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Diastereoselective Zinc-Catalyzed Conjugate Addition of Alkynes

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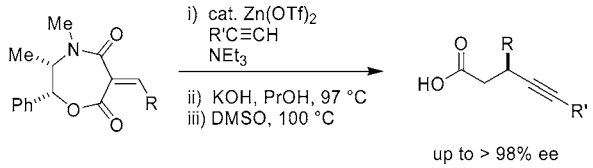
ABSTRACT



The conjugate addition of in situ generated zinc alkynylides is reported. The use of chiral, ephedrine derived acceptors provides access to enantiomerically enriched β-alkynyl acids in good yields.

Conjugate addition reactions of organometallic species are well-established approaches for the stereoselective formation of carbon−carbon bonds.[1] In such processes, the use of Cu(I) in stoichiometric or catalytic quantities has enjoyed wide application with alkyl, alkenyl, and aryl carbanions. Until recently, alkynes rarely have been used as nucleophiles for this process, mainly due to the low tendency of the corresponding copper alkynylides to undergo conjugate addition.[2] However, some exceptions have been documented.[3,4] Other metal alkynylides can be used, such as those of aluminum,[5]boron,[5b,c,6,7] and zinc.[8] In the only report documenting the use of alkynylzinc reagents, these were prepared upon mixing a lithium alkynylide with $ZnBr_2$ and prescribed the use of tBuMe$_2$SiOTf as an activating agent for the addition to α,β-unsaturated ketones.[8] We have recently described the Cu(I)-catalyzed conjugate addition reaction of acetylenes to Meldrum's acid-derived acceptors, which provides access to racemic alkynyl acids.[4] Given the utility of these compounds as useful building blocks, it would be advantageous to have available methodology that furnishes them in enantiomerically enriched form. To the best of our knowledge, neither diastereoselective nor enantioselective approaches have been described for ester-derived acceptors and alkynylzinc reagents. Herein we document an approach that involves the in situ activation of terminal acetylenes by Zn(II) and an amine base and their subsequent participation in conjugate addition reactions to chiral oxazepanedione acceptors derived from ephedrine and malonates.

We have previously described the facile generation of zinc alkynylides by treating terminal alkynes with $Zn(OTf)_2$ and an amine base.[9−12] The in situ produced zinc alkynylides have been shown to undergo addition to electrophiles including nitrones,[9] acyliminiums,[10] and aldehydes.[11] Because

(1) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 569−592.

(2) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211.

(3) The addition of copper alkynylides to enones has been reported to proceed in the presence of activating agents such as TMSI/LiI or TBDMSOTf, see: (a) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238−7244. (b) Kim S.; Park, J. H.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 783−786.

(4) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054−6055.

(5) (a) Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320−7322. (b) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, *13*, 2627−2630. (c) Bruhn, M.; Brown, C. H.; Collins, P. W.; Palmer, J. R.; Dajani, E. Z.; Pappo, R. *Tetrahedron Lett.* **1976**, *17*, 235−238. (d) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053−3061.

(6) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954−956.

(7) Chong and co-workers have reported the use of alkynylboronates prepared from 3,3′-diphenyl-BINOL in enantioselective additions to unsaturated ketones: Chong, J. M.; Shen, L. X.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822−1823.

(8) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627−7630.

(9) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245−11246. (b) Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331−2333. (c) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056.

(10) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497−1499.

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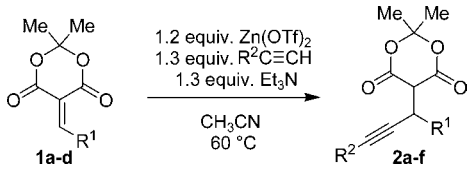
Table 1. Zinc-Mediated Conjugate Addition of Alkynes to **1**



entry	acceptor (R^1)	compd no.	alkyne (R^2)	time, h	yield, %
1	Pr	**1a**	$Ph(CH_2)_2$	2	88
2	*i*Pr	**1b**	$Ph(CH_2)_2$	2	89
3	*i*Pr	**1b**	Me_3Si	1.5	86
4	*i*Pr	**1b**	Ph	3	85
5	*t*Bu	**1c**	$Ph(CH_2)_2$	2	87
6	Ph	**1d**	$Ph(CH_2)_2$	1	90

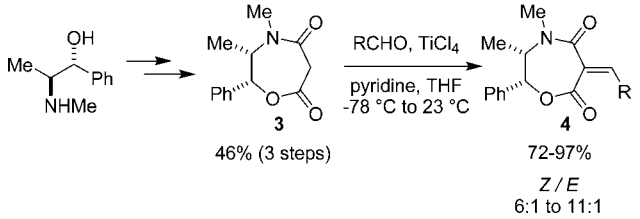
the alkynylzinc reagents produced (RC≡C−ZnOTf)[12] are distinct from those that have been previously examined, derived from transmetalation (RC≡C−Li + $ZnCl_2$) or metalation (RC≡C−H + Me_2Zn or Et_2Zn), we have been interested in exploring their reactivity in a host of different processes.

