First Meerwein−Ponndorf−Verley Alkynylation: Nonorganometallic Way for Carbonyl Alkylations

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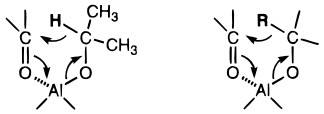
Undoubtedly the Meerwein−Ponndorf−Verley (MPV) reduction is one of the most classical, yet important organic transformations.[1−3] Advantages of the MPV reduction include its chemoselectivity, mild reaction conditions, operational simplicity, safe handling, and ready adaptation both in the laboratory and on a large scale.[4] This reaction is applicable to various carbonyl substrates with aluminum alkoxides, generally $Al(OPr^i)_3$ as the catalyst and *i*-PrOH as the hydride source, as shown in [**A**].[5] However, the corresponding alkylation, i.e., MPV alkyla-

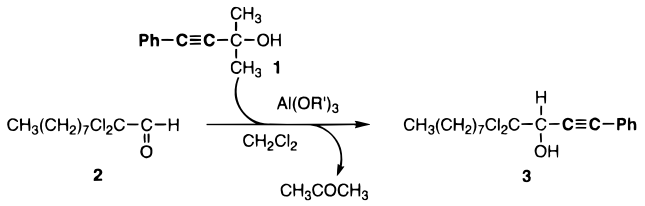


A **B**

tion, has never been realized mainly because of the inertness of alkyl transfer [**B**] compared to the facile hydride transfer [**A**] in the MPV reduction. We here report the first example of MPV alkynylations for various aldehydes as illustrated in Scheme 1. *This truly represents a nonorganometallic way of effecting carbonyl alkylation of aldehydes.* The success of the present approach relies heavily on the discovery of a ligand-accelerated mode for the MPV alkynylations, which shows beneficial effect on the rate of alkyl transfer.

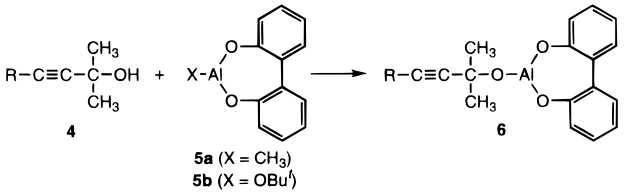
A typical Al reagent, $Al(OC(CH_3)_2C{\equiv}CPh)_3$ for the MPV alkynylation was prepared by treatment of propargylic alcohol **1** (3 equiv) in CH_2Cl_2 with a 1 M hexane solution of Me_3Al (1 equiv) at room temperature for 30 min.[6] When an equimolar mixture of 2,2-dichlorodecanal (**2**)[7,8] and the in situ generated $Al(OC(CH_3)_2C{\equiv}CPh)_3$ was stirred at room temperature for 5 h, acetylenic alcohol **3** was obtained in only a trace amount. The choice of aluminum ligands is crucial in enhancing the rate of alkynylation. When two phenoxy ligands were introduced to prepare $PhC{\equiv}CC(CH_3)_2OAl(OPh)_2$ [derived from **1** and $MeAl(OPh)_2$], the alcoholic product **3** was obtainable in higher yield (16%) under otherwise identical conditions. Switching the two phenoxy ligands to *o*-phenylenedioxy and *o*,*o*′-biphenylenedioxy ligands, the alkynylation was further accelerated to give **3** in 20% and 53% yields, respectively (entry 4 in Table 1). In the latter

Scheme 1



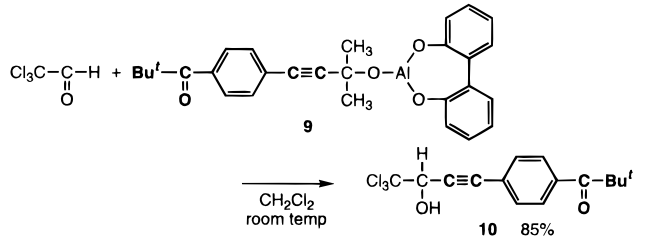
case, the use of 3 equiv of propargylic alcohol **1** provided a synthetically useful level of chemical yield (entry 5).

