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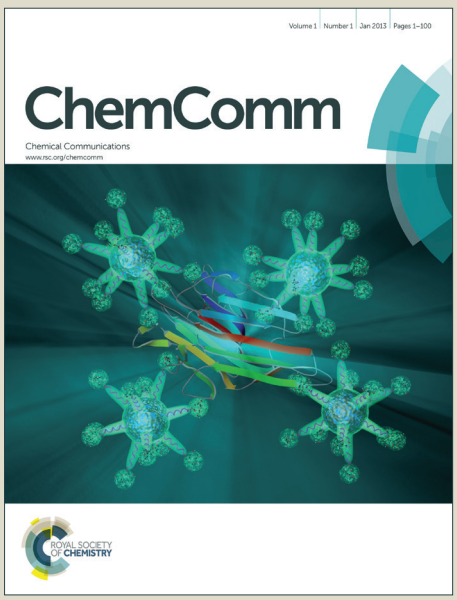

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ARTICLE TYPE

A Lewis Acid Activated Reaction of Zn with EtI to Promote Highly Enantioselective Alkyne Additions to Aldehydes

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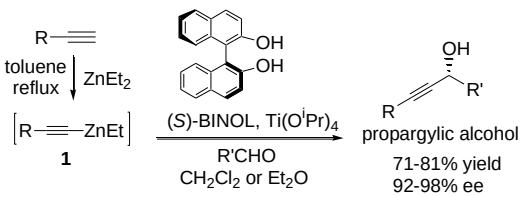
An easily available BINOL-Ti(O^{i}Pr)$_4$ catalyst system is found to activate the reaction of Zn powder with EtI for the asymmetric alkyne addition to aldehydes at room temperature. It allows the synthesis of a number of synthetically useful chiral propargylic alcohols with both high yields and high enantioselectivity (up to >96% ee).

Catalytic asymmetric alkynylzinc addition to aldehydes can generate chiral propargylic alcohols that are versatile synthons in organic chemistry. A number of chiral catalysts have been developed in the past decade which have allowed the synthesis of structurally diverse chiral propargylic alcohols with high enantioselectivity.[1-8] For example, Carreira discovered a highly enantioselective catalyst based on N-methyl ephedrine for the alkynylzinc addition to *aliphatic* aldehydes by using Zn(OTf)$_2$.[1] We found that 1,1'-bi-2-naphthol (BINOL) in combination with $ZnEt_2$ and Ti(O^{i}Pr)$_4$ is a highly enantioselective catalyst for the asymmetric reaction of alkynes with both aromatic and aliphatic aldehydes (Scheme 1).[6,7] In this method, an alkyne was first converted to an alkynylzinc intermediate **1** by heating with $ZnEt_2$ in refluxing toluene which then added to an aldehyde in the presence of (*S*)-BINOL and Ti(O^{i}Pr)$_4$ with high enantioselectivity. Later, we improved this method by adding a Lewis base additive such as Cy_2NH which can facilitate the deprotonation of a terminal alkyne with $ZnEt_2$ to form a nucleophilic alkynylzinc like **1** and allow the entire process to be conducted at room temperature to generate a variety of chiral propargylic alcohols with high enantiomeric purity.[8] The mild reaction conditions and broad substrate scope make this catalyst system practically useful in organic laboratory. However, because $ZnEt_2$ used in this method is a spontaneously combustible liquid on contact with moist air, its transportation, storage and usage present an important safety issue for application in large scale industrial production. In order to meet this challenge, we have explored the possibility to conduct the BINOL-based asymmetric alkynylzinc addition to aldehydes without the direct use of $ZnEt_2$ while still maintaining the high



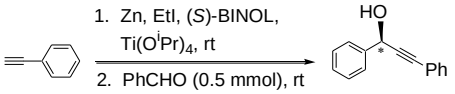
Scheme 1. Using $ZnEt_2$ for the BINOL-Based Catalytic Asymmetric Alkyne Addition to Aldehyde.

enantioselectivity. We have recently found that the Lewis acidic BINOL-Ti(O^{i}Pr)$_4$ complex can activate the reaction of Zn powder with EtI which can then promote the highly enantioselective alkyne addition to aldehydes. Herein, these results are reported.

