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Trimethylsilyl Trifluoromethanesulfonate-Accelerated Addition of Catalytically Generated Zinc Acetylides to Aldehydes

C. Wade Downey,* Brian D. Mahoney, and Vincent R. Lipari

Gottwald Center for the Sciences, University of Richmond, Richmond, Virginia 23173

wdowney@richmond.edu

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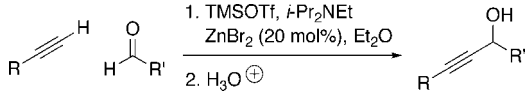
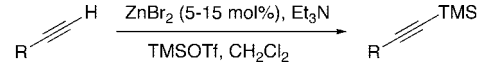


In the presence of TMSOTf, a wide variety of terminal acetylenes add rapidly and efficiently to aldehydes via a catalytically generated zinc acetylide. In the absence of TMSOTf, no reaction is observed under otherwise identical conditions.

Metal-catalyzed addition of terminal acetylenes to aldehydes[1] remains an active area of research because of the synthetic utility of the propargyl alcohol products.[2] Zinc catalysis in particular has been a fruitful field, as popularized by the development of an enantioselective system by Careirra and co-workers.[3] The frequent requirement for elevated temperatures in these reactions[1c,d,3] and our own continued interest in silylation-induced reactivity[4] attracted us to the possibility that trimethylsilyl trifluoromethanesulfonate (TMSOTf) might accelerate these reactions. Herein, we report the results of our efforts in this area, which demonstrate that TMSOTf remains active as a silylating agent and/or Lewis acid even in the presence of a carbanion nucleophile.

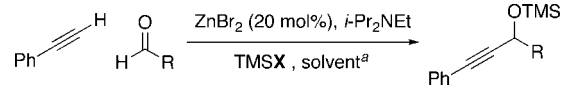
At the outset of these experiments, our primary concern was that terminal silylation of the zinc acetylide might occur under our reaction conditions. Indeed, Shaw and Rahaim have very recently shown that zinc acetylides react with TMSOTf in excellent yield under reaction conditions very similar to those we planned to employ (eq 1).[5] Interestingly, we found that replacement of TMSOTf with TMSCl prevented acetylene silylation from occurring.



(1)

Accordingly, we began our investigation by studying the addition of phenylacetylene to benzaldehyde in the presence of $ZnBr_2$, *i*-Pr_2NEt, and TMSCl in CH_2Cl_2 (Table 1, entry 1).Because ample precedent demonstrates that zinc acetylide formation occurs under these conditions,[6] we were disappointed in the very low conversion observed. When TMSCl was replaced with TMSOTf, however, acetylide silylation was suppressed in favor of propargyl alcohol formation (entry 2). Unfortunately, side reactions hampered generality with respect to aldehyde under these conditions by reducing conversion to the desired product (entry 3).[7] A simple change in medium to Et_2O provided a more reliable and general system (entry 7), and final adjustments in stoichiometry resulted in our optimized reaction conditions (entries 9 and 10).

TABLE 1. Reaction Optimization



entry	R	X	solvent	temp	conv (%)[b]
1	Ph	Cl	CH_2Cl_2	rt	<5
2	Ph	OTf	CH_2Cl_2	rt	93
3	4-anisyl	OTf	CH_2Cl_2	rt	65
4	Ph	OTf	THF	rt	72
5	Ph	OTf	CH_3CN	rt	<5
6	Ph	OTf	toluene	rt	61
7	Ph	OTf	Et_2O	rt	78
8	Ph	OTf	Et_2O	0 °C	73
9[c]	**Ph**	**OTf**	**Et_2O**	**rt**	**89**
10[c]	**4-anisyl**	**OTf**	**Et_2O**	**rt**	**88**

[a] Standard reaction conditions: phenylacetylene (0.5 mmol), $ZnBr_2$ (0.1 mmol), *i*-Pr_2NEt (0.75 mmol), RCHO (1.0 mmol), TMS**X** (0.55 mmol), solvent (3 mL), 1 h. [b] Conversion determined by ^1H NMR spectroscopy of the unpurified reaction mixture. [c] Modified stoichiometry for *i*-Pr_2NEt and TMSOTf: *i*-Pr_2NEt (1.0 mmol), TMSOTf (0.6 mmol).