Other selected examples are listed in Table 1. The requisite (propargyloxy)aluminum reagents **6** are readily accessible from either (1) (*o*,*o*′-biphenylenedioxy)methylaluminum (**5a**) and the corresponding propargylic alcohols **4** or (2) (*o*,*o*′-biphenylenedioxy)(*t*-butoxy)aluminum (**5b**) and **4** by the ligand exchange.



The second preparative method works equally well (entries 6, 11, and 21). In general, a series of the reactive aldehydes, 2-haloaldehydes, 2,2′-dihaloaldehydes, chloral, bromal, and pentafluorobenzaldehyde can be transformed to the corresponding secondary propargylic alcohols **8** under the MPV alkynylation conditions using stoichiometric **6** (R = Ph, CH=CHPh).[9] Acetylenic aldehyde can be also alkynylated under similar reaction conditions (entry 25).[10] In certain cases, the alkynylation proceeds under catalytic conditions (entries 3, 12, and 22). Since the MPV reaction is reversible, the overall efficiency is subtly influenced by the steric and electronic properties of the aldehydic substrates **7** and alkynyl donors **4** as well as reaction conditions as shown in Table 1.

One characteristic feature of the MPV alkynylation is the chemoselective transfer of functionalized alkynyl groups to aldehyde carbonyls. Indeed, reaction of chloral with functionalized Al reagent **9**[11] in CH_2Cl_2 proceeds nicely at room temperature to furnish alcohol **10** in good yield, leaving the keto



(1) Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem.* **1925**, *444*, 221.
(2) Verley, A. *Bull. Soc. Chim. Fr.* **1925**, *37*, 537.
(3) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138.
(4) De Graauw, C.; Peters, J.; Van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007.
(5) Review: Wilds, A. L. *Org. React.* **1944**, *2*, 178.
(6) This Al reagent can also be generated from the ligand exchange of $Al(OPr^i)_3$ and **1** (3 equiv) in CH_2Cl_2 by the azeotropic removal of the in situ generated *i*-PrOH.
(7) 2,2-Dichlorodecanal (**2**) was readily prepared from decanal according to the literature procedure. See: Verhe, R.; Kimpe, N. D.; Buyck, L. D.; Schamp, N. *Synthesis* **1975**, 455.
(8) We chose 2,2-dihaloaldehydes as representative reactive aldehydes because of the ease of further manipulation of the alkylation products by simple dehalogenation. For the C−Cl bond cleavage, see: (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849. (b) Pinder, A. R. *Synthesis* **1980**, 425. (c) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.
(9) Attempted allylation of aldehyde **2** with 2-methyl-4-penten-2-ol and **5a** under otherwise similar reaction conditions gave none of the desired homoallylic alcohols, hence, excluding the possibility of the stabilized carbocation mechanism in our system. We acknowledge the reviewer for a valuable comment on this point. For a recent example of allyl-transfer reaction, see: Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609.
(10) α,β-Acetylenic aldehydes can be synthesized from terminal alkynes with high efficiency. Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.
(11) The functionalized propargylic alcohol was synthesized from 2-methyl-3-butyn-2-ol in 40% yield as follows: (i) 1-bromo-4-iodobenzene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_2Cl_2, room temperature. (ii) BuLi (2 equiv), ether, 0 °C.; then pivaloyl chloride, −78 to −20 °C.