$ZnEt_2$ cannot be prepared by simply mixing Zn with EtI at room temperature. Elevated temperature and addition of Cu are required for the synthesis of $ZnEt_2$.[9] Since it is our goal to conduct the asymmetric alkyne addition to aldehydes at room temperature without directly using $ZnEt_2$, we have explored the idea to activate the reaction of Zn with EtI by using a Lewis acid catalyst. We envision that interaction of EtI with a Lewis acid should make the ethyl group more electron-deficient which should be more reactive with a reducing metal like Zn. Therefore, we tested the reaction of Zn with EtI in the presence of BINOL and Ti(O^{i}Pr)$_4$. It is proposed that reaction of BINOL with Ti(O^{i}Pr)$_4$ should generate a stronger Lewis acid complex than Ti(O^{i}Pr)$_4$ which might enhance the reaction of EtI with Zn. To this reaction mixture, phenylacetylene and benzaldehdye were added in order to produce the desired propargylic alcohol in one pot. The reagents of this reaction were combined in two steps: (1) Mixing (*S*)-BINOL, Ti(O^{i}Pr)$_4$, Zn powder, EtI and phenylacetylene in a solvent at room temperature; (2) Adding benzaldehyde. The results of this experiment under various conditions are summarized in Table 1. As shown in entry 1, when diethyl ether was used as the solvent for both steps, no reaction was observed. This indicates that no nucleophilic alkynylzinc reagent like **1** could be generated under these conditions. However, when we changed the solvent of the first step to THF and still used diethyl ether as the solvent for the second step, we were excited to find that the desired propargylic alcohol product was obtained with 96% ee and 85% yield (entry 2). Thus, there is a dramatic solvent effect for the asymmetric alkyne addition to aldehyde in the presence of Zn and EtI. The chiral configuration of the product 1,3-diphenyl-prop-2-yn-1-ol is determined to be *R* by comparison with the previously reported analytical data.

The result shown in entry 2 is very remarkable since it is known that not only free $ZnEt_2$ cannot be generated by simple combination of Zn with EtI at room temperature but the deprotonation of a terminal alkyne with $ZnEt_2$ also cannot proceed easily at room temperature without the addition of an appropriate Lewis base catalyst. The work here demonstrates that the asymmetric alkyne addition promoted by the BINOL-Ti(O^{i}Pr)$_4$-Zn-EtI system should proceed in a mechanism very different from the previously reported direct use of $ZnEt_2$. (*S*)-BINOL and Ti(O^{i}Pr)$_4$ should be intrinsically involved in the generation of the nucleophilic alkynyl reagent for the addition to aldehyde. We tested the reaction without the addition of either Ti(O^{i}Pr)$_4$ (entry 3) or Zn (entry 4), and found no alkyne addition.

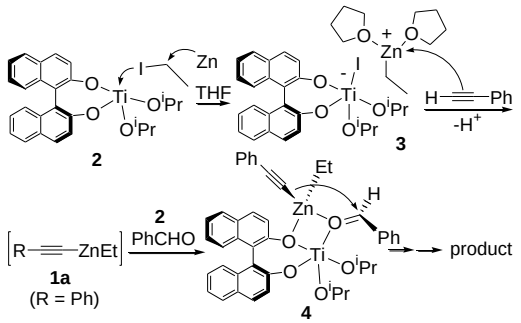
Table 1. Conditions for the Addition of Phenylacetylene to Benzaldehyde Using Zn and EtI at Room Temperature



Entry	Zn (equiv)	EtI (equiv)	alkyne (equiv)	$Ti(O^iPr)_4$ (equiv)	(*S*)-BINOL (equiv)	ee (%)
1[a]	6	12	4	1	0.4	N.R
2[b]	**6**	**12**	**4**	**1**	**0.4**	**96(85)**[d]
3[b]	6	12	4	0	0.4	N.R.
4[b]	0	12	4	1	0.4	N.R.
5[b]	4	8	4	1	0.4	77
6[b]	6	12	2	1	0.4	87
7[b]	6	12	4	0.5	0.4	88
8[b]	6	12	4	1	0.2	70
9[c]	6	12	4	1	0.4	<70

[a]Diethyl ether was used for both steps (1 mL in the first step and 10 mL in the second step). [b]THF (1 ml) was used in the first step and diethyl ether (10 mL) was used in the second step. [c]Only THF (10 mL) was used. [d]Isolated yield (%) in parenthesis.

