tert-Butoxide-Mediated Protodeformylative Decarbonylation of α-Quaternary Homobenzaldehydes

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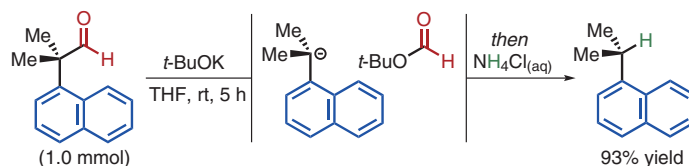
- straightforward access to cumene derivatives via *tert*-butoxide-mediated deformylation
- 21 examples with isolated yield >60% (including monocyclic and polycyclic arenes)
- the aldehyde reactants are accessible via cross-coupling in many cases

Abstract *tert*-Butoxide mediates the Haller–Bauer-type (protodeformylative) decarbonylation of readily accessed α-quaternary homobenzaldehydes and related compounds at room temperature, generating cumene products. Both geminal dialkyl and geminal diaryl substituents are tolerated. *gem*-Dimethyls are sufficient for decarbonylation of polycyclic arenyl substrates whereas monocyclic aromatic homobenzaldehydes require cyclic *gem*-dialkyls or *gem*-diaryls for significant decarbonylation.

Key words decarbonylation, C–C bond cleavage, protodeformylation, Haller–Bauer reaction, *tert*-butoxide, benzylic anion, cumenes

The decarbonylation of aldehydes is an important C–C bond-cleaving reaction in synthesis and in nature.[1,2] Chemosynthetic decarbonylations mediated by stoichiometric rhodium complexes were first developed by Tsuji and Wilkinson[3] and are notable for their application in natural products total synthesis;[4] flow-type and catalytic variants have been developed to lower the cost.[5] Haller and Bauer popularized the base-mediated debenzoylation of aromatic ketones in the early 1900s;[6] a room-temperature Haller–Bauer-type *tert*-butoxide-mediated protodebenzoylation was used as the third step to achieve formal protodeformylation of non-enolizable aldehydes (Scheme 1A).[7] Recently, Madsen and co-workers studied the mechanism of Haller–Bauer-type decarbonylations of enolizable aldehydes (Scheme 1B) as well as non-enolizable aldehyde substrates like 2,6-dichlorobenzaldehyde (not shown).[8] Similar conditions are known to be capable of deformylating certain non-

enolizable aldehydes like triphenylacetaldehyde[9] despite benzaldehydes being especially sensitive to hydroxide-mediated Cannizzaro-type disproportionation into the alcohol and carboxylic acid.[10] Other methods for formal protodeformylation of aldehydes have also been described.[11–13] Of the single-pot approaches (specifically Wilkinson and Haller–Bauer-type), a mild and general decarbonylation of α-quaternary aldehydes has not been described. Herein, we show that a wide variety of readily accessed α-quaternary
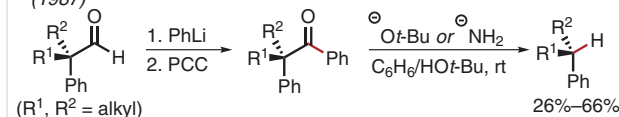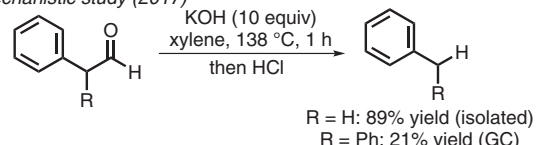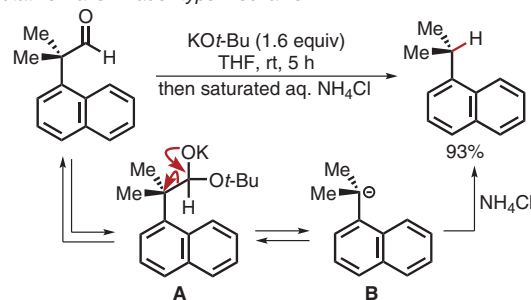

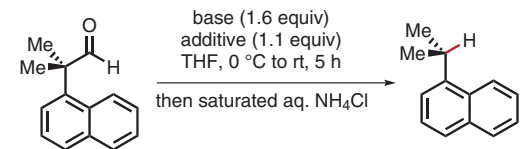**Scheme 1** Comparison of Haller–Bauer-type aldehyde decarbonylation methods

homobenzaldehydes are deformylated at ambient temperature using *tert*-butoxide in THF to afford isopropyl arene (cumene) derivatives (Scheme 1C).[14] Mechanistically, this presumably occurs via stabilized anion **B** generated from *tert*-butoxide adduct **A**.[15]

The impetus for developing this method stemmed from our interest in alkene functionalization reactions of α-quaternary homobenzylstyrenes and related compounds,[16] whereby we occasionally observed competing decarbonylation of α-quaternary homobenzaldehydes during Wittig olefination if excess *tert*-butoxide was present. We sought to optimize this reaction using the homonaphthaldehyde substrate shown in Table 1.[17] Excitingly, the use of 1.6 equivalents of KO*t*-Bu afforded complete substrate conversion and good yield at ambient temperature upon aqueous workup (entry 1). Evaluation of solvent effects showed that DMF was also well tolerated (entry 2) whereas HO*t*-Bu did not allow appreciable reaction (not shown).[18] The reaction must be performed air-free (entry 3), and the yield decreased somewhat when molecular sieves were employed (entry 4). Adding TEMPO inhibited substrate conversion somewhat (entry 5). NaO*t*-Bu was similarly effective as KO*t*-Bu (entry 6), whereas the use of lithium diisopropyl amide (LDA) resulted in complex decomposition (entry 7). Potassium hydroxide afforded no reaction in THF, with or without HO*t*-Bu present as additive (entries 8 and 9, respectively). Taken together, none of these data refute the canonical mechanism shown in Scheme 1C.[19] It should be noted that product formation can take place prior to workup via quench by adventitious water, but excess water in the reaction will lead to competing detrimental Cannizzaro disproportionation.

In terms of breadth of scope, phenyl analogues (**1a–c**) afford lower yield than the optimized naphthyl substrate (Scheme 2A). In particular, cumene (**2a**) was only produced in 11% NMR yield; the yield improved significantly by substitution with a *para*-phenyl group, thereby accessing **2d** in 67% yield. In revision, the *para*-trifluoromethyl analogue was prepared and protodeformylated to afford a modest 20% yield of the corresponding cumene by ¹H NMR analysis.[20] Strained cyclic *gem*-dialkyl-containing substrates like α-cyclopropyl (**1e**) and α-cyclobutyl (**1f**) afford just 9% and 24% yield of their respective methine products, whereas cyclopentyl (**1g**) and cyclohexyl (**1h**) substrates were decarbonylated in useful yield (44% and 76%, respectively). Other monoarenyl substrates evaluated include tetralin **1i** and triphenylacetaldehyde **1j**, both of which afforded decarbonylation products in good yield (61% and 79%, respectively). *tert*-Butanol was a common byproduct after workup, potentially arising from hydrolysis of the implied *tert*-butylformate byproduct of C–C bond cleavage of intermediate **A** in Scheme 1C.

Fused bicyclic and tricyclic substrates afforded generally excellent decarbonylation yields (Scheme 2B and C), presumably because the extended conjugation in these compounds affords a relatively stabilized benzylic anion. Among bicyclic arenes (Scheme 2B), cyclopentane-containing product **4a** was accessed with double the yield of the analogous monocyclic arene **2g**. A 1.0 mmol scale reaction of 1-naphthyl substrate **3b** afforded the highest decarbonylation yield that we observed in the study (93% yield of **4b**). 2-Naphthyl and 4-benzofuranyl analogues (**4c** and **4d**) were also accessed in good yield. In contrast, 3-benzofuranyl analogue **4e** was not prepared efficiently and a significant amount of dearomatized product **7** was formed (Scheme 3). A number of benzyl-protected 4-substituted indole analogues (**3f–j**) were also decarbonylated efficiently, as were a number of benzothiophenyl substrates (**3k–n**), with the exception of the 3-substituted analogue **3o**, which may be prone to dearomatization as observed for **3e**.

Finally, we evaluated four fused tricyclic arenes as shown in Scheme 2C, including carbazoles (**5a** and **5b**), a dibenzothiophene (**5c**), and a dibenzofuran (**5d**), all of which afforded the corresponding decarbonylated products (**6a–d**) in good yield.

In conclusion, we have developed a *tert*-butoxide-mediated protodeformylative decarbonylation of α-quaternary homobenzaldehydes.[21,22] The method enables efficient access to a variety of cumenes. Efforts to expand the scope and better understand the mechanism are ongoing in our lab.

Table 1 Optimization of Aldehyde Decarbonylation[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	air	>95	17
4[e]	KO*t*-Bu	4 Å MS	>95	70
5	KO*t*-Bu	TEMPO	78	62
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 solvent (1.1 mL) under an atmosphere of N₂ unless otherwise noted. Conversions and yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard (n.d. = not detected).
[b] Formulations of bases 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] Solid KO*t*-Bu and DMF as solvent.
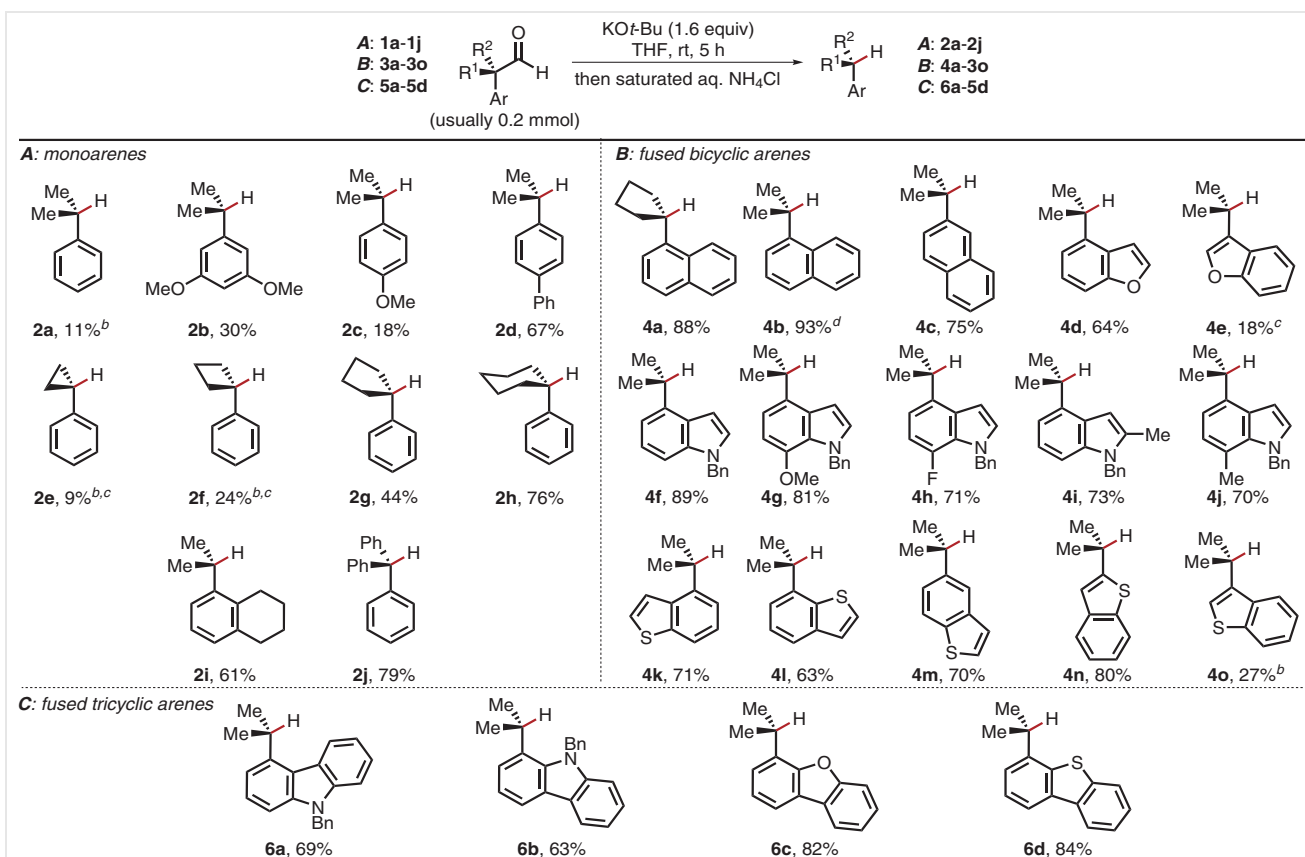[d] Reaction was conducted open to air.
[e] 100% w/w of molecular sieves.
[f] Base and HO*t*-Bu (1.6 equiv) sonicated for 5 minutes.

49

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Scheme 2 Evaluation of the generality of the protodeformylation of α-quaternary homobenzaldehydes. [a] Reactions were conducted with 0.2 mmol of aldehyde unless otherwise noted, and yields refer to isolated yields unless otherwise noted. [b] Yield was determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Product is volatile under high vacuum. [d] Reaction was executed on 1.0 mmol scale of **3b**.
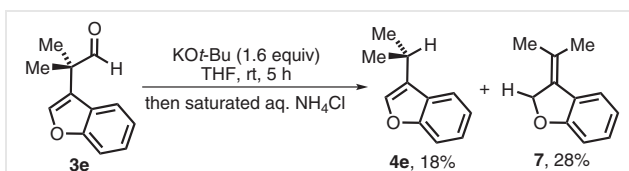
Scheme 3 Dearomative protodeformylation predominates in the case of benzofuran **3e**.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2231-3108.

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50

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(20) See the Supporting Information for details.

(21) **Protodeformylation; General Procedure:** An oven-dried 25-mL round-bottom flask was charged with a PTFE-coated magnetic stir bar, fitted with a rubber septum, and purged with nitrogen for 2 min. Then, under ambient pressure of N_2, KOt-Bu solution (1.6 M in THF, 0.3 mmol, 1.6 equiv, 0.2 mL) was added to the flask, and further diluted with anhydrous THF (1.0 mL). To the flask, an anhydrous THF solution of aldehyde (0.2 M, 1.0 equiv, 1.0 mL) was added dropwise at room temperature. The mixture was then allowed to stir for 5 h under ambient pressure of N_2. The reaction was diluted with EtOAc (2 mL), saturated aqueous NH_4Cl (5 mL) was added, and the mixture was allowed to stir until the solution became decolored. The aqueous layer was then extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo to afford the crude decarbonylated product, which was then purified by silica gel chromatography..

(22) Characterization data of representative product **4b**: Yield (1.0 mmol scale): 158 mg (93%); colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.16 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.90–7.84 (m, 1 H), 7.73 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.62–7.38 (m, 4 H), 3.79 (sept, *J* = 6.9 Hz, 1 H), 1.44 (d, *J* = 6.9 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 144.6 (C), 133.9 (C), 131.3 (C), 128.9 (CH), 126.3 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 123.3 (CH), 121.7 (CH), 28.5 (C), 23.6 (CH$_3$)..

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