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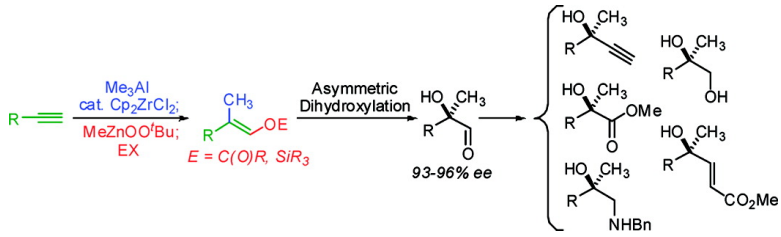

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Preparation of Substituted Enol Derivatives From Terminal Alkynes and Their Synthetic Utility

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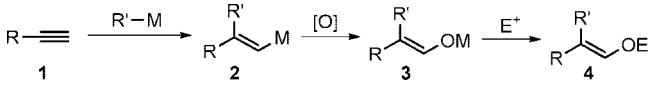
Stereodefined enol derivatives of α-branched aldehydes (**4**) represent valuable building blocks for organic synthesis, but limited access to them has compromised their utility. They are most often prepared from the corresponding aldehyde, although these approaches generally afford mixtures of olefin 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 carbometalation-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**, M = Cu) was oxidized with ^{t}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**, R′ = Me). As described below, we have accomplished this objective and have begun to explore the asymmetric transformations of stereodefined enol derivatives.

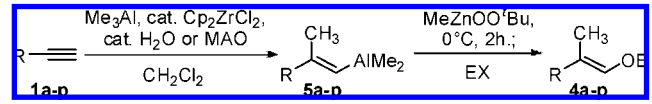
Scheme 1

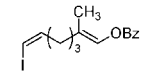
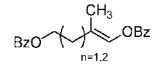
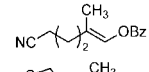
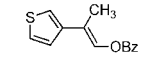
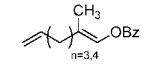
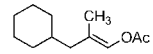
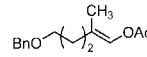
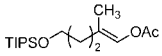
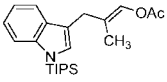
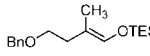
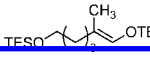


Negishi's catalytic methylalumination reaction provides a complementary method for carbometalation.[5] Methylalumination-oxygenation of monosubstituted olefins has been reported,[6] but analogous chemistry of alkynes is unknown. Since trialkyl alanes are oxidized cleanly with molecular oxygen, our initial investigations aimed to oxidize *alkenyl* aluminum intermediates (**5**, Table 1) with O_2. These experiments proved unsuccessful as incomplete conversion and overoxidation limited yields. Results with the oxenoid ^{t}BuOOLi were more promising.[7] With this reagent, we observed 65% conversion of vinylalane **5a** (R = *n*-$C_{10}H_{21}$) 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 $AlMe_3$) at 0 °C and subsequently trapped with Bz_2O, 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]

Table 1. Preparation of Enol Derivatives from Terminal Alkynes[a]



Entry	Alkyne	EX	Product	Yield (%)[b]
1	**1a**	Bz_2O[c]	R = $C_{10}H_{21}$; E = Bz	78
2	**1b**	Bz_2O[c]	R = CH_2Ph; E = Bz	89
3	**1c**	Bz_2O[c]		82
4	**1d**	Bz_2O[c]	R = Ph; E = Bz	80
5	**1e, 1f**	Bz_2O[c,d]		**4e:** n = 1, 59 **4f:** n = 2, 79
6	**1g**	Bz_2O[c]		71
7	**1h**	Bz_2O[c]		83
8	**1i, 1j**	Bz_2O[c]		**4i:** n = 3, 75 **4j:** n = 4, 76
9	**1k**	Ac_2O		91
10	**1l**	Ac_2O		97
11	**1m**	Ac_2O		92
12	**1n**	Ac_2O		90
13	**1o**	TESOTf		79
14	**1p**	TESOTf		83

[a] Conditions: 1.0 equiv alkyne, 1.2−4 equiv Me_3Al, 5−30 mol % Cp_2ZrCl_2, 2.5−30 mol %, H_2O or MAO, 0.3 M in CH_2Cl_2; MeZnOO^{t}Bu (0.3 M in toluene, 1.3−1.4 equiv to Me_3Al). [b] Isolated yields (chromatography not necessary for entries 9−14). [c] Catalytic ^{n}Bu$_3$P added. [d] BzCl was added after benzoylation of the enolate. See Supporting Information for complete experimental details.

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

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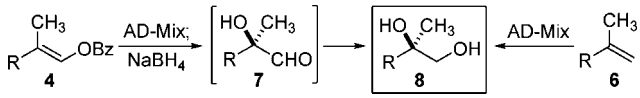
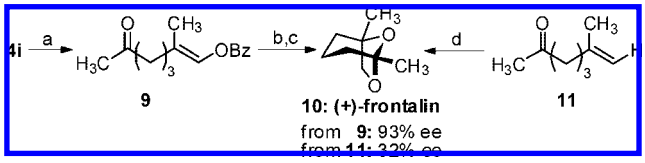
Table 2. Asymmetric Dihydroxylation (AD) of Enol Benzoates[a]



Entry	R	ee (%)[b] from: 4	6	Product	Yield (%)[c]
1	^{n}C$_{10}$H$_{21}$	96	78	**8a**	78
2	PhCH$_2$	94		**8b**	84
3		96		**8c**	59
4	Ph	95	94[d]	**8d**	75
5		96		**8g**	87
6		95	32	**8q**[e]	75

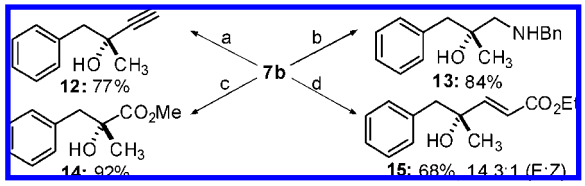
[a] All AD reactions were performed under standard conditions: AD-mix, 0.1 M in ^{t}BuOH/H$_2$O, 0 °C. [b] Unless noted otherwise, ee values determined by HPLC. See Supporting Information for details. [c] Isolated yields from **4**. [d] Percent ee from ref 11a. [e] Reaction run with 1.0 equiv MeSO$_2$NH$_2$ added.

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



[a] Reagents and conditions: (a) PdCl$_2$, CuCl,O$_2$, DMF/H$_2$O (7:1), quant; (b) AD-mix-β, MeSO$_2$NH$_2$, NaHCO$_3$, ^{t}BuOH/H$_2$O (1:1), 0 °C, 18 h, 85%; (c) [Me$_4$N]BH(OAc)$_3$, AcOH, CH$_3$CN, 76%; (d) AD-mix-β, ^{t}BuOH/H$_2$O, 0 °C.

Scheme 3. Transformations of α-Hydroxy Aldehydes[a]

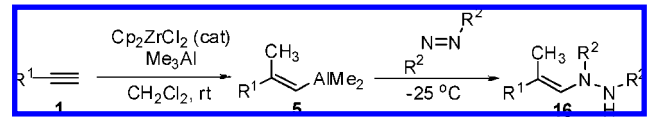


[a] Reagents and conditions: (a) (MeO)$_2$POCN$_2$COMe, K$_2$CO$_3$, MeOH, 0 °C−room temp; (b) BnNH$_2$, toluene, 4 Å MS, 105 °C; NaBH$_4$, MeOH, 0 °C; (c) I$_2$, KOH, MeOH, 0 °C; (d) Bu$_3$PCH$_2$CO$_2$EtBr, NaHCO$_3$, toluene, 90 °C.

(Table 2, all entries ≥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 NaBH$_4$, 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 [Me$_4$N]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]

Table 3. Synthesis of Stereodefined Ene-hydrazines (**16**) from Terminal Alkynes[a,b]



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$_2$^{t}Bu	**16f**	84

[a] Methylalumination as in Table 1; 1.5−3 equiv azodicarboxylate. See Supporting Information for complete experimental details. [b] Isolated yields.

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.

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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.

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(18) See Supporting Information for complete experimental details.

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