In consistent with the above experimental observations, we propose a working hypothesis to account for the activated reaction of Zn with EtI. As shown in Scheme 2, a Lewis acid complex **2** generated from the reaction of (*S*)-BINOL with $Ti(O^iPr)_4$ could promote the oxidative addition of Zn with EtI to form an ionic intermediate **3**. In the intermediate **3**, multiple THF molecules could coordinate to the electron-deficient Zn(II) center to help stabilize the cationic zinc alkyl unit. Formation of the THF-stabilized cationic zinc alkyl intermediate **3** could explain the observed dramatic solvent effect shown in entries 1 and 2. Since diethyl ether is a less nucleophilic solvent than THF, its coordination to the cationic zinc alkyl center like that in **3** is expected to be much weaker which might not provide enough stabilization for the formation of such an intermediate, leading to the observed inactivity when only diethyl ether was used as the solvent (entry 1). Coordination of the triple bond of phenylacetylene to the electron-deficient zinc center of **3** is expected to activate the deprotonation of the terminal alkyne molecule to generate the nucleophilic alkynylzinc reagent **1a**. This cationic zinc alkyl species is proposed for the activated



Scheme 2. Working Hypothesis for the (*S*)-BINOL-$Ti(O^iPr)_4$ Promoted Reaction of Zn, EtI, Phenylacetylene and Benzaldehyde.

alkyne deprotonation since the neutral $ZnEt_2$ cannot deprotonate a terminal alkyne under these reaction conditions as we observed before. A number of species in the reaction system such as the basic alkoxy oxygen atoms of the complexes **2** and **3** could all act as the proton acceptor to facilitate the formation of the alkynylzinc reagent **1a**. The combination of **1**, **2** and benzaldehyde could form an intermediate like **4**. Migration of the alkynyl group from Zn to the coordinated aldehyde carbonyl group would generate a chiral zinc propargylate intermediate. The enantioselectivity of this reaction should be controlled by the chiral (*S*)-BINOL unit in **4**. The zinc propargylate formed from **4** could dissociate from the BINOL-Ti(IV) unit to regenerate the chiral Lewis acid catalyst **2** to complete the catalytic cycle. Upon aqueous workup, the zinc propargylate will be converted to the propargylic alcohol product. In this mechanism, (*S*)-BINOL plays two roles: (1) It reacts with $Ti(O^iPr)_4$ to generate a Lewis acidic Ti(IV) complex **2** to activate the reaction of Zn with EtI. (2) The BINOL-Ti(IV) complex also catalyze the enantioselective addition of the alkynylzinc intermediate to the aldehyde as shown by **4**.

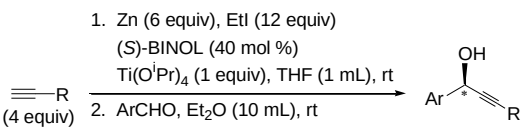
The mechanism depicted in Scheme 2 might be an oversimplified picture for the events occurring during the course of this reaction since complexes containing multiple BINOL and Ti(IV) centers could also be involved as demonstrated by Walsh.[10] As shown in Table 1, when we reduced the amount of Zn and EtI (entry 5), or the alkyne (entry 6), or $Ti(O^iPr)_4$ (entry 7), while maintaining the amount of the chiral ligand (*S*)-BINOL, the enantioselectivity decreased in each case. When the amount of (*S*)-BINOL was reduced, there was a greater reduction in enantioselectivity (entry 8). These experiments do imply a more complex stereo control process than that represented by the intermediate **4**. More work is needed in order to gain a better understanding of this reaction.

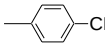
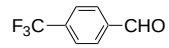
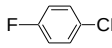
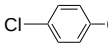
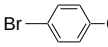
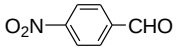
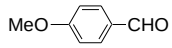
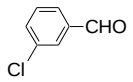
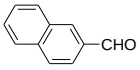
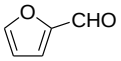
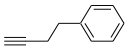
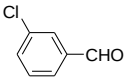
When only THF was used as the solvent for both steps, the ee was reduced to be less than 70% (entry 9). This demonstrates that although THF is important to generate the nucleophilic alkynyl reagent, diethyl ether is important for the observed high enantioselectivity in entry 2. It is possible that the more nucleophilic THF molecule could coordinate to the Zn or Ti centers to alter the stereoselectivity of the reaction. Therefore, a large excess of diethyl ether versus THF (10:1) is necessary in the second step in order to achieve the observed high enantioselectivity.