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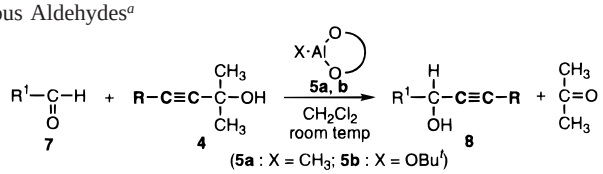
Table 1. MPV Alkynylation of Various Aldehydes[a]

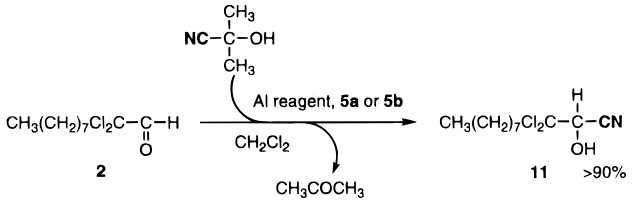


entry	aldehyde, **7**	alkyl source **4** (equiv)	Al reagent, **5**	reaction time (h)	product, **8** % yield[b]
1	$R^1 = CHCl(CH_2)_7CH_3$	R = Ph (3)	**5a**	2	40 (78:32)[c]
2		R = CH=CHPh (3)	**5a**	1	80 (75:25)[c]
3		R = CH=CHPh (3)	**5a** (10 mol %)	5	72 (76:24)[c]
4	$R^1 = CCl_2(CH_2)_7CH_3$	R = Ph (1)	**5a**	5	53
5		R = Ph (3)	**5a**	5	70
6		R = Ph (3)	**5b**	5	61
7		R = CH=CHPh (1)	**5a**	2	42
8		R = CH=CHPh (3)	**5a**	2	66
9	$R^1 = CCl_3$	R = Ph (1)	**5a**	5	81
10		R = Ph (3)	**5a**	5	97
11		R = Ph (3)	**5b**	5	84
12		R = Ph (3)	**5a** (20 mol %)	12	63
13		R = CH=CHPh (1)	**5a**	2	85
14		R = CH=CHPh (2)	**5a**	5	99
15	$R^1 = CBr_3$	R = Ph (1)	**5a**	5	52
16		R = Ph (3)	**5a**	5	81
17		R = CH=CHPh (1)	**5a**	2.5	58
18		R = CH=CHPh (3)	**5a**	2.5	89
19	$R^1 = C_6F_5$	R = Ph (1)	**5a**	5	67
20		R = Ph (3)	**5a**	5	85
21		R = Ph (3)	**5b**	5	75
22		R = Ph (3)	**5a** (10 mol %)	12	51
23		R = CH=CHPh (1)	**5a**	1.5	79
24		R = CH=CHPh (3)	**5a**	1.5	99
25	$R^1 = C{\equiv}CPh$	R = Ph (5)	**5a**[d]	1	54[e]

[a] Unless otherwise noted, alcohol **4** was reacted with Al reagent **5** (1 equiv) in CH_2Cl_2 at room temperature for 30 min and then treated with aldehyde **7** under the given reaction conditions. [b] Isolated yield. [c] *erythro*/*threo* Ratio of **8** (R = Ph or CH=CHPh) was determined by ^{1}H NMR analysis. The relative configuration of these isomers was correlated, after hydrogenation to the corresponding saturated chlorohydrins, with that of alkylation products of 2-chlorodecanal by the corresponding Grignard reagents. See: Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, DC, 1976; p 99. [d] Use of 5 equiv of Al reagent. [e] The alkynylation product **8** (R = Ph) works as a hydride source for the MPV reduction of the starting aldehyde to furnish 1,5-diphenyl-1,4-pentadiyn-3-one (17%) as a side-reaction product.

functionality intact. Such transformation is not easily realized by the ordinary alkynylation procedures because of the difficulty of generating functionalized alkynylmetal reagents.

The present approach is also applicable to the cyanation of aldehydes with commercially available acetone cyanohydrin as cyanide source. For example, treatment of 2,2-dichlorodecanal (**2**) with acetone cyanohydrin under the influence of aluminum reagent **5a** or **5b** afforded the corresponding cyanohydrin **11** in high yield.



In summary, we have successfully developed a MPV alkynylation procedure which is highly effective for the selective alkynylation of aldehydes under mild conditions. The alkynylation proceeds without organometallic reagent by taking advantage of the push−pull effect of modified aluminum reagents. A more appropriate choice of metals and a more sophisticated design of the MPV alkylation system for general applicability are the subjects of our ongoing study.

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