homobenzylstyrenes and related compounds[12] we occasionally observed competing decarbonylation of the precursor tertiary homobenzaldehydes[13] during Wittig olefination if excess *tert*-butoxide was present. We sought to optimize this process using a homonaphthaldehyde substrate (Table 1). Excitingly, 1.6 equivalents of KO*t*-Bu afforded full substrate conversion and good yield at ambient temperature (entry 1). Solvent evaluation revealed that DMF was also well tolerated (entry 2), while HO*t*-Bu inhibited the reaction (not shown).[14] Decarbonylation was largely prevented when the reaction

Table 1. Optimization of the Aldehyde Protodeformylation[a]



entry	base[b]	additive	conv. (%)	yield (%)
1	KO*t*-Bu	none	>95	89
2[c]	KO*t*-Bu	none	>95	74
3[d]	KO*t*-Bu	O_2 (ambient)	>95	17
4	KO*t*-Bu	TEMPO	78	62
5[e]	KO*t*-Bu	4 Å mol. sieves	>95	70
6	NaO*t*-Bu	none	>95	87
7	LDA	none	>95	<5
8[f]	KOH	HO*t*-Bu	<5	n.d.
9	KOH	none	<5	n.d.

[a] Reactions were conducted on 0.1 mmol scale in 1.1 mL of solvent under an atmosphere of N_2 unless otherwise noted. Conversions and yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. N.d. = not detected. [b] Base formulations unless otherwise noted: KO*t*-Bu (1.6 M solution in THF); KOH (solid); LDA (2.0 M solution in THF/*n*-heptane/ethylbenzene); NaO*t*-Bu (2.0 M in THF). [c] Used solid KO*t*-Bu and DMF as solvent. [d] Reaction was conducted open to air. [e] Used 100% w/w of molecular sieves. [f] Base and 1.6 equiv of HO*t*-Bu sonicated for 5 minutes.

