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Direct Zinc(II)-Catalyzed Enantioconvergent Additions of Terminal Alkynes to α -Keto Esters

Blane P. Zavesky and Prof. Dr. Jeffrey S. Johnson

Department of Chemistry, University of North Carolina at Chapel Hill Chapel Hill, NC 27599-3290 (USA)

Abstract

The addition of terminal alkynes to racemic β -stereogenic α -keto esters was achieved in high levels of stereoselectivity, affording versatile tertiary propargylic alcohols containing two stereocenters. This environmentally benign enantioconvergent reaction proceeds with perfect atom economy, requires no solvent, and is catalyzed by a non-toxic zinc salt. The alkyne moiety can be leveraged in downstream transformations including hydrogenation to the corresponding saturated tertiary alcohol, which represents the product of a formal enantioconvergent aliphatic nucleophile addition.

Graphical abstract

A perfect transformation: The addition of terminal alkynes to racemic β -stereogenic α -keto esters was achieved in high levels of stereoselectivity, affording versatile tertiary propargylic alcohols containing two stereocenters. This environmentally benign enantioconvergent reaction proceeds with high atom economy, requires no solvent, and is catalyzed by a non-toxic zinc salt.

Keywords

alkynes; asymmetric; catalysis; green; chemistry; synthetic; methods; zinc

Since the foundational report from Noyori and co-workers describing the dynamic kinetic hydrogenation of β -keto esters,^[1] enantioconvergent reactions that proceed by addition to racemic, configurationally labile electrophiles have been recognized for their ability to furnish stereochemically complex alcohol building blocks. Because of their high acidity, which facilitates substrate enantiomerization, β -dicarbonyl derivatives have remained the factotum substrate in enantioconvergent alcohol syntheses and the majority of these

Correspondence to: Jeffrey S. Johnson.

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Conflict of interest

The authors declare no conflict of interest.

reactions proceed via reduction to furnish secondary alcohols.^[2] In contrast, examples of enantioconvergent reactions employing less activated substrates are underexplored. Similarly, relatively few enantioconvergent additions proceed via carbon–carbon bond formation to furnish tertiary alcohol products.^[3] We recently reported an enantioconvergent addition employing arylboronic acids and α -keto ester electrophiles catalyzed by a chiral(diene) rhodium(I) complex which furnishes complex tertiary glycolate derivatives (Scheme 1A).^[4] The integration of other non-stabilized nucleophilic partners under this reaction manifold carries with it the opportunity to generate novel, stereochemically complex glycolate architectures. The purpose of this communication is to convey experimental results regarding the enantioconvergent addition of alkynes to configurationally labile α -keto esters, a reaction that furnishes tertiary alkynyl glycolates.

As a result of their versatility,^[5] propargyl alcohols are routinely employed in total synthesis.^[6] The addition of metal acetylides to carbonyls is a venerable method for the synthesis of propargyl alcohols.^[7] Following Mukaiyama's pioneering report describing the asymmetric addition of lithium acetylides to aldehydes,^[8] many synthetically useful asymmetric acetylide additions have been disclosed. The $\text{Zn}(\text{OTf})_2$ /*N*-methylephedrine catalyzed variant reported by Carreira and co-workers is a preeminent example;^[9] the use of $\text{Zn}(\text{OTf})_2$ as a catalyst avoids the use of pyrophoric dialkyl zinc promoters and allows the reaction to be rendered catalytic in zinc.^[10] While this discovery has led to a thorough investigation of compatible aldehyde substrates, much less attention has been paid to ketone electrophiles.^[7a,c,d] A notable exception comes from the Jiang group, who disclosed the alkynylation of α -keto esters (Scheme 1 B).^[11] Despite the reaction's reported intolerance of enolizable substrates, we were intrigued by the potential to construct complex tertiary propargylic alcohols via enantioconvergent acetylide additions (Scheme 1C).