In initial investigations with the alkynylzinc reagent derived from 4-phenyl-1-butyne and $Zn(OTf)_2/Et_3N$, we observed that doubly activated Michael acceptors were required for conjugate addition. In this respect, Meldrum's acid derived acceptors **1**[4,13,14] (Table 1) are useful, since they can be easily prepared by simply heating Meldrum's acid and aldehydes in water[15] and, furthermore, the product of conjugate addition can be easily hydrolyzed and decarboxylated to yield the corresponding β-alkynyl acids by heating in wet DMF.[4]

Under optimized conditions, the in situ generated zinc alkynylides add to **1a**−**d** to form adducts **2a**−**f** in acetonitrile at 60 °C in 1.5−3 h. The method allows addition of alkyl-, aryl-, and silyl-alkynylides to acceptors substituted with propyl, isopropyl, *tert*-butyl, and phenyl groups in 85−90% isolated yield (Table 1). This unprecedented process with Zn(II) is notable because of its ease of execution with short reaction times.

We next decided to investigate chiral Michael acceptors with Zn-alkynylides. We speculated that the optically active oxazepanedione acceptors developed by Mukaiyama[16] would be useful reaction partners leading to optically active

Scheme 1



β-alkynyl acids provided they were sufficiently electrophilic toward an alkynylzinc (Scheme 1). They are accessed from ephedrine and dimethylmalonate in useful yields.[17] Condensation of **3** with aldehydes is mediated by $TiCl_4$ and pyridine[16c,18] and gives predominantly the (*Z*)-alkylidene products (6−11:1, 72−97% yield);[19] importantly, the minor (*E*)-isomers can be conveniently removed by silica gel chromatography. These acceptors **4** have been used in asymmetric nickel-catalyzed conjugate additions of Grignard reagents,[16] hetero-Diels−Alder reactions,[20] and trimethylenemethane cycloadditions.[21] However, the use of alkynylmetal nucleophiles was not examined in these studies.

We have found that the addition of zinc alkynylides to **4** proceeds to completion at 23 °C in CH_2Cl_2. Optimal results were obtained by using 60 mol % of $Zn(OTf)_2$ furnishing the adducts **5a**−**e** in 63−95% yield in 18 h as a mixture of diastereomers, because the C_α stereocenter produced upon protonation of the enolate is formed nonselectively. The selectivity at C_β was assayed by converting the adducts into the corresponding β-alkynyl acids **6a**−**e** and analyzing their ee (Table 2). Thus, alkaline hydrolysis of **5a**−**e** with KOH in refluxing 1-propanol led to intermediate diacids, which were decarboxylated in DMSO at 100 °C (Table 2) furnishing **6a**−**e** in 84−92% yield over two steps.

We found that the addition is highly diastereoselective for acceptors with branched substituents (95→98% ee, Table 2). The adduct is formed with lower stereocontrol (82% ee) for an acceptor bearing an unbranched alkyl chain. Additions to acceptors with aromatic or unsaturated residues were not observed to proceed. The high selectivities at room temperature are noteworthy, as alkyl Grignard additions previously reported were selective only at −78 °C with these acceptors.[16c] The loading of Zn(II) could be lowered to 20 mol %, when the reaction was conducted at 60 °C in toluene,[11b] although the selectivities and isolated yields were somewhat lower (Table 2). The stereoselectivity of addition is consistent with

(11) (a) Frantz, D. E.; Fässler, 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. (c) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (d) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964−971. (e) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606. (f) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813−6817.

(12) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843−5845.

(13) For enantioselective Et_2Zn additions to Meldrum's acid derived acceptors see: Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557−4558.

(14) Kruse, L. I.; Kaiser, W. E. D.; Chambers, P. A.; Goodhart, P. J.; Ezekiel, M.; Ohlstein. *J. Med. Chem.* **1988**, *31*, 704−706.

(15) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203−5205.

(16) (a) Mukaiyama, T.; Takeda, T.; Osaki, M. *Chem. Lett.* **1977**, 1165−1168. (b) Mukaiyama, T.; Hirako, Y.; Takeda, T. *Chem. Lett.* **1978**, 461−464. (c) Mukaiyama, T.; Takeda, T.; Fujimoto, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368−3372.

(17) For details see the Supporting Information.

