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Preparation of Substituted Enol Derivatives From Terminal Alkynes and Their Synthetic Utility

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Abstract

Stereodefined enol derivatives of aldehydes are prepared from terminal alkynes. Specifically, terminal alkynes are known to undergo Cp_2ZrCl_2 -catalyzed methylalumination. Here, we show that the resultant vinylalanes can be oxygenated with peroxyzinc species to generate trisubstituted enolates. Electrophilic trapping with carboxylic anhydrides or silyl triflates yields trisubstituted enol esters or silanes, respectively. The tandem carbometallation/oxygenation tolerates free and protected alcohols, heterocycles, olefins and nitriles. Likewise, amination can be accomplished using azodicarboxylates. Stereodefined enol esters can undergo asymmetric dihydroxylation to yield optically-active α -hydroxy aldehydes. Reduction with NaBH_4 provides the diols of 1,1-disubstituted olefins in excellent ee. An application of this methodology to the enantioselective synthesis of the insect pheromone frontalinal is presented. Finally, α -hydroxy aldehydes are shown to undergo homologation to a terminal alkyne, reductive amination, oxidation and olefination. Preliminary results indicate that tandem carbometallation/amination can be accomplished with azodicarboxylates. In this way, ene-hydrazines are formed in excellent yield.

Stereodefined enol derivatives of α -branched aldehydes (**4**) represent valuable building blocks for organic synthesis, but limited access to them has compromised their utility. They are most often prepared from the corresponding aldehyde, although these approaches generally afford mixtures of olefin stereoisomers.¹ Furthermore, current strategies for obtaining the α -substituted aldehydes *themselves* are limited in reaction scope and require multiple synthetic operations.² An alternative synthesis of trisubstituted enol derivatives might involve tandem carbometallation-oxygenation of terminal alkynes (Scheme 1). In this regard, we previously documented the carbocupration-oxygenation of terminal alkynes, in which a vinyl copper intermediate (**2**, $\text{M} = \text{Cu}$) was oxidized with $t\text{BuOOLi}$.³ Electrophilic trapping of the resultant *E*-enolate (**3**) generated *E*-enol esters and silanes. However, methyl-substituted products were not accessible by this method because methyl-cupration of alkynes is not efficient.⁴ Accordingly, we sought a general method for obtaining methyl-substituted enol esters and ethers (**4**, $\text{R}' = \text{Me}$). As described below, we have accomplished this objective and have begun to explore the asymmetric transformations of stereodefined enol derivatives.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Negishi's catalytic methylalumination reaction provides a complimentary method for carbometalation.⁵ Methylalumination-oxygenation of monosubstituted olefins has been reported,⁶ but analogous chemistry of alkynes is unknown (**5**; Table 1). Trialkyl alanes are oxidized cleanly with molecular oxygen. Therefore, our initial investigations aimed to oxidize *alkenyl* aluminum intermediates with O₂, but these experiments proved unsuccessful. Under these conditions, incomplete conversion and over-oxidation limited yields. Results with the oxenoid *t*BuOOLi were more promising.⁷ With this reagent, we observed 65% conversion of vinylalane **5a** (R = *n*-C₁₀H₂₁) to the corresponding aldehyde (E⁺ = H) with 2-methyl-1-dodecene accounting for the remainder of the starting material. Further evaluation of peroxymetal oxidants revealed that peroxyzinc reagents EtZnOO*t*Bu and MeZnOO*t*Bu effected the oxidation of **5a** to the corresponding aldehyde with 85% and 98% conversions, respectively. Thus when **5a** was oxidized with freshly prepared MeZnOO*t*Bu (1.3 equiv to AlMe₃) at 0°C and subsequently trapped with Bz₂O, enol benzoate **4a** was obtained in 78% isolated yield (Table 1, entry 1). Zinc peroxides have been used in epoxidation reactions,⁸ but, to the best of our knowledge, they have not been used previously to oxidize carbanions.

The methylalumination-oxygenation reaction tolerates considerable functionality including protected and free alcohols, heterocycles, and olefins.⁹ Electrophilic trapping is not limited to benzoylation: enol acetates and TES enol ethers (entries 9–14) were prepared in high yields as well. Furthermore, in every case studied to date, the enol derivative has been isolated as a single regioisomer with a high E-isomer content (all E/Z ratios > 20/1).¹⁰

Trisubstituted, stereodefined enol derivatives of this type were previously inaccessible, and their ready availability allowed us to explore new chemistry and evaluate their synthetic utility. In particular, we envisioned an entry to chiral α -hydroxy aldehydes (**7**) and 1,2-diols (**8**) by employing the enol benzoates in catalytic asymmetric dihydroxylation (AD) reactions.^{11,12} As expected, the enol benzoate substrates afforded dihydroxylated products in high enantiomeric purity (Table 2, all entries $\geq$ 94% ee from **4**). In contrast, many 1,1-disubstituted olefins (**6**) are poor substrates for AD; therefore, AD of the enol benzoates, followed by a reductive workup with NaBH₄, presents a highly enantioselective route to these substances. Of note, controlling stereochemistry of the olefin is critical: a 9:1 E/Z mixture of **4a** was converted to **8a** in 81% ee under the conditions outlined in Table 2. The utility of the AD reaction was exemplified in the total synthesis of the insect pheromone (+)-frontalin (**10**; Scheme 2).¹³ Enol benzoate **9** was treated consecutively with AD-mix β and [Me₄N]BH(OAc)₃ to yield (+)-frontalin in 93% ee and in 49% overall yield from the commercially available alkyne **1i**. In comparison, the 1,1-disubstituted olefin **11** was dihydroxylated with poor selectivity and in low yield with AD-mix β .

The enantioenriched α -hydroxy aldehydes obtained from the dihydroxylations are useful materials for further synthetic manipulation (Scheme 3). For example, following AD, an Ohira-Bestmann homologation of aldehyde **7b** provided propargylic alcohol **12** in 77% yield. Reductive amination of **7b** proceeded smoothly to yield the corresponding amino alcohol (**13**, 84% yield).¹⁴ Alternatively, the same starting material (**7b**) could be oxidized to its methyl ester (**14**, 92%),¹⁵ or undergo olefination to afford an α,β -unsaturated ester (**15**, 68%, E:Z = 14.3:1).¹⁶

Tandem carbometalation-oxidation is not limited to carbon-oxygen bond formation. Indeed, in preliminary experiments we found that vinyl alane **5** could be aminated in high yields with azodicarboxylates (Table 3).¹⁷ Hydrogenation and deprotection of **16f** provided the free amine in >90% yield.¹⁸ With access to stereodefined enol and enamine derivatives, future studies will seek to engage these materials in a variety of asymmetric transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2. Total Synthesis of (+)-Frontalin^a

^aReagents and conditions: (a) PdCl₂, CuCl, O₂, DMF/H₂O (7:1), quant; (b) AD-mix-β, MeSO₂NH₂, NaHCO₃, ^tBuOH/H₂O (1:1), 0 °C, 18 h, 85%; (c) [Me₄N]BH(OAc)₃, AcOH, CH₃CN, 76%; (d) AD-mix-β, ^tBuOH/H₂O, 0 °C.

Scheme 3. Transformations of α -hydroxy aldehydes^a

^aReagents and conditions: (a) $(\text{MeO})_2\text{POCN}_2\text{COMe}$, K_2CO_3 , MeOH , $0\text{ }^\circ\text{C}$ -r.t.; (b) BnNH_2 , Toluene, $4\text{ \AA}$ MS, $105\text{ }^\circ\text{C}$; NaBH_4 , MeOH , $0\text{ }^\circ\text{C}$; (c) I_2 , KOH , MeOH , $0\text{ }^\circ\text{C}$; (d) $\text{Bu}_3\text{PCH}_2\text{CO}_2\text{EtBr}$, NaHCO_3 , Toluene, $90\text{ }^\circ\text{C}$.