Our working hypothesis regarding the reaction mechanism is outlined in Scheme 1.[8] Formation of zinc acetylides by treatment of a terminal alkyne with $ZnBr_2$ and an amine base is well documented.[3,6] Subsequently, addition of the acetylide to the aldehyde takes place, followed by silylation of the zinc alkoxide by TMSOTf, to release the product and regenerate the catalyst (Scheme 1A). In this reaction mechanism, TMSOTf

(1) For recent work, see the following. (a) Ti: Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122–125. (b) In: Sakai, N.; Kanada, R.; Hirasawa, M.; Konokahara, T. *Tetrahedron* **2005**, *61*, 9298–9304. (c) Ag: Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395–4398. (d) Cu: Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901–3904. (e) Zn: Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733–5736. For a Lewis base-catalyzed approach, see: (f) Lettan, R. B.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227–3230.

(2) For the use of propargyl alcohols as building blocks in organic synthesis, see: (a) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197–3199. (b) Kabalka, G.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929–3931. (c) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.

(3) (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.

(4) (a) Downey, C. W.; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559–3562. (b) Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299–3302.

(5) Rahaim, R. J., Jr.; Shaw, J. T. *J. Org. Chem.* **2008**, *73*, 2912–2915.

(6) (a) Lee, K. Y.; Park, D. Y.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1617–1619. (b) Leeuwenbergh, M. A.; Timmers, C. M.; van der Marel, B. A.; van Boom, J. H.; Mallet, J.-M.; Sinaÿ, P. G. *Tetrahedron Lett.* **1997**, *38*, 6251–6254.

(7) Cannizzaro reaction appears to be competitive with the desired reaction for some substrates when CH_2Cl_2 is employed as solvent. For additions to benzaldehyde and anisaldehyde, ^1H NMR analysis of the unpurified reaction mixtures revealed the presence of benzyl alcohol and *p*-methoxybenzayl alcohol, respectively.

(8) Although the catalyst is represented as $ZnBr_2$ in these mechanistic schemes, it may be in equilibrium with the equally active $Zn(OTf)_2$ under these reaction conditions.

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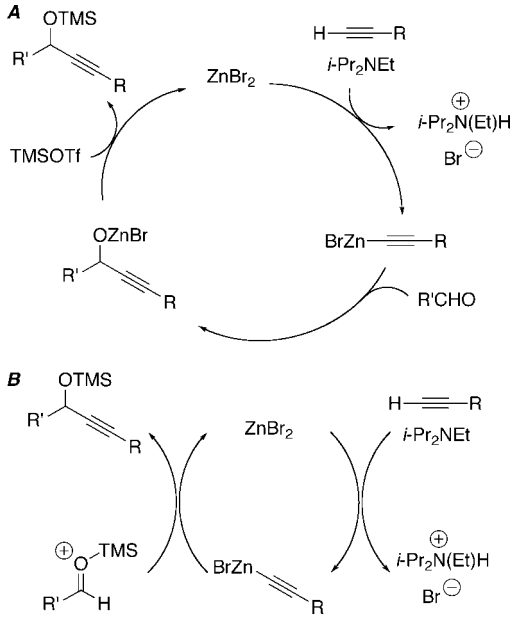
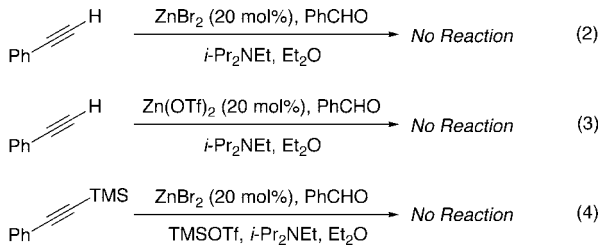
SCHEME 1. Proposed Mechanisms