Our investigation began with the coupling of α -keto ester **1a** and phenyl acetylene (Table 1). Initially, we chose to carry out the reaction using stoichiometric $\text{Zn}(\text{OTf})_2$ and ligand in order to first to probe the diastereo- and enantioselectivity of the reaction. Following Carreira's conditions,^[9] glycolate product **3a** was formed in 2.5:1 dr and 87:13 er (entry 1). When the ligand was changed to the amino alcohol developed by the Jiang group, which is accessible in 2 steps from commercially available (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol,^[11, 12] an increase in both diastereo- and enantioselectivity was observed (entry 2). Encouraged by this result, we next turned to rendering the process catalytic. Increasing the temperature while reducing catalyst loading to 20 mol% resulted in low conversion to product **3a** (entry 3). Zinc acetylide additions are ligand accelerated,^[13] thus we probed the hypothesis that reactivity could be improved by employing stoichiometric $\text{Zn}(\text{OTf})_2$ and catalytic ligand with-out negatively impacting enantioselectivity (entry 4). Although conversion was increased, a significant drop in enantioselectivity led us to abandon this strategy. When the reaction was run neat at 70°C,^[10] excellent conversion and enantioselectivity were obtained (entry 5). Finally, lowering the temperature of the reaction to 40°C improved the diastereoselectivity of the reaction, affording product **3a** in quantitative conversion, 8.7:1 dr, and 99:1 er (entry 6).

Under our optimized conditions, a variety of terminal alkynes were added to α -keto ester **1a** (Table 2). Electron-rich aryl alkyne **2b** was used to deliver alcohol **3b** in good diastereo- and

enantiocontrol. 4-Fluorophenyl acetylene (**2c**) proved to be an excellent coupling partner as well. Ene-yne product **3d** was obtained in 6.3:1 dr and 98.5:1.5 er. Alkyl substituted alkynes also proved to be viable substrates. In general, forming these products required slightly higher reaction temperatures. Alkyl alkynes substituted with heteroatoms gave satisfactory results. The use of a protected primary alcohol, as represented by product **3f**, was well tolerated. Acetal **3g** was assembled with only modest diastereoselectivity (4.6:1 dr) but almost perfect enantioselectivity (99.5:0.5 er). Amine **2h** restored higher levels of diastereoselectivity. When alkynes with α -tertiary centers (**2i**, **2j**) were added to **1a**, the highest levels of diastereoselectivity were obtained. A free alcohol was tolerated in the formation of **3i**. Finally, (+)-citronellal-derived alkyne **2k** was employed, which gave product **3k** in excellent selectivity and yield.

Next, the generality of the α -keto ester partner was probed (Table 2). α -Keto ester **1l**, which contains an electron-rich substituent on the aryl ring, provided glycolate product **3l** with exquisite selectivity. The formation of product **3m** in 78% yield, 8.2:1 dr, and 96.5:3.5 er indicates that this reaction is viable for substrates containing electronegative substituents and arenes bearing *ortho* substitution. When β -allyl α -keto esters were employed (**1n** and **1o**), an increase in temperature to 50°C was required, resulting in reduced levels of diastereoselectivity. Glycolate product **3o**, containing a *meta*-substituted aryl ring, was formed with the lowest enantioselectivity (93.5:6.5 er), which indicates that substitution about the arene can have a noticeable effect on enantioselectivity. When α -keto esters containing strongly electron-withdrawing groups on the arene or substitution at the γ -position, poor conversions were observed, even at elevated temperatures.

An X-ray diffraction study revealed the stereochemistry of **3b** to be (2*S*,3*R*).^[14] The relative configuration indicates that the favored transition state follows the Felkin–Anh model (Figure 1)^[15] and the absolute stereochemistry agrees with the results of Carreira^[10] and Jiang.^[11, 12]

To evaluate the synthetic utility of the propargylic alcohol products, a number of secondary transformations were carried out (Scheme 2). Tetrabutylammonium fluoride (TBAF) mediated removal of the trimethylsilyl group from compound **3j** afforded the terminal alkyne **4** in 59% yield. Compound **3a** underwent nickel boride-catalyzed partial hydrogenation to form *syn*-alkene **5** in high yield. Boron substituted alkene **6** was formed through the method of Tsuji and co-workers.^[16] Finally, a palladium on carbon catalyzed hydrogenation furnished product **7** in excellent yield. This hydrogenation shows that for these products, the alkyne functionality can act as an alkane surrogate,^[11] an important feature due to a lack of alternative reliable methods for accomplishing this net transformation stereoselectively.^[17] Furthermore, the enantioconvergent alkynylation reaction of **1a** and phenylacetylene was conducted on a gram scale. Since excess alkyne served only the role of solubilizing the reaction mixture, the amount of phenylacetylene was decreased to 1.5 molar equivalents. An equal volume amount of toluene was added in place of excess alkyne to dissolve the reagents.^[18] This modification produced no significant decrease in yield or stereoselectivity.

In conclusion, we have developed a stereoconvergent alkynylation reaction of β -stereogenic α -keto esters. This coupling of α -keto esters and alkynes constitutes a rare example of the addition of a nonstabilized carbon nucleophile to a C=O π -electrophile proceeding in an enantioconvergