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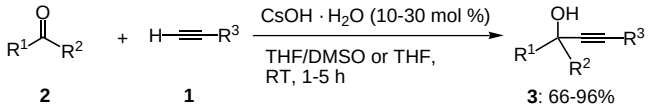
Cesium Hydroxide: A Superior Base for the Catalytic Alkynylation of Aldehydes and Ketones and Catalytic Alkenylation of Nitriles**

Dimitrios Tzalis and Paul Knochel*

The metal-catalyzed formation of new carbon–carbon bonds is an important synthetic tool.[1] Particularly attractive in this category of reactions are additions to multiple bonds that proceed without the formation of side products (atom economic reactions).[2] Thus, the metal-catalyzed addition of alkynes of type **1** to carbonyl compounds of type **2** that lead to propargyl alcohols of type **3** has a considerable synthetic and industrial importance. Whereas the performance of these reactions that use a stoichiometric amount of a base such as an organolithium or organomagnesium reagent to generate an intermediate metal acetylide[3] has been extensively described, only a few reports concerning the catalytic activation of an alkyne and subsequent addition to the carbonyl derivative have been reported.[4, 5] They are mostly restricted to acetylene itself[4] or are applicable only to some carbonyl compounds such as cycloalkanones.[5] Herein, we report the exceptional activity of cesium hydroxide[6, 7] for the catalytic generation of highly nucleophilic, stabilized organometallic species (Scheme 1). Thus, in the presence of a catalytic



2 **1** **3**: 66-96%

Scheme 1. CsOH-catalyzed alkynylation of aldehydes and ketones with terminal alkynes. R^1, R^2 = alkyl or H, R^3 = alkyl, aryl, alkenyl.

amount of $CsOH \cdot H_2O$ (10 mol%) phenylacetylene (**1a**: 1.5 equiv) adds to cyclohexanone (**2a**) in THF within 1 h at RT. The desired propargyl alcohol (**3a**) is isolated after workup in 88% yield (entry 1 of Table 1). Under these conditions phenylacetylene adds to various aliphatic ketones[8] or to aliphatic aldehydes in yields between 66 and 96%. In many cases, these reactions are complete within five minutes at RT. A 1:1 mixture of THF and DMSO was used as solvent together with $CsOH \cdot H_2O$ (30 mol%) for the addition of less acidic alkynes. Under these conditions most terminal alkynes undergo a smooth addition to secondary or tertiary aliphatic aldehydes or aliphatic ketones to give the corresponding propargyl alcohols of type **3** (Table 1). To avoid competitive aldol reactions a slow addition of the aldehyde with a syringe pump was performed (addition of 0.5 mL h^{-1}). The addition of alkynes to carbonyl compounds with diastereotopic faces such as 2-methylcyclohexanone (**2b**) or the

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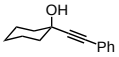
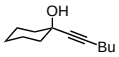
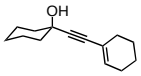
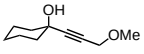
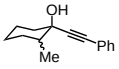
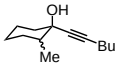
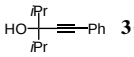
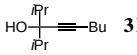
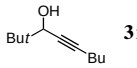
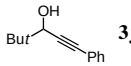
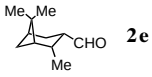
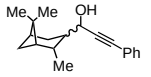
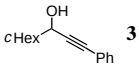
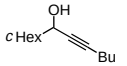
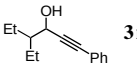
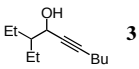
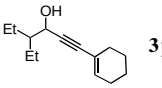
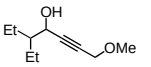
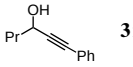
Table 1. Preparation of propargyl alcohols of type **3** by CsOH-catalyzed addition of alkynes to aldehydes and ketones.

Entry	Electrophile	Nucleophile	Product	Method	Yield [%][a]
1	 **2a**	HC≡CPh **1a**	 **3a**	A	88
2	**2a**	HC≡CBu **1b**	 **3b**	B	82 (81)[b]
3	**2a**	 **1c**	 **3c**	B	96
4	**2a**	HC≡CHCH$_2$OMe **1d**	 **3d**	B	91
5	 **2b**	**1a**	 **3e**	A	72
6	**2b**	**1b**	 **3f**	B	74
7	*i*PrCO*i*Pr **2c**	**1a**	 **3g**	A	91
8	**2c**	**1b**	 **3h**	B	59
9	*t*BuCHO **2d**	**1a**	 **3i**	A	86
10	**2d**	**1b**	 **3j**	B	74
11	 **2e**	**1a**	 **3k**	A	96
12	*c*HexCHO **2f**	**1a**	 **3l**	A	90
13	**2f**	**1b**	 **3m**	B	91
14	Et$_2$CHCHO **2g**	**1a**	 **3n**	A	81
15	**2g**	**1b**	 **3o**	B	91
16	**2g**	**1c**	 **3p**	B	91
17	**2g**	**1d**	 **3q**	B	90
18	PrCHO **2h**	**1a**	 **3r**	A	66 (72)[b]

[a] Yield of isolated, analytically pure product. [b] The yield in parenthesis corresponds to a reaction performed in NMP.

aldehyde **2c** produces a 1:1 mixture of diastereomeric propargyl alcohols (entries 5, 6, and 11 of Table 1). It is possible to use *N*-methylpyrrolidinone (NMP) instead of DMSO with the same reaction time to get similar yields (entries 2 and 18 of Table 1).

Functionalized alkynes such as propargylamine (**1e**) have also been used with success. Thus, the addition of **1** to cyclohexanone and 2-ethylbutyraldehyde furnishes the desired 1,4-aminopropargyl alcohols **3s** and **3t** in 85 % and 70 % yield, respectively (Scheme 2).

In order to explore further the utility of CsOH · H$_2$O in the activation of acetylenic C–H bonds we have examined the reaction of benzylic nitriles with alkynes.[9] A very fast addition of the phenylacetonitriles **4a**,**b** to phenylacetylene

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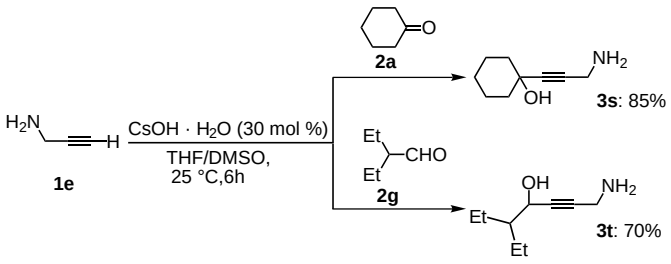
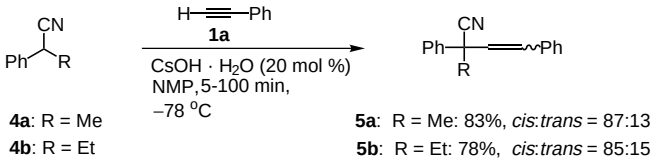
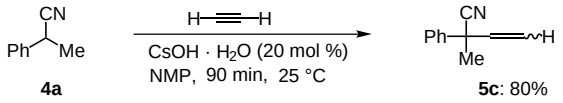


Scheme 2. CsOH-catalyzed alynylation of propargylamine.

occurs in the presence of catalytic amounts of $CsOH \cdot H_2O$ (20 mol %) in NMP ($-78\,^{\circ}C$, 5–100 min) to provide a *cis*:*trans* mixture of the addition products **5a** and **b** in 78–83 % yield (Scheme 3 and Method C). The use of acetylene allows a mild vinylation of phenylacetonitrile **4a** to give the unsaturated adduct **5c** in good yield (Scheme 4 and Method D).



Scheme 3. CsOH-catalyzed vinylation of phenylacetonitriles with phenylacetylene under mild reaction conditions.



Scheme 4. Efficient CsOH-catalyzed vinylation of phenylacetonitrile with acetylene.

In summary, we have shown that $CsOH \cdot H_2O$ allows a catalytic C–H activation of various alkynes that leads, in the presence of aliphatic aldehydes or ketones, to propargylic alcohols in good yields. It was also possible to perform the vinylation of phenylacetonitriles with $CsOH \cdot H_2O$ (20 mol %). We are currently investigating the scope of CsOH for the catalytic generation of other stabilized and unstabilized carbanions.[10]

Experimental Section

Preparation of propargyl alcohols by CsOH catalysis:

Method A: Reaction with phenylacetylene (**1a**): Preparation of 4-ethyl-1-phenyl-1-hexyn-3-ol (**3n**): A 25-mL Schlenk flask was charged with $CsOH \cdot H_2O$ (68 mg, 0.41 mmol). THF (10 mL) and phenylacetylene (660 mg, 6.0 mmol) were added successively by syringe. The reaction mixture was vigorously stirred and 2-ethylbutyraldehyde (410 mg, 4.1 mmol) was added slowly and stirred at RT for 1 h. The reaction mixture was poured into diethyl ether (150 mL), and washed with H_2O (2×75 mL) and brine (75 mL). The combined ethereal layers were dried ($MgSO_4$). After evaporation of the solvent the residue was purified by flash chromatography (pentane/ethyl acetate, 9/1) to afford the desired product as a colorless oil (650 mg, 81 %).

Method B. Reactions with other alkynes: Preparation of 3-ethyl-5-decyn-1-ol (**3o**): A 25-mL Schlenk flask was charged with $CsOH \cdot H_2O$ (205 mg, 1.23 mmol). A 1:1 mixture of THF:DMSO (10 mL) and hexyne (670 mg, 8.2 mmol) were added successively by syringe. The reaction mixture was vigorously stirred and a solution of 2-ethylbutyraldehyde (410 mg, 4.1 mmol) in a 1:1 mixture of THF and DMSO (2 mL) was added slowly by syringe pump (0.5 mL h^{-1}), and then stirred at RT for 3 h. After work-up as described in Method A the product was obtained as a colorless oil (670 mg, 90 %).

CsOH catalyzed vinylation.

Method C. Reaction with phenylacetylene (**1a**): Preparation of 2-methyl-2,4-diphenyl-3-butenenitrile (**5a**): A 10-mL Schlenk flask was charged with $CsOH \cdot H_2O$ (12 mg, 72 μmol). NMP (1 mL), 1-phenylethyl cyanide (**4a**) (50 μL, 0.38 mmol), and phenylacetylene (80 μL, 0.76 mmol) were added successively by syringe at $-78\,^{\circ}C$ and the mixture stirred vigorously for 5 min. The reaction was poured into diethyl ether (30 mL) and washed with H_2O (2×20 mL) and brine (10 mL). The ethereal layer was dried ($MgSO_4$). After evaporation of the solvent the product was purified by flash chromatography (pentane/ethyl acetate, 9/1) to yield the desired product as a colorless oil (68 mg, 83 %).

Method D. Reaction with acetylene: Preparation of 2-methyl-2-phenyl-3-butenenitrile (**5c**): A 50-mL Schlenk flask was charged with $CsOH \cdot H_2O$ (254 mg, 1.5 mmol), NMP (20 mL), and 1-phenylethyl cyanide (**4a**) (1 g, 7.6 mmol). The reaction mixture was stirred vigorously and acetylene was slowly bubbled through the solution for 1.5 h. After work-up as described in Method C, the product was obtained as a colorless oil (955 mg, 80 %).

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Keywords: alkynylation · C–H activation · carbonyl compounds · cesium hydroxide · vinylation

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[6] $CsOH \cdot H_2O$ is commercially available (Aldrich) and has found applications as a catalyst in the polymerization of cyclic siloxanes.

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[8] Aromatic aldehydes and ketones seem to undergo side reactions and are not suited for this catalysis.

[9] The phase transfer catalyzed vinylation of phenylacetonitriles with stoichiometric amounts of NaOH has been described, see M. Makosza, *Tetrahedron Lett.* **1966**, 5489.

[10] A patent has been filed in colaboration with BASF AG (Ludwigshafen).

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