The result of entry 2 in Table 1 has encouraged us to apply the conditions to the reactions of other substrates. As summarized in Table 2, the reactions of phenylacetylene with *ortho*-, *meta*-, or *para*-substituted benzaldehydes containing electron-donating or electron-withdrawing substituents gave the corresponding chiral propargylic alcohols with excellent enantioselectivity and good yields (entries 1-10). This reaction can tolerate the nitro group on the aldehyde (entry 8). High enantioselectivity was also observed for the alkyne addition to other aromatic aldehydes such as 1-naphthaldehyde, and 2-naphthaldehyde, and 2-furaldehyde (entries 11-13). By increasing the reaction time of the first step to 36 h, aliphatic and vinyl alkynes also reacted with aldehydes to afford the corresponding chiral propargylic alcohols with high ee's and good yields (entries 14-17). The configurations of the propargylic alcohols are assigned by analogy with the reaction of phenylacetylene with benzaldehyde as well as those reported before.

Following describes a typical experimental procedure for the asymmetric alkyne addition to aldehydes in the presence of Zn, EtI, (*S*)-BINOL and $Ti(O^iPr)_4$: Under nitrogen, to a dry 25 mL flask was added Zn powder (3 mmol, 6 equiv) and (*S*)-BINOL (0.2 mmol, 0.4 equiv). Then EtI (6 mmol, 12 equiv), an alkyne (2

Table 2. Addition of Alkynes to Aldehydes in the Presence of Zn, EtI, (*S*)-BINOL and $Ti(O^iPr)_4$.[a]



entry	alkyne	aldehyde	isolated yield (%)	ee (%)
1			85	96
2			90	91
3			70	91
4			95	96
5			90	91
6			96	95
7			92	96
8			82[c]	92
9			92	90
10			92	93
11			75	96
12			76	95
13			60	91
14[b]			58	92
15[b]			78	90
16[b]			72	91
17[b]			80	91

[a]First step: Zn (3 mmol, 6 equiv), (*S*)-BINOL (0.2 mmol, 0.4 equiv). EtI (6 mmol, 12 equiv), an alkyne (2 mmol, 4 equiv), THF (1 mL), $Ti(O^iPr)_4$ (1 equiv), 24 h at room temperature. Second step: Et_2O (10 mL), an aldehyde (0.5 mmol), ~12 h. [b]36 h in the first step. [c]On the basis of the ^1H NMR spectrum.

mmol, 4 equiv), THF (1 mL) and $Ti(O^iPr)_4$ (1 equiv) were added via syringe under nitrogen. After the mixture was stirred at room temperature for 24 h (36 h for aliphatic alkynes), diethyl ether (10 mL) was added which was stirred for 1 h. An aldehyde (0.5 mmol) was added and the stirring was continued for 12 h. The reaction was then quenched with the addition of saturated ammonia chloride solution. After extraction with methylene chloride and concentration under vacuum, the residue was purified by passing through a short silica gel column to afford the pure propargylic alcohol product. The enantiomeric composition was determined by using HPLC-chiral column.

In summary, we have discovered that the reaction of Zn with EtI can be activated at room temperature by using BINOL and $Ti(O^iPr)_4$ which can then promote the highly enantioselective alkyne addition to aromatic aldehydes. This method allows the synthesis of a number of chiral propargylic alcohols with high enantiomeric purity under very mild reaction conditions. It avoids the direct use of the spontaneously combustible $ZnEt_2$, making it possible to conduct a much safer operation in large scale industrial production. In addition, this method provides a new way to activate the reaction of Zn with an alkyl halide. We are currently working on expanding the scope of this asymmetric addition to include substrates such as functional alkynes and aliphatic aldehydes and also increasing the overall efficiency of this reaction. The concept of using a Lewis acid to activate the reaction of Zn with an alkyl halide will also be applied to other organozinc reactions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures. Additional plots of spectral analysis data. See DOI: 10.1039/b000000x/

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