Table 1Preparation of Enol Derivatives from Terminal Alkynes^a

$ \begin{array}{c} \text{R} \text{---} \text{C} \equiv \text{C} \text{---} \text{H} \\ \text{1 a-p} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Me}_3\text{Al, cat. Cp}_2\text{ZrCl}_2, \text{cat. H}_2\text{O or MAO}} \begin{array}{c} \text{CH}_3 \\ \\ \text{R} \text{---} \text{C} = \text{C} \text{---} \text{AlMe}_2 \\ \text{5a-p} \end{array} \xrightarrow[\text{EX}]{\text{MeZnOO}^t\text{Bu}, 0^\circ\text{C}, 2\text{h.};} \begin{array}{c} \text{CH}_3 \\ \\ \text{R} \text{---} \text{C} = \text{C} \text{---} \text{OE} \\ \text{4a-p} \end{array} $			
Entry	Alkyne	EX	Product
1	1a	Bz ₂ O ^c	R = C ₁₀ H ₂₁ ; E = Bz
2	1b	Bz ₂ O ^c	R = CH ₂ Ph; E = Bz
3	1c	Bz ₂ O ^c

4	1d	Bz ₂ O ^c	R = Ph; E = Bz

Entry	Alkyne	EX	Product
5	1e, 1f	Bz ₂ O ^{c,d}

6	1g	Bz ₂ O ^c	
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Entry	Alkyne	EX	Product
7	1h	Bz ₂ O ^c	
8	1i, 1j	Bz ₂ O ^c	
9	1k	Ac ₂ O	
10	1l	Ac ₂ O	
11	1m	Ac ₂ O	
12	1n	Ac ₂ O	
13	1o	TESOTf	
14	1p	TESOTf	

^a 1.0 equiv alkyne, 1.2–4 equiv Me₃Al, 5–30 mol% Cp₂ZrCl₂, 2.5–30 mol%, H₂O or MAO, 0.3 M in CH₂Cl₂; MeZnOO^tBu (0.3M in Toluene, 1.3–1.4 equiv to Me₃Al).

^b Isolated yields (chromatography not necessary for entries 10–14).

^c Catalytic ⁿBu₃P added.

^d BzCl was added after benzylation of the enolate. See supporting information for complete experimental details.

Table 2

Asymmetric Dihydroxylation (AD) of Enol Benzoates^d

Entry	R	ee (%) ^b from:			Product	Yield (%) ^c
		4	6	6		
1	ⁿ C ₁₀ H ₂₁				8a	78
2	PhCH ₂				8b	84
3					8c	59
4	Ph	95	94 ^d		8d	75
5		96			8g	87
6		95	32		8q ^e	75

^a All AD reactions were performed under standard conditions: AD-mix β, 0.1M in *t*-BuOH/H₂O, 0°C.

^b Unless noted otherwise, ee's determined by HPLC. See supporting information for details.

^c Isolated yields from **4**.

^d % ee from reference 11a.

^e 1.0 equiv. MeSO₂NH₂ was added to the reaction.

Table 3Synthesis of Stereodefined Ene-hydrazines (**16**) from Terminal Alkynes.^a

$ \begin{array}{c} \text{R}^1\text{---}\equiv \\ \mathbf{1} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{Cp}_2\text{ZrCl}_2 \text{ (cat)} \atop \text{Me}_3\text{Al}} \begin{array}{c} \text{CH}_3 \\ \\ \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{AlMe}_2 \\ \mathbf{5} \end{array} \xrightarrow[\text{-25 } ^\circ\text{C}]{\text{N}=\text{N}\text{---}\text{R}^2} \begin{array}{c} \text{CH}_3 \\ \\ \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{N}(\text{R}^2)\text{---}\text{N}(\text{R}^2)\text{H} \\ \mathbf{16} \end{array} $				
Entry	R ¹	R ²	Product	Yield (%) ^b
1	ⁿ C ₁₀ H ₂₁	CO ₂ ⁱ Pr	16a	79
2	CH ₂ Ph	CO ₂ ⁱ Pr	16b	90
3	-(CH ₂) ₃ OH	CO ₂ ⁱ Pr	16c	86
4	-(CH ₂) ₃ OSi(ⁱ Pr) ₃	CO ₂ ⁱ Pr	16d	83
5	3-Thienyl	CO ₂ ⁱ Pr	16e	77
6	CH ₂ Ph	CO ₂ ⁱ Bu	16f	84

^a Methylalumination as in Table 1; 1.5–3 equiv azodicarboxylate. See supporting information for complete experimental details.^b Isolated yields.