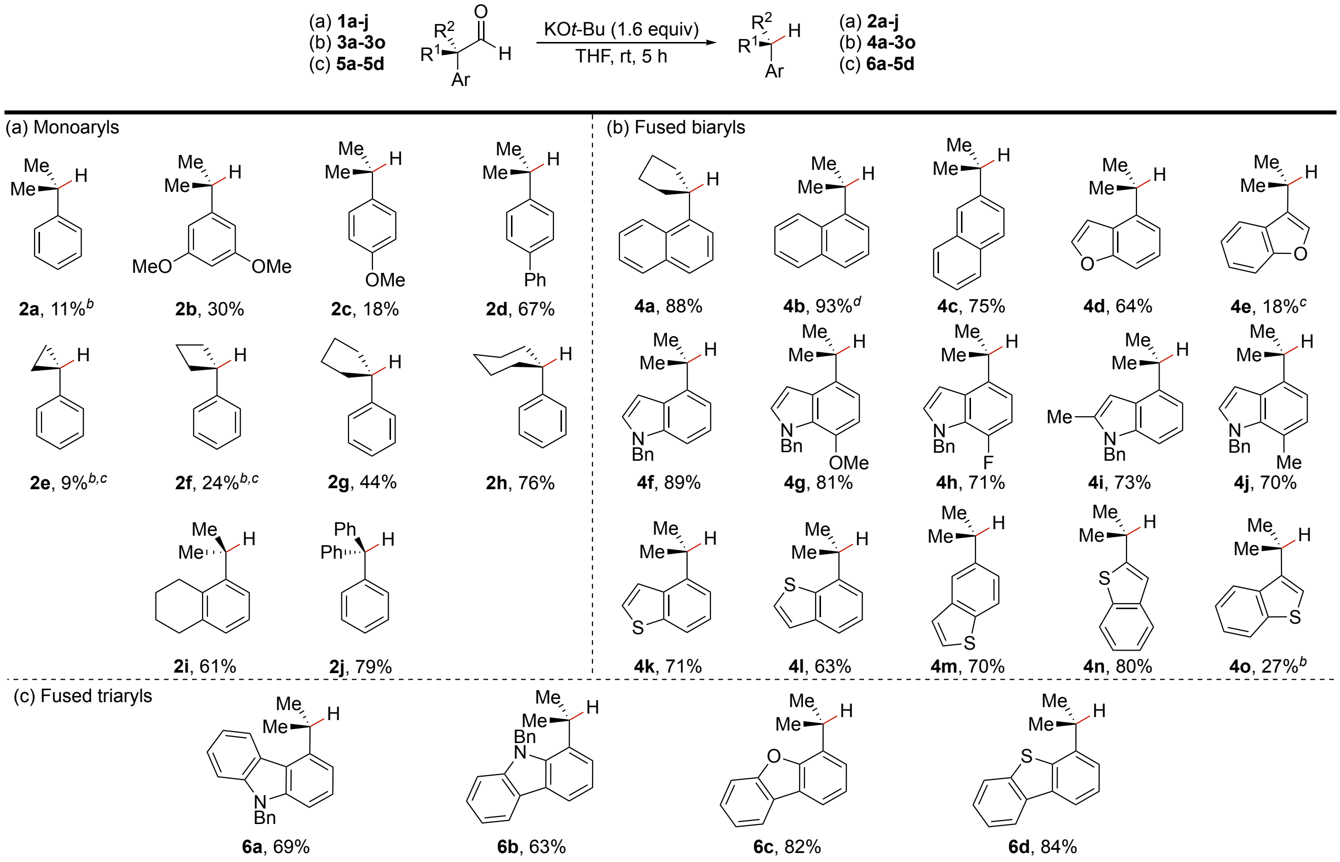


Table 2. Evaluation of the generality of the *tert*-butoxide-mediated protodeformylation of tertiary aldehydes. [a] Reactions were conducted on 0.2 mmol of aldehyde (0.09 M in THF) unless otherwise noted, and yields refer to isolated yields unless otherwise noted. [b] Yield was measured by ^{1}H NMR using 1,3,5-trimethoxybenzne as an internal standard. [c] Product is volatile under high vacuum. [d] Reaction was executed on 1.0 mmol scale of **3b**.

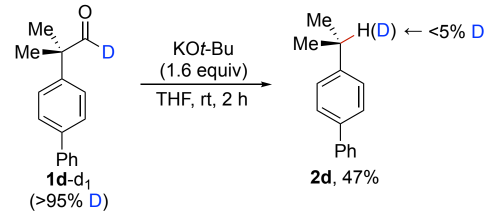
was executed open to air, (entry 3) and adding TEMPO inhibited reaction conversion significantly (entry 4). Conversion decreased slightly when molecular sieves were employed (entry 5). NaO*t*-Bu was similarly effective (entry 6), but lithium di-*iso*-propyl amide (LDA) led to decomposition (entry 7).[15] Potassium hydroxide afforded no reaction in aprotic or protic solvents (entries 8 and 9, respectively).

In terms of breadth of scope (Table 2a), phenyl analogs of the naphthyl substrate afford lower yield than the aforementioned naphthyl analog (**1a**–**1c**). In particular, **2a** is only observed in 11% NMR yield, although the yield can be improved significantly by substituting with a *para* phenyl group, which affords access to **2d** in 67% yield. Strained cyclic *gem*-dialkyl-containing substrates like α-cyclopropyl (**1e**) and α-cyclobutyl (**1f**) are decarbonylated in just 9% and 24% yield, whereas cyclopentyl (**1g**) and cyclohexyl (**1h**) substrates are isolated in useful yield (44% and 76%, respectively). Other monoaryl substrates evaluated include tetralin **1i** and triphenylacetaldehyde **1j**, both of which undergo decarbonylation in good yield (61% and 79%, respectively).