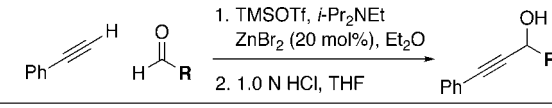
serves to induce catalyst turnover. We are disinclined toward this mechanism at present because no product is observed in the absence of TMSOTf (vide infra), even with stoichiometric quantities of $ZnBr_2$. Alternatively, preactivation of the aldehyde oxygen by the Lewis acidic TMSOTf would preclude the necessity for subsequent silylation of an alkoxide species (Scheme 1B). Furthermore, the ability of TMSOTf to activate the aldehyde toward nucleophilic attack may explain the remarkable rate acceleration observed. Indeed, this mechanism is analogous to our mechanistic hypothesis regarding the TMSOTf-induced one-pot enol silane formation−Mukaiyama aldol reaction previously reported by our laboratory.[4a]

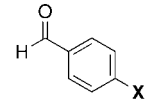
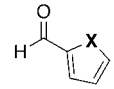
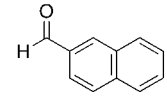
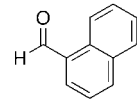
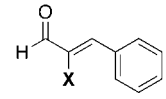
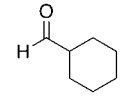
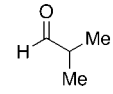
The control experiments illustrated below are in agreement with both variations of the proposed mechanisms and serve to illustrate the remarkable ability of TMSOTf to accelerate these reactions. As shown in eq 2, no reaction occurs in the absence of TMSOTf under otherwise optimized reaction conditions. Furthermore, we have eliminated the possibility that TMSOTf acts merely as an agent to transform $ZnBr_2$ into $Zn(OTf)_2$ by showing in eq 3 that $Zn(OTf)_2$ is also an ineffective catalyst in the absence of TMSOTf.[9] We also considered the possibility that a silylated acetylide was acting as the nucleophile in these reactions, in a manner somewhat analogous to the Mukaiyama aldol reaction. In the event, however, we confirmed that the independently synthesized and purified silyl acetylide is inactive under our reaction conditions (eq 4). In summary, these experiments show that TMSOTf is necessary for reactivity but does not appear to react directly with either the acetylide or the zinc catalyst.



After the determination of optimized reaction conditions and preliminary verification of the reaction mechanism, we examined

TABLE 2. Addition of Phenylacetylene to Various Aldehydes[a]



entry	RCHO		product	yield (%)[b]
1		**X** = H	**1**	95
2		**X** = OMe	**2**	86
3		**X** = Me	**3**	92
4		**X** = O	**4**	89
5		**X** = S	**5**	93
6			**6**	89
7			**7**	85
8		**X** = H	**8**	90
9		**X** = Me	**9**	94
10			**10**	92
11			**11**	88

[a] See Supporting Information for experimental procedures, which vary by substrate. [b] Isolated yield after chromatography.

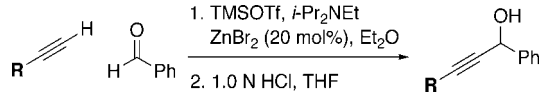
the scope of this reaction by performing a survey of various aldehydes (Table 2). Aromatic aldehydes are exceptional substrates for this reaction (entries 1−3), including electron-rich aromatic and heteroaromatic electrophiles (entries 4 and 5). The electron-poor *p*-nitrobenzaldehyde, however, was hampered by poor solubility in diethyl ether and also reacted poorly (<50% yield) in CH_2Cl_2 (not shown). Bulky naphthyl-substituted aldehydes (entries 6 and 7) and cinnamyl aldehydes (entries 8 and 9) are also excellent acceptors. Saturated aldehydes were more problematic as a result of competing aldol and enol silane formation reactions.[10]Nonetheless, portionwise addition of aldehyde, *i*-Pr_2NEt, and TMSOTf allowed successful addition to α-branched aliphatic aldehydes in high yield (entries 10 and 11). The representative unbranched propionaldehyde failed to react efficiently (<50% conversion, not shown).

After the establishment of the aldehyde scope, we conducted a survey of a range of terminal acetylenes in order to more fully determine the reaction scope. The addition of various acetylenes to the representative electrophile benzaldehyde is summarized in Table 3. To our pleasure, both electron-rich and electron-

(9) When TMSOTf is present, $Zn(OTf)_2$ reacts in a manner comparable to that of $ZnBr_2$.

(10) Aldehyde-derived enol silane was detectable by ^1H NMR spectroscopy of the unpurified reaction mixture.

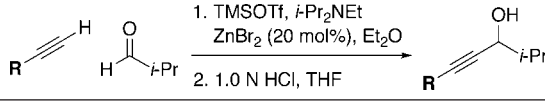
TABLE 3. Addition of Various Acetylenes to Benzaldehyde[a]



entry	acetylene	product	yield (%)[b]
1	X = 4-H	**1**	95
2	X = 4-OMe	**12**	97
3	X = 4-*n*-pentyl	**13**	95
4	X = 2-NO_2	**14**	92
5	Et_3Si	**15**	90
6	Me	**16**	89
7	EtO, O	**17**	78

[a] See Supporting Information for experimental procedures, which vary by substrate. [b] Isolated yield after chromatography.

TABLE 4. Addition of Various Acetylenes to Isobutyraldehyde[a]



entry	acetylene	product	yield (%)[b]
1	X = 4-H	**11**	88
2	X = 4-OMe	**18**	96
3	X = 4-*n*-pentyl	**19**	94
4	X = 2-NO_2	**20**	94
5	Et_3Si	**21**	59
6	Me	**22**	72
7	EtO, O	**23**	80

[a] See Supporting Information for experimental procedures, which vary by substrate. [b] Isolated yield after chromatography.

poor aromatic acetylenes reacted in exemplary yields (entries 1−4). Alkyl and trialkylsilyl acetylenes were also competent substrates, demonstrating the wide scope of reactivity under these conditions (entries 5 and 6). Ethyl propiolate also reacted competently to provide good yield of the γ-hydroxy ynoate product (entry 7).

We next targeted isobutyraldehyde for a survey of the addition of the same acetylenes to an aliphatic substrate (Table 4). Because the aldehyde competitively converts to an enol silane under these reaction conditions, we anticipated generally lower yields. To our delight, however, aromatic-substituted alkynes again reacted in outstanding yields (entries 1−4). Reactivity with other alkynes did suffer somewhat (entries 5−7), but moderate to good yields were still obtained for this challenging substrate class.

In conclusion, TMSOTf remarkably accelerates the zinc-catalyzed addition of terminal acetylenes to aldehydes, without significant competing acetylene silylation. The TMSOTf may induce catalyst turnover by silylation of the nascent zinc alkoxide or may precomplex and activate the aldehyde electrophile. The reaction scope includes both aromatic and aliphatic acetylenes and aldehydes. We anticipate the extension of this general strategy to other zinc-catalyzed alkyne addition reactions, including stereoselective variants.

Experimental Section

Typical Procedure for TMSOTf-Accelerated Addition of Terminal Acetylenes to Aldehydes. Synthesis of Product 1.[2c] To an oven-dried round-bottomed flask under N_2 atmosphere was added $ZnBr_2$ (104 mg, 0.398 mmol). The flask was charged with Et_2O (12 mL), and then phenylacetylene (220 μL, 205 mg, 2.00 mmol), diisopropylethylamine (700 μL, 519 mg, 4.01 mmol), benzaldehyde (408 μL, 426 mg, 4.01 mmol), and TMSOTf (432 μL, 530 mg, 2.39 mmol) were added sequentially. The heterogeneous mixture was stirred for 1 h and then passed through a plug of silica (1.0 cm × 3.0 cm) with Et_2O. The mixture was concentrated in vacuo and then dissolved in THF (6 mL). The solution was stirred with 1.0 M HCl (3 mL) for 15 min, then diluted in Et_2O and washed with water (1×) and saturated $NaHCO_3$ (1×). The organic layer was diluted with hexanes (1:2 hexanes/Et_2O) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography (5−20% EtOAc/hexanes) as a yellow oil (95% yield): IR (film) 3348, 1480, 1437, 1021, 955, 901, 750, 726, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.3 Hz, 2H), 7.53−7.49 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.40−7.32 (m, 4H) 5.73 (s, 1H), 2.28 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 131.8, 128.7, 128.6, 128.5, 128.3, 126.8, 122.5, 88.7, 86.7, 65.2; HRMS (ESI) exact mass calcd for $C_{15}H_{12}ONa$ $[M + Na]^+$ 231.0780, found 231.0790.

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

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