

Me₂Zn-Mediated Addition of Acetylenes to Aldehydes and Ketones

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Received January 20, 2005



Contrary to expectations, commercially available 2 M Me₂Zn in toluene is able to promote the addition of phenylacetylene to aldehydes and ketones. This reactivity is determined by a new, unprecedented mechanism, which involves activation of the zinc reagent via coordination with carbonyl substrates that behave "ligand like". Broad scope, high tolerance to functional groups, and a simple procedure make this new method highly interesting for the synthetic chemist.

The addition of acetylides to carbonyl substrates gives access to propargylic alcohols, which are valuable building blocks and useful intermediates for the synthesis of complex natural products.¹ Moreover, the addition of alkynes to ketones is a practical strategy to create tertiary alcohols with a new stereogenic center under mild conditions (Figure 1).²

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FIGURE 1. Acetylenic alcohols as precursors of valuable compounds.

SCHEME 1. Addition of Acetylenes 2a-d to Carbonyl Compounds Promoted by Me₂Zn



Traditionally, propargylic alcohols are synthesized by addition of a metal acetylide to aldehydes or ketones with a stoichiometric or catalytic amount of a base.³ However, the reported methods possess some drawbacks and hence a general, highly tolerable and simple procedure for the selective alkynylation of enolizable aldehydes and ketones, is desirable. We found that mixtures of Me₂Zn and acetylenes add to aldehydes and ketones affording the desired products in good to excellent yields (Scheme 1).

Thus, when the commercially available 2 M solution of Me₂Zn in toluene was mixed with of phenylacetylene (1.5 equiv each) at room temperature and reacted with benzaldehyde (1 equiv) at 0 °C, the addition product **3a** was isolated in 45% yield after 24 h (entry 1, Table 1). Performing the reaction at room temperature gave **3a** in 89% yield (entry 2, Table 1). Consequently, this protocol was used for all further reactions.

A substrate screening revealed that other acetylenes were also applicable although they proved to be less reactive than phenylacetylene (Table 1, entries 3-5). Various aldehydes reacted smoothly giving the corresponding propargylic alcohols in good to high yields at room temperature. Table 2 shows that aromatic and aliphatic ketones reacted as well.

When a Me₂Zn/phenylacetylene mixture was used (1.5 equiv each with respect to the carbonyl compound), only aliphatic ketones furnished addition products in high yields, while aromatic ketones were rather unreactive substrates. The introduction of an electron-withdrawing group enhanced the reactivity of the latter substrates. The use of 3 equiv of the Me₂Zn/phenylacetylene mixture increased the yield in the addition to acetophenone and chloroacetophenone (Table 2, entries 2 and 3), but the

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 TABLE 1.
 Alkynylation of Aldehydes Using Me₂Zn as

 Promoter

$entry^a$	aldehyde	\mathbb{R}^3	product	yield ^b (%)
1	benzaldehvde	Ph	3a	45^c
2	benzaldehyde	Ph	3a	30^d
3	benzaldehvde	Ph	3a	78
4	benzaldehyde	TMS	3b	48
5	benzaldehyde	nBu	3c	80
6	benzaldehyde	CO_2Et	3d	30
7	4'-chlorobenzaldehyde	Ph	3e	83
8	4'-bromobenzaldehyde	Ph	3f	70
9	3'-fluorobenzaldehyde	Ph	3g	92
10	3'-bromobenzaldehyde	Ph	3h	86
11	4'-trifluoromethylbenzaldehyde	Ph	3i	90
12	4'-nitrobenzaldehyde	Ph	3j	79
13	4'-methylbenzaldehyde	Ph	3k	68
14	1-naphthylaldehyde	Ph	31	86
15	trans-cinnamaldehyde	Ph	3m	70
16	octanal	Ph	3n	91
17	cyclohexylaldehyde	Ph	30	89

 a All reactions were carried out in anhydrous toluene at room temperature, employing 1.5 equiv of a Me₂Zn/phenylacetylene mixture. b Yield after flash chromatography. c The reaction was performed at 0 °C. d The reaction was performed using a 1.1 M toluene solution of Et₂Zn.

TABLE 2.Alkynylation of Ketones with PhenylAcetylene Using Me2Zn as Promoter

$entry^a$	ketone	product	yield ^{b} (%)
1	acetophenone	4a	14
2	acetophenone	4a	36^c
3	4'-chloroacetophenone	4b	40^c
4	4'-fluoroacetophenone	4c	31
5	4'-bromoacetophenone	4d	44
6	3'-trifuoromethylacetophenone	4e	94
7	3'-cyanoacetophenone	4f	41
8	4-phenylbut-3-en-2-one	4g	66
9	oxo-phenylacetic acid methylester	4h	80
10	2-pentanone	4i	85
11	1-hexen-5-one	4j	86
12	4-methyl-2-pentanone	4 k	59
13	3-methyl-2-butanone	41	77
14	4-phenyl-2-butanone	4m	75
15	methylcyclopropyl ketone	4n	40
16	2,2-dimethyl-1-cyclopentanone	4o	55
17	cyclohexanone	4 p	80

^{*a*} All reactions were carried out in anhydrous toluene at room temperature, employing 1.5 equiv of Me₂Zn/phenylacetylene mixture. ^{*b*} Yield after flash chromatography. ^{*c*} The reactions were performed using 3 equiv of Me₂Zn/phenylacetylene mixture.

results were still not satisfactory. As demonstrated with various substrates, the procedure is highly tolerant to a broad range of functional groups.

These results are intriguing also from a theoretical point of view, because they open the reaction mechanism to questions. It was previously reported that the addition of Me₂Zn to a solution of phenylacetylene did not show any change in the ¹H and ¹³C spectra, indicating that no reaction took place between the two compounds.⁴ More recent studies revealed that the formation of MeZnCCPh is promoted by the adventitious presence of moisture, although the reaction is incomplete.⁵ Apparently, in both studies it was necessary to activate the Me₂Zn in order to make it a more reactive base toward acetylenes. It is well-known that amino alcohols activate alkyl-,⁶ aryl-,⁷ and alkynylzinc³ derivatives toward the attack of carbonyl substrates. This activation is crucial to make reaction with the carbonyl compound possible.⁸ Our results indicate that the carbonyl oxygen might behave in a "ligand like" fashion promoting the reaction of Me₂Zn with an alkyne by coordination of its lone pairs to the Me₂Zn. To elucidate the nature of the deprotonation and of the subsequent addition step, we have undertaken a DFT study of a small model system, consisting of Me₂Zn, acetone, and acetylene.

All calculations were performed at the B3LYP/LACVP* level (Hay–Wadt double- ζ valence + ECP for Zn,⁹ 6-31G* for other atoms) in Jaguar 4.2 from Schrödinger, Inc.¹⁰ Stationary points were verified by analytic normal-mode analysis. All reaction barriers were calculated from the lowest preceding point on the potential energy surface, always a precomplex of all reactants. Initially, we investigated the deprotonation of acetylene by Me₂Zn (Figure 1).

In the absence of activation, the barrier is calculated to be 155 kJ/mol, too high to be expected to show significant reactivity at room temperature. Coordinating a molecule of acetone to the Zn atom lowers the barrier to 138 kJ/mol, a value more in line with the observed reactivity. Adding harmonic corrections to these figures (ZPE or $\Delta\Delta G$) changes the absolute numbers, but does not affect the trend. Looking at the structures, we can see that acetone coordination induces a bending in the linear and nonpolar Me₂Zn molecule, increasing the basicity of the methyl group.

We also investigated the subsequent addition of MeZnCCH to a ketone. In the simplest possible mechanism, starting from the favored adduct in the preceding deprotonation step, the acetylene is simply transferred to the carbonyl carbon in a four-membered monocyclic TS (Figure 2).

This reaction has an activation barrier of only 83 kJ/ mol, indicating that in the presence of ketone, the alkynylzinc species is reacted as soon as it is formed.

In consideration of the accepted mechanism for ligandassisted addition of Et_2Zn to aldehydes,^{6b} we also investigated the possibility that a zinc ketone complex acts as a bifunctional catalyst, bringing together an additional 1 equiv of ketone and zinc reagent in a bicyclic TS (Figure 3). This reaction has an even lower barrier, only 66 kJ/ mol, but at the cost of a higher molecularity and thus an unknown entropic cost. The relative importance of the two pathways will be determined by the propensity of the zinc species to form higher order complexes, which in turn will be strongly affected by the solvent. However,

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FIGURE 2. TSs for the deprotonation of acetylene.



FIGURE 3. Transition states found for the addition of acetylene to acetone.

the relatively low barrier to reaction indicates that the alkynyl zinc, already complexed to the ketone, may react through the monocyclic TS before encountering other activating species.

In conclusion, we have described the unexpected and facile addition of phenylacetylene to aldehydes and ketones promoted by Me_2Zn without the employment of specific ligands. This reaction has an interesting potential for the direct synthesis of tertiary propargylic alcohols. Furthermore, our study demonstrates that the substrate itself can become a ligand and catalyze a background reaction, which might result in lowering the enantiose-lectivity in a desired asymmetric transformation.

Experimental Section

1,3-Diphenyl
prop-2-yn-1-ol $(\bf 3a),^{11}$ 1-phenyl-3-trimethylsilyl-prop-2-yn-1-ol
 $(\bf 3b),^{12}$ 1-phenylhept-2-yn-1-ol $(\bf 3c),^{13}$ 4-hydroxy-

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nyl)-4-phenylbut-3-yn-2-ol (4b),22 2-(4-fluorophenyl)-4-phenylbut-3-yn-2-ol (4c),^{3c} 2-(4-bromophenyl)-4-phenylbut-3-yn-2-ol (4d),^{3c} 2-(3-trifluoromethylphenyl)-4-phenylbut-3-yn-1-ol (4e),^{3c} 3-methyl-1,5-diphenylpent-1-en-4-yn-3-ol (4g),²³ 2-hydroxy-2,4-diphenylethyl-but-3-ynoate (4h),²⁴ 3methyl-1-phenylhex-1-yn-3-ol (4i),²⁵ 3,5-dimethyl-1-phenylhex-1-yn-3-ol (4k),²⁶ 3,4-dimethyl-1-phenylpent-1-yn-3-ol (41),
27 3-methyl-1,5-diphenylpent-1-yn-3-ol (4m), $^{\rm 3c}$ 2-cyclopropyl-4-phenylbut-3-yn-2-ol (4n),^{3c} 2,2-dimethyl-1-phenylethynylcyclopentanol (40),3c and 1-phenylethynyl-1-cyclohexanol $(4p)^{27}$ are known compounds.

Typical Procedure for the Alkynylation of Carbonyl Compounds. In an oven-dried flask connected to a nitrogen/ vacuum line was placed phenylacetylene (1.6 mmol) followed by the slow addition of Me₂Zn 2 M solution in toluene (1.5 mmol, 0.75 mL). The resulting solution was stirred at room temperature for 30 min. Then, the aldehyde or ketone (1 mmol) was added dropwise to the reaction mixture. The resulting solution was stirred at room temperature for 24 h, and then the reaction mixture was diluted with diethyl ether (5 mL) and quenched with water (10 mL). The mixture was stirred for 10 min and then filtered over Celite. The aqueous phase was separated and extracted with diethyl ether $(2 \times 5 \text{ mL})$. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to give a crude oil which was purified by flash chromatography (cyclohexane/diethyl ether 8:2-9:1 or cyclohexane/acetone 8:1-9:1 as eluant).

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4-(1-Hydroxy-1-methyl-3-phenylprop-2-yl-benzonitrile) (4f). ¹H NMR (CDCl₃, 300 MHz) δ: 1.87 (s, 3H); 7.37-7.34 (m, 3H); 7.53-7.47 (m, 3H); 7.64 (m, 1H); 7.98 (m, 1H); 8.04 (t, 1H, J = 1.2 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ : 33.6; 69.7; 85.7; 91.1; 112.4; 118.8; 121.9; 128.4; 128.9; 129.2; 129.6; 131.3; 131.7; 147.2; 176.4. Anal. Calcd: C, 88.13; H, 8.05; N, 5.71. Found: C, 88,06; H, 8.18; N, 5.75.

3-Methyl-1-phenylhept-6-en-1-yn-3-ol (4j). ¹H NMR (CDCl₃, 300 MHz) 5: 1.64 (s, 3H); 1.88–1.97 (m, 3H); 2.35–2.47 (m, 2H); 5.03-5.18 (m, 2H); 5.89-6.00 (m, 1H); 7.22-7.30 (m, 3H); 7.36-7.39 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ: 29.3; 30.0; 42.7; 68.5; 83.7; 92.5; 114.9; 122.7; 128.2; 131.6; 138.4; 140.6. Analysis calcd: C, 83.96; H, 8.05. Found: C, 84,00; H, 8.01.

Acknowledgment. P.G.C. thanks FIRB and MIUR (Rome) "Progetto Stereoselezione in Chimica Organica. Metodologie ed Applicazioni" and the University of Bologna (funds for selected research topics) for financial support of this research. C.T. thanks MURST Cofin 2002 ("Sintesi di peptidi ciclici o lineari contenenti amminoacidi inusuali analoghi di arginina, glicina o acido aspartico (RGD) come nuovi inbitori di integrine"), FIRB 2001 ("Eterocicli azotati come potenziali inbitori enzimatici"), and 60% (Ricerca Fondamentale Orientata). C.B. and J.R. are grateful to the Fonds der Chemischen Industrie and to the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 and the Graduiertenkolleg (GRK) 440 for financial support. P.-O.N. thanks the Carlsberg Foundation and the Danish Natural Science Research Council for providing computational resources.

Supporting Information Available: Copies of ¹H NMR for compounds 3a-o and 4a-e,g-i,k-o and energies and Cartesian coordinates, TS energies (Hartree), zero potential energy (kJ/mol), and lowest frequencies (cm⁻¹) for reactants and complexes determined at the B3LYP/LACVP* level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050115R

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