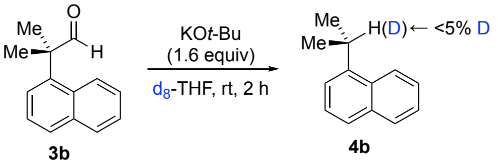
Compared to many of the examples in Table 2a, fused biaryl substrates afford generally excellent yields (Table 2b), which suggests the reaction may proceed via a benzylic radical intermediate. For example, cyclopentane-containing product **4a** is accessed in twice as high a yield as the corresponding monocyclic arene **2g**. A 1.0 mmol scale reaction of 1-naphthyl substrate **3b** affords the best yield we observed (93% of **4b**). 2-Naphthyl analogue **4c** is also accessed in good yield, as is 4-substituted benzofuran **4d**, but 3-substituted benzofuran analogue **4e** cannot be prepared efficiently; rather, a dearomatized byproduct is formed in higher yield (see below). A number of benzyl-protected indole analogues with the aldehyde linked at the 4-position are also decarbonylated efficiently (**3f**–**3j**). Decarbonylation of other heteroaromatic substrates, such as benzothiophenes, is also generally fruitful (**4k**–**4n**), except when the aldehyde is linked to the 3-position as in **3o**, which may be prone to dearomatization like **3e** is.

We also evaluated four fused tricyclic arenes including carbazoles (**5a** and **5b**), a dibenzothiophene (**5c**), and a dibenzofuran (**5d**), all of which afford the corresponding decarbonylated products in good yield (Table 2c).

Attempts to trap the putative cleavage intermediate with exogenous electrophiles including Selectfluor®, bromoethane, and D_2O were made, but neither F, nor Br, nor D were incorporated, respectively (see Supporting Information for details). To rule out a canonical decarbonylation, deuteriated aldehyde **1d**-**d$_1$** was prepared and afforded a 20% reduction in yield compared to **1d**, with no deuterium observed by ^{1}H NMR at the benzylic position of **2d** (eq 1). Employing d_8-THF as a potential •D trap also yielded no appreciable deuteriation (eq 2).



(1)



(2)

A hypothetical mechanism is shown in Scheme 1C above, wherein attack by *tert*-butoxide forms congested intermediate **A** which may homolyze to give stabilized radical **B** followed by hydrogen radical abstraction.[16] In addition to the reaction inhibition caused by air and TEMPO (Table 1, entries 3 and 4), support for a radical mechanism is derived from the case of substrate **3e**, wherein the alkyl aldehyde is attached to C3 of the benzofuran. In this case, dihydrobenzofuran **7** is isolated as the major product (Figure 2). This kinetic product could manifest as a result of delocalization of the radical onto the oxygen atom (as in **D→D'**), whereas the corresponding anionic intermediate **E** is destabilized.

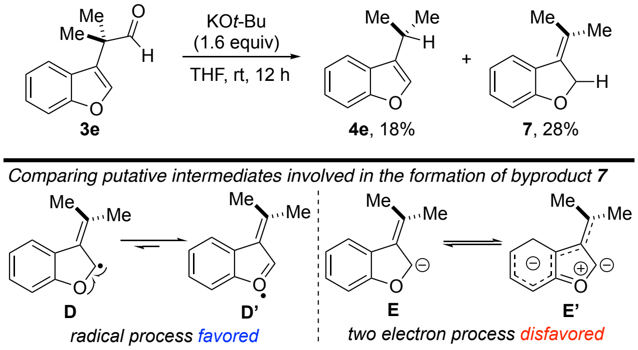


Figure 2. Formation of exocyclic alkene byproduct **7** as evidence of a radical mechanism.

In conclusion, we have developed a *tert*-butoxide mediated protodeformylation of tertiary homobenzaldehydes that may proceed via a stabilized tertiary benzylic radical generated upon homolytic C–C cleavage. Efforts to understand the mechanism in greater detail and to apply the method to selected targets are ongoing.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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