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Ligand-accelerated Enantioselective Propargylation of Aldehydes via Allenylzinc Reagents

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ABSTRACT

An enantioselective propargylation of aldehydes using an allenylzinc reagent generated *in situ* via a zinc−iodine exchange reaction is described. The enantioselectivity is controlled by addition of a catalytic amount of readily accessible and highly tunable amino alcohol ligand L13. A wide range of aldehydes can be propargylated to afford valuable and versatile homopropargyl alcohols in good to excellent yields with high levels of enantiopurity.

Chiral homopropargyl alcohols are useful synthetic building blocks that are routinely utilized in the synthesis of a wide variety of bioactive natural products and pharmaceutical compounds.[1] Moreover, these compounds offer an opportunity for dual reactivity: (1) the alkyne functional group can undergo hydration or oxidative cleavage to provide aldehydes or ketones, and can be reduced to provide olefins or alkanes,[2] and (2) the chiral alcohols frequently act as directing groups for many essential reactions, such as epoxidation, cyclopropanation, carbonyl reduction, and hydrosilylation.[3,4] In addition, the homopropargyl alcohol itself is readily converted to synthetically useful heterocycles such as polyhydrofurans and polyhydropyrans in a highly chemoselective and atom-economical fashion.[5]

The most attractive and straightforward method for synthesizing enantiopure homopropargylic alcohols is the direct *catalytic* rather than stoichiometric asymmetric carbonyl propargylation. Several approaches have been established for this purpose. For example, Keck and Denmark have respectively reported a Lewis acid-[6] and Lewis base-catalyzed[7] asymmetric carbonyl propargylation, yet these methods employed a stoichiometric amount of highly toxic tin reagents. Catatlytic asymmetric Nozaki−Hiyama propargayltions have also been reported with respectable levels of enantioselectivity, but the requirement of toxic chromium source and long reaction time is still of concern with this method.[8] During the course of our studies,

(1) For selected examples: (a) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913–3916. (b) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194–2207. (c) Trost, B. M.; Dong, G. B. *Nature* **2008**, *456*, 485–488. (d) Liu, S. B.; Kim, J. T.; Dong, C. G.; Kishi, Y. *Org. Lett.* **2009**, *11*, 4520–4523. (e) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett.* **2010**, *12*, 340–343.

(2) Stang, P. J.; Diederich, F. *Modern Acetylene Chemistry*; VCH: New York, 1995.

(3) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(4) For review of hydrosilation of alkynes, see: Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853–887.

(5) (a) Quayle, P.; Rahman, S.; Ward, E. L. M.; Herbert, J. *Tetrahedron Lett.* **1994**, *35*, 3801–3804. (b) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648–6659. (c) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680–11683. (d) Consorti, C. S.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, *43*, 753–755. (e) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483.

(6) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, *35*, 8323–8324.

(7) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199–6200.

(8) (a) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Polyhedron* **2000**, *19*, 537–539. (b) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1063–1069. (c) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977–2980. (d) Usanov, D. L.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8345–8348.

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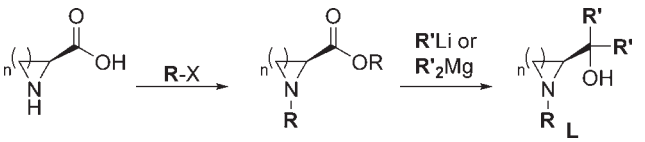
Fandrick and co-workers reported a highly enantioselective copper-catalyzed asymmetric carbonyl silylpropargylation, but a costly and elaborate ligand was employed.[9]

In our recent efforts toward the synthesis of bryostatin 16, we required an asymmetric carbonyl propargylation reaction that was straightforward and facile to employ.[1c] We envisioned that the addition of allenylzinc species to aldehydes would be ideal because the allenylzinc can be generated *in situ* from a propargyl iodide via zinc−iodine exchange. The use of allenylzinc reagents would obviate the need to isolate sensitive allenylmetal reagents and circumvent the use of toxic allenylstannane complexes. The availability of a wide range of propargyl halides would also allow for the formation of a variety of allenylzinc reagents. Importantly, the corresponding addition of alkylzinc reagents to aldehydes is known to be ligand-accelerated by a variety of amino alcohol ligands. We hypothesized that the same would hold true for additions with allenylzinc complexes, providing a strategy for the development of an asymmetric propargylation reaction. Chiral amino alcohol ligands can be easily accessed from a commercially available chiral pool, which offers great ligand tunability for various substrates.

Prior reports attempting to use these zinc reagents proved disappointing.[10] Unlike the ligand-accelerated additions of diaryl- or dialkyl-zinc to carbonyl compounds, where the uncatalyzed reaction undergoes a disfavored four-centered transition structure,[11] the uncatalyzed addition of allenylzinc species[12] to aldehydes proceeds via a six-centered transition structure to afford the racemic homopropargyl alcohol.[13] The fast background reaction has hampered the development of highly enantioselective ligand-accelerated carbonyl propargylation reactions using allenylzinc reagents. Therefore, there is a great need to develop active amino alcohol ligands that induce high chirality transfer. Herein, we report the *first* systematic efforts toward the development of a ligand-accelerated enantioselective propargylation of various aldehydes utilizing allenylzinc reagents, and readily accessible and highly tunable chiral amino alcohols as putative ligands for Zn(II).

Our interest in chiral aminoalcohol ligands is attributed to their low cost, easy accessibility and high modularity. Most of these ligands can be synthesized from the commercially available amino acids via protection followed by additions of Grignard or organolithium reagents (Scheme 1). Each of these steps allows independent modification of the chiral space of the ligands. Therefore, the chiral amino alcohol offers a versatile template, enabling well-defined structure-selectivity studies. Amino alcohols **L** present three structural elements that may be independently optimized: (a) the backbone of the ligand, (b) the amine protecting group, and (c) the groups appended to the tertiary carbinol center.

Scheme 1. Chiral Amino Alcohol Ligand Synthesis



Our initial studies focused on the reaction of cinnamaldehyde (**1a**) with *in situ*-generated allenylzinc[14] in the presence of a catalytic amount of various amino alcohols (Table 1). After an extensive ligand screen, we found that the enantioselectivity of the reaction was sensititve to the ring size of the amino alcohol ligands (entries 1−4). Interestingly, while five-membered ring derivative **L3** afforded the product with the highest enantiomeric ratio (entry 3), both three- and six-membered ring systems failed to induce any chirality (entries 1 and 4). Replacement of the methylene group at the C-4 position with a sulfur atom had a detrimental effect on the asymmetric induction of the reaction (entry 5). We also found that the N-protecting group of the aminoalcohol ligand has a great influence on the enantioselectivity. Ligands with a free secondary amine (**L6**) or a N-methyl protecting group (**L7**) afforded product **2a** with lower er (entries 6 and 7). Highly bulky protecting groups such as 9-anthracenylmethyl (**L8**) also furnished the product with diminished selectivity (entry 8). We next turned our attention to examining the impact of the substituents at the carbinol carbon (entries 9−13). While an electron-rich substituent slightly suppressed the enantioselectivity of the reaction, an electron-deficient substituent gave comparable results to the phenyl system (entries 9 and 10). Using the ligand with alkyl substituents afforded the product with low enantiomeric purity (entry 11). Although 2-naphthyl-substituted ligand **L12** afforded the product with disappointing selectivity, 1-naphthyl-substituted ligand **L13** provided homopropargyl alcohol **2a** with the highest asymmetric induction (entries 12 and 13).

With ligand **L13** in hand, we explored the effect of various solvents on the enantioselectivity (Table 2, entries 1−4).

(9) (a) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z. L.; Tang, W. J.; Capacci, A. G.; Rodriguez, S.; Song, J. H. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600–7601. For copper-catalyzed asymmetric propargylation of ketones, see: (b) Shi, S. L. L.; Xu, W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639.

(10) Several cases of applying amino alcohol ligated allenylzinc species in total syntheses were reported, but they proceeded with very low enantioselectivities, for examples, see: (a) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664–1668. (b) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008–4013.

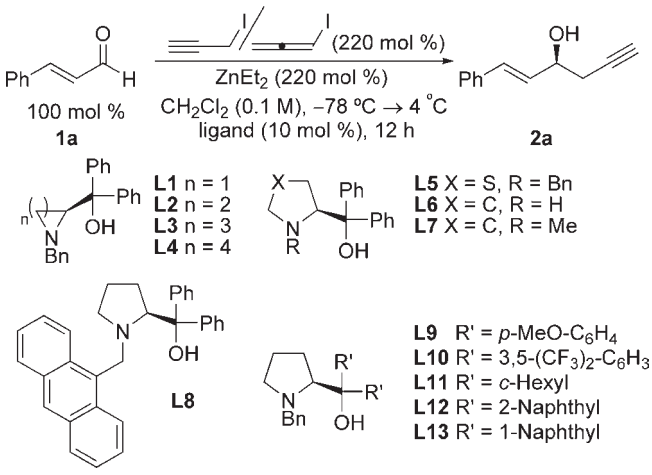
(11) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824 and references cited therein.

(12) Propargylzinc and allenylzinc species are interconvertable through a facile propargylic rearrangement. In the absence of a substiutent on the allenyl portion, allenylzinc species are thermodynamically more stable than propargylzinc species. This results in selective formation of the propargyl product. Marshall, J. A.; Gung, B. W.; Grachan, M. L. *Modern Allene Chemistry*; VCH: Weinheim, Germany, 2004.

(13) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 88–91.

(14) A mixture of propargyl/allenyl iodide solution (85 wt % in toluene) was prepared from propargyl bromide solution (80 wt % in toluene) and sodium iodide through a Finkelstein reaction protocol.

Table 1. Selected Ligand Optimization Studies[a]

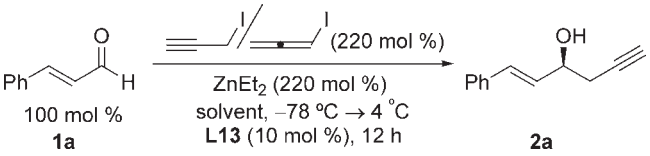


entry	ligand	conv(%)	er[b]
1	**L1**	100	50:50
2	**L2**[c]	100	44:56
3	**L3**	100	75.5:24.5
4	**L4**[c]	100	50:50
5	**L5**	100	52.5:47.5
6	**L6**	100	60:40
7	**L7**	100	65:35
8	**L8**	100	71:29
9	**L9**	100	70:30
10	**L10**	100	75.5:24.5
11	**L11**	100	57:43
12	**L12**[c]	100	48.5:51.5
13	**L13**	100	83:17

[a] See Supporting Information for detailed experimental procedures. [b] Er was determined by chiral HPLC. [c] (*R*)-enantiomerwas used.

We found that dichloromethane (CH_2Cl_2) was superior to toluene, THF and hexane. It is noteworthy that CH_2Cl_2 needed to be degassed, otherwise the reaction afforded the product with lower yield and enantioselectivity (entries 1 and 5). We believe this result is caused by the formation of highly reactive propargyl radicals when oxygen is present.[15] Indeed, performing the reaction in the presence of 2,6-di-*tert*-butylphenol as a radical scavenger afforded the product with quantitative yield and 83:17 er (entry 6). Replacing diethylzinc with dimethylzinc failed to give any desired product (entry 7). In additional studies, we found that varying the reaction concentration diminished the reaction conversion and the enantioselectivity (entries 8 and 9). The source of propargyl/allenyl halide also has a remarkable effect on the reaction. For example, propargyl bromide did not give any homopropargylic alcohol product. Instead, only the ethyl transfer byproduct was obtained (entry 10). Presumably, this can be attributed to the slow zinc−bromine exchange relative to the addition of ethyl group to the aldehyde. Interestingly, it is crucial to use a propargyl/allenyl iodide *solution* (85 wt % in toluene). Performing the reaction employing a neat proparyl/allenyl iodide reagent afforded homopropargyl alcohol **2a** with poorer yield and selectivity (entry 11).[16] The exact role of toluene additive remains unclear, and is currently under investigation.

Table 2. Selected Reaction Optimization Experiments[a]



entry	solvent[b]	concn (M)	yield (%)[c]	er[d]
1	CH_2Cl_2	0.1	99	83:17
2	Toluene	0.1	95	64:36
3	THF	0.1	80	57:43
4	Hexane	0.1	80	60:40
5	CH_2Cl_2[e]	0.1	83	78:22
6	CH_2Cl_2[e,f]	0.1	99	83:17
7	CH_2Cl_2[g]	0.1	0	
8	CH_2Cl_2	0.05	80	81:19
9	CH_2Cl_2	0.25	86	77:23
10	CH_2Cl_2[h]	0.1	0[i]	
11	CH_2Cl_2[j]	0.1	80	74:26

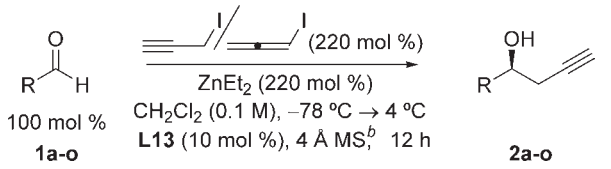
[a] See Supporting Information for detailed experimental procedures. [b] Solvents were degassed by freeze−pump−thaw procedures. [c] Isolated yields. [d] Er was determined by chiral HPLC. [e] CH_2Cl_2 was used without degassing. [f] 2,6-Di-*tert*-butylphenol (50 mol %). [g] $ZnMe_2$ (220 mol %) was used. [h] Propargyl bromide (80 wt % in toluene) was used. [i] Only ethyl transfer by product was obtained. [j] Neat propargyl/allenyl iodide was used.

Under the standard reaction conditions using a mixture of propargyl/allenyl iodide solution (85 wt % in toluene), a range of alkenyl, aryl, heteroaryl, alkyl aldehydes were surveyed to determine the scope of this method (Table 3). While cinnamaldehyde afforded the product (**2a**) in excellent yield with 83:17 er, α-methyl cinnamaldehyde gave the product (**2b**) with quantitative yield and enhanced enantiomeric ratio (90:10) (entries 1 and 2). Aryl aldehydes bearing different substituents proceeded smoothly to furnish the corresponding products in good to excellent yields with high levels of enantiopurity (entries 3−12). In addition, heteroaromatic aldehydes such as 2-formyl furan and 2-formyl thiophene, and aliphatic aldehydes participated in the propargylation reaction with high yields and useful levels of enantioselectivity (entries 13−15). The absolute stereochemistry of **2c** was determined by comparison of the HPLC retention time with that of the literature data,[8c] and the stereochemistry of the other homopropargyl alcohols were tentatively assigned by analogy.

(15) For reviews on dialkylzinc in radical reactions, see: (a) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260–265. (b) Akindele, T.; Yamada, K. I.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345–355.

(16) After screening a wide range of arene additives, we were able to restore the reaction conversion and selectivity by addition of 150 mol % naphthalene. However, the homopropargyl alcohol product was accompanied with 15% ethyl transfer byproduct. More studies are underway to examine the exact role of an arene additive in this transformation.

Table 3. Substrate Scope of the Ligand-Accelerated Asymmetric Proparylation of Aldehydes **1a**−**1o**[a]



entry	substrate		yield (%)[c]	er (*S*/*R*)[d]
1	PhCH=CH-	**1a**	99	83:17
2	PhCH=C(Me)-	**1b**	99	90:10
3	Ph-	**1c**	99	93:7
4	*p*-MeO-C_6H_4-	**1d**	98	96:4
5	*p*-Me-C_6H_4-	**1e**	93	94:6
6	*m*-Me-C_6H_4-	**1f**	90	92:8
7	*o*-Me-C_6H_4-	**1g**	85	94.5:5.5
8	*p*−F-C_6H_4-	**1h**	98	93:7
9	*p*−Cl-C_6H_4-	**1i**	80	87.5:12.5
10	*p*−Br-C_6H_4-	**1j**	80	90.5:9.5
11	2-Napthyl	**1k**	95	92:8
12	4-MeO-1-napthyl	**1l**	94	96:4
13	Furyl	**1m**	80	90:10
14	Thiophenyl	**1n**	97	85:15
15	*c*-Hexyl	**1o**	80	80:20

[a] See Supporting Information for detailed experimental procedures. [b] MS (4 Å) was added to give better reproducibility. [c] Isolated yields. [d] Er was determined by chiral HPLC.

While a detailed mechanism for the overall catalytic process is yet to be determined, a plausible reaction mechanism and stereochemical model is depicted in Figure 1.[17] Entry into the catalytic cycle via deprotonation of the amino-alcohol ligand with diethylzinc species affords active catalyst **I**.[18] Coordination of the allenylzinc species (generated *in situ* via the zinc−iodine exchange process) to catalyst **I** furnishes dinuclear zinc complex **II**, which then binds to the aldehyde to give intermediate **III**. The aldehyde approaches so as to avoid a steric interaction with the benzyl group on the ligand and exposes its *si*-face to the allenyl group (**IIIa** vs **IIIb**). Propargylation of the aldehyde via a six-centered transition structure delivers propargyl alkoxide **IV** with the stereochemistry in agreement with the experimental data. Dissociation of zinc alkoxide **V** regenerates active catalyst **I** to complete the catalytic cycle.

(17) The proposed dinuclear-zinc mechanism is based on the well-developed aminoalcohol catalyzed asymmetric dialkyl- and diarylzinc addition to aldehydes, see ref 11. One of the referees suggested a mononuclear-zinc mechanism, which cannot be ruled out at this stage.

(18) The reaction does not show nonlinear effects (see Supporting Information), so a single Zn-complex is depicted in the proposed reaction mechanism.

In summary, we have developed a tin-free catalytic asymmetric propargylation of a wide range of aldehydes employing allenylzinc reagents and readily available chiral amino alcohol ligands. The simple nature of the reaction protocol and the ready availability of the amino alcohol ligand make this new asymmetric propargylation an attractive alternative to currently existing methods. In addition, the low toxicity and low cost of the allenylzinc reagents are of particular interest from an environmental and an economic point of view. Further efforts will be devoted to studying reaction mechanism, assessing synthetic applications, and expansion of the substrate scope.

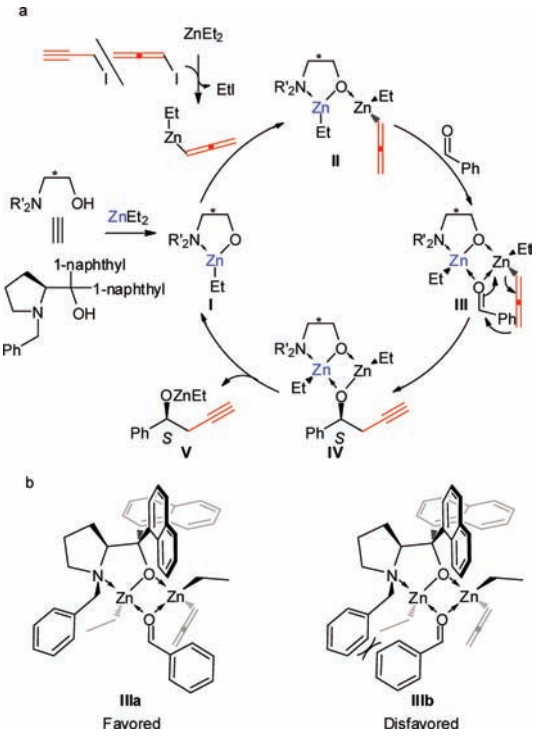


Figure 1. (a) Proposed reaction mechanism and (b) stereochemical model for the ligand-accelerated propargylation of aldehydes.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.