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Dinuclear Zn-Catalyzed Asymmetric Alkynylation of Unsaturated Aldehydes

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Our recent development[1a] of the proline-derived bimetallic catalyst system **1** has led to a number of efficient, catalytic, enantioselective transformations,[1] including the asymmetric Henry[1c] and Mannich[1d] reactions, desymmetrization of *meso* 1,3-diols,[1e] and the direct aldol reaction[1b] of traditionally difficult substrates, including both ynones[1f] and methylvinyl ketone.[1g] All of the nucleophiles utilized to date have been highly stabilized (enolates, nitronates, etc.). In considering less stabilized nucleophiles, examination of the literature on alkynylations of aldehydes led us to postulate that our system might be well suited to catalyze such a transformation.[2]

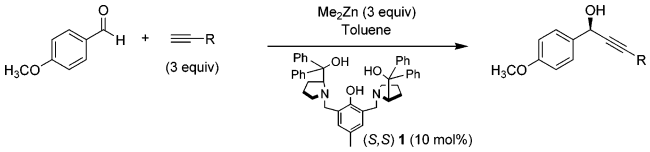
The catalytic enantioselective addition of terminal alkynes to aldehydes has recently generated a tremendous amount of interest.[2] The resulting propargylic alcohols are versatile building blocks for fine chemicals, pharmaceuticals, and natural products.[3] While the vast majority of current alkynylation protocols focus solely on the addition of phenyl acetylene to aromatic aldehydes, there have been some significant advances to generalize both the alkyne and the aldehyde. While impressive results have been obtained with stoichiometric chiral inducing agents, general catalytic systems are less common. Additionally, α,β-unsaturated aldehydes remain particularly challenging substrates, often requiring stoichiometric or catalytic titanium in addition to the zinc. Furthermore, generalization of the alkyne would greatly improve the synthetic utility of the products.

Herein, we report a practical and general alkynylation of aromatic and α,β-unsaturated aldehydes using our proline-derived dinuclear zinc catalyst system. Early optimization showed that toluene was the most suitable solvent, and 10 mol % ligand was adequate for both high reactivity and selectivity. The reaction proceeded at a faster rate and, curiously, with slightly higher enantiomeric excess (ee) at increased temperatures (Table 1, entries 1 and 2). An interesting effect on concentration was observed (Table 1, entries 3−6). While no effect on ee was observed between 0.2 and 0.5 M, a decrease in ee occurred upon further doubling the concentration to 1.0 M (Table 1, entry 6). Adopting the conditions of Table 1, entry 5 as optimal, testing the reaction scope ensued.

Alkynylation of a series of aromatic aldehydes proceeded efficiently and cleanly with a wide variety of alkynes (Table 2). Both electron-rich and electron-poor aromatic aldehydes participated, and substitution on each aromatic carbon was tolerated. Interestingly, electron-donating substituents were found to be beneficial for both the yield and selectivity. Substituents in the ortho positions of the benzaldehyde raised both yield and ee. A similar effect was seen with chelating electrophiles in related zinc-catalyzed aldol reactions.[1b] Although the initial studies were carried out with phenylacetylene, trimethylsilylacetylene is a particularly desirable alkyne due to the possible use of the desilylated product for alkylation or the Sonogashira[4] coupling. Although more sterically demanding, TMS acetylene participates with comparable efficiency and selectivity. Ethereal alkynes and ethyl propiolate are also suitable nucleophiles.

To expand the scope of this reaction, we also examined α,β-unsaturated aldehydes as electrophiles to produce chiral propargylic allylic alcohols, recently shown to be efficient substrates in a Au(I)-catalyzed Rautenstrauch rearrangement.[5] Previously, these compounds were available with high ee by stoichiometric reduction of the corresponding ketone with Alpine-Borane.[6] Catalytic alkynylation under our standard conditions proceeded with both high yield and ee (Table 3). It is noteworthy that the enantioselectivity of the reaction is dependent on the substitution of the aldehyde. The alkynylation of cinnamaldehyde with TMS acetylene (entry 1) was highly enantioselective, while the alkynylation of *trans*-nonenal (entry 4) exhibited poor enantioinduction. This poor enantioselectivity could be overcome by employing α-bromo-nonenal (entry 5), which was alkynylated with high enantioselectivity to provide a product containing a vinyl bromide capable of a variety of subsequent transformations. The difference in ee between the phenyl and *n*-hexyl β-substituents seems to result primarily from steric factors. Incorporating an isopropyl group in the β position of the aldehyde restored high enantioselectivity (entry 10). Interestingly, α substitution provided the necessary steric bulk to yield a product with high ee even in the absence of β substitution (entry 9). In an

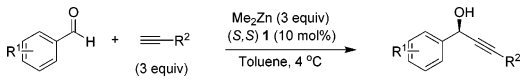
Table 1. Initial Optimization



entry	R	[alkyne]	temp	time (h)	yield (%)[a]	ee (%)[b]
1	Ph	0.2 M	rt	48	77	83
2	Ph	0.2 M	−20 °C	45	60	77
3	TMS	0.2 M	3 °C	21	35	85
4	TMS	0.3 M	3 °C	21	50	85
5	TMS	0.5 M	3 °C	24	74	85
6	TMS	1.0 M	3 °C	21	87	75

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC; absolute configuration determined by comparison with known compounds.[2]

Table 2. Substrate Scope



entry	R^1	R^2	yield (%)[a]	ee (%)[b]
1	2-NO_2	Ph	84	92
2	3-NO_2	Ph	91	68
3	4-NO_2	Ph	78	83
4	H	Ph	95	81
5	C_4H_4 (2-naphth)	Ph	89	75
6	2,4-$(OCH_3)_2$-3-CH_3	Ph	87	92
7	2,6-$(OCH_3)_2$	Ph	87	99
8	4-OCH_3	TMS	74	85
9	2,6-$(OCH_3)_2$	TMS	79	97
10	2-furyl	TMS	81	84
11	2-OCH_3	$-CH_2OCH_3$	86	84
12	2-OCH_3	$-CO_2Et$	95	82

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC; absolute configuration determined by comparison with known compounds.[2]

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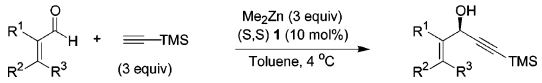
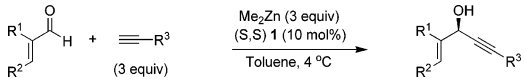
Table 3. Variation of the α,β-Unsaturated Aldehyde



entry	R^1	R^2	R^3	yield (%)[a]	ee (%)[b]
1	H	Ph	H	89	91
2	H	Ph	Ph	80	76
3	$-(CH_2)_4-$		H	81	90
4	H	$-C_6H_{13}$	H	90	36
5	Br	$-C_6H_{13}$	H	66(14)[c]	91
6	CH_3	$-CO_2Et$	H	75	86
7	Br	Ph	H	68	95
8	CH_3	$-CH_2CH_3$	H	67	87
9	CH_3	H	H	74	91
10	H	$-CH(CH_3)_2$	H	100	94

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC; absolute configuration determined by comparison with known compounds or by analogy. [c] Fourteen percent methyl addition product was isolated.

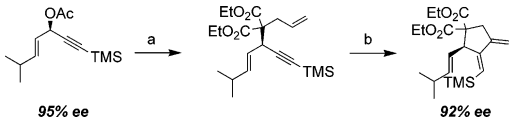
Table 4. Variation of the Alkyne



entry	R^1	R^2	R^3	yield (%)[a]	ee (%)[b]
1	CH_3	H	$-CO_2CH_3$	94	90
2	H	$-C_6H_{13}$	$-CO_2CH_3$	86	97[c]
3	H	$-CH(CH_3)_2$	$-CO_2CH_3$	97	97
4	H	Ph	$-CO_2CH_3$	92	95
5	H	Ph	$-SiMe_2Bn$	100	73
6	H	Ph	$-C_6H_{13}$	100	77
7	H	$-CH(CH_3)_2$	$-CH(OEt)_2$	85	87[d]
8	H	Ph	$-CH(OEt)_2$	85	82

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC; absolute configuration determined by comparison with known compounds or by analogy. [c] Absolute configuration determined by formation of the methyl mandelate.[7] [d] Enantiomeric excess determined by chiral HPLC of benzoyl ester.

Scheme 1. Formation of 1,2-Dialkylidenecyclopentane[a]



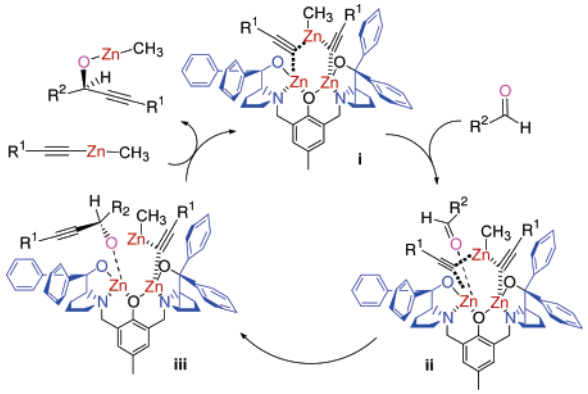
[a] Conditions: (a) $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %), PPh_3 (15 mol %), diethyl allylmalonate, NaH, THF, r.t. 76%; (b) $Pd(OAc)_2$, (15 mol %), BBEDA (bisbenzylidene ethylene diamine) (15 mol %), benzene, 100 °C, 10 h, 77%.

effort to realize our goal of generating synthetically useful products, a wide variety of alkynes were used (Table 4). In addition to TMS acetylene, methyl propiolate is an important nucleophile because its conjugation to the alkyne greatly differentiates the alkene from the alkyne for further functionalization of the product.

To our delight, methyl propiolate gave the highest enantioselectivity and was not affected by the substitution of the aldehyde. Even with *trans*-nonenal, the addition proceeded with 97% ee (Table 4, entry 2) compared to only 31% ee with TMS acetylene (Table 3, entry 4). This led us to postulate that the ester group of the propiolate could be a point of binding in our catalyst system. Alkyl and acetal alkynes were also compatible with our reaction (Table 4, entries 6−8).

The chiral information in these products can be transferred via a Pd-catalyzed allylic alkylation while maintaining regioselectivity (Scheme 1). Pd-catalyzed displacement of the allylic acetate with diethyl allylmalonate followed by a Pd-catalyzed cycloisomerization[8] yielded a scalemic 1,2-dialkylidenecyclopentane with little erosion of ee. The resulting 1,2-dialkylidenecyclopentane, a useful

Scheme 2. Proposed Catalytic Cycle



substrate for the Diels−Alder reaction,[8] is a particularly difficult 1,3-diene to form through traditional methods due to the thermodynamic instability of the exocyclic double bonds.

A possible catalytic cycle that accounts for the observed absolute stereochemistry is shown in Scheme 2. Coordination of 2 equiv of zinc alkynylide to the complex followed by the coordination of the aldehyde to the most sterically accessible site forms intermediate **ii**. Alkyne transfer sets the stereochemistry, and transmetalation to another zinc alkynylide forms the alkoxide of the product and restarts the cycle.

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Supporting Information Available: Characterization data, NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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