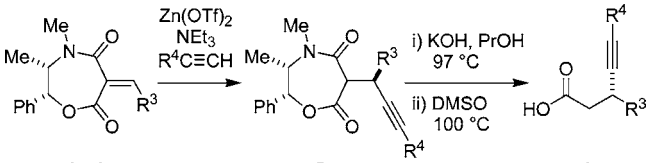
(18) Lehnert, W. *Tetrahedron Lett.* **1970**, *11*, 4723−4724.

(19) Proved by the X-ray structure of **4d** (R^3 = *t*Bu), see Supporting Information. The stereochemistry was initially missassigned (ref 15), but later corrected (refs 19 and 20).

(20) (a) Tietze, L. F.; Brand, S.; Pfeiffer, T. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 784−786. (b) Tietze, L. F.; Brand, S.; Pfeiffer, T.; Antel, J.; Harms, K.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 921−923.

(21) Trost, B. M.; Yang, B. W.; Miller, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 6482−6484.

Table 2. Zinc-Catalyzed Conjugate Addition of Alkynes to **4**



4a-d **5a-e** **6a-e**

acceptor (R^3)	compd no.	alkyne (R^4)	mol % of Zn^{II}	yield of **6**, %	ee of **6**, %[d]
Pr	**4a**	$Ph(CH_2)_2$	60[a]	82	82
			20[b]	75	68
*i*Pr	**4b**	$Ph(CH_2)_2$	60[a]	76	>98
			20[b]	75	96
*i*Pr	**4b**	Et_3Si	60[a]	79[c]	95
			20[b]	68[c]	89
cC_6H_{11}	**4c**	$Ph(CH_2)_2$	60[a]	83	>98
			20[b]	63	84
*t*Bu	**4d**	$Ph(CH_2)_2$	60[a]	55	>98

[a] Additions conducted in CH_2Cl_2 at 23 °C for 18 h. [b] Additions conducted in toluene at 60 °C for 24 h. [c] The Et_3Si- group was cleaved off during treatment with KOH. [d] ee was determined either by ^{19}F NMR analysis of the Mosher ester of the corresponding alcohol or by chiral HPLC (see the Supporting Information for details).

attack of the Zn-alkynylides from the convex face of the oxazepane, namely syn to the substituents on the ring,[22] which is in agreement with earlier mechanistic studies involving cycloadditions and conjugate additions by Grignard reagents.[20b,23]

It is interesting to note the contrasting behavior between the two acceptors that have been presented herein vis a vis Zn(II) loading. Thus, although the additions to Meldrum's acid acceptors (**1** → **2**) necessitate, at the current level of development, the use of stoichiometric amounts of $Zn(OTf)_2$ to observe full conversion, the additions to oxazepanedione acceptors (**4** → **5**) can be carried out with substoichiometric amounts of Zn(II). As a possible explanation for this observation, it is important to note that in the course of additions to **1**, a precipitate is observed, whose structure by ^1H NMR spectroscopy is consistent with that of a zinc-enolate. By contrast, in the additions to the oxazepanediones no such precipitation is observed. The phase separation that occurs with the former can be speculated to obviate turnover.

In summary, we have shown for the first time that zinc alkynylides generated in situ under mild conditions by the action of $Zn(OTf)_2$ and Et_3N on terminal acetylenes undergo conjugate addition to Meldrum's acid derived acceptors in good yields for a range of substrates. In the diastereoselective addition to ephedrine-derived oxazepanedione acceptors, $Zn(OTf)_2$ can be used in catalytic amounts and the adducts obtained can be converted into enantiomerically enriched β-alkynyl acids. These are a useful class of chiral building blocks that are otherwise not easily accessed.[24] In a broader sense, the results described expand the scope of zinc alkynylide reagents beyond the C═O and C═N additions reported to date and thus provide new avenues for further investigations with these reagents.

Acknowledgment. We thank Dr. Schweizer for the X-ray analysis of **4d** and the Roche Research foundation for support of T.F.K.

Supporting Information Available: Characterization data for compounds **2**, **4**, and **6**, X-ray structure of **4d**, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Assigned by determination of the absolute stereochemistry of **6c** (R^3 = *i*Pr, R^4 = H) by converting it into the corresponding alkane with H_2, PtO_2 in EtOAc (quant.) and comparing the optical rotation with a reported value: Enders, D.; Rendenbach, B. E. M *Tetrahedron* **1986**, *42*, 2235−2242.

(23) Addition of 4-phenyl-1-butyne to (*E*)-**4d** with use of 60 mol % of zinc and converting the adduct into the β-alkynyl acid gave *ent*-**6d** in 84% yield and 95% ee (not shown).

(24) For a different approach to a related class of compounds possessing C_α and C_β substitution, see: (a) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128−3130. (b) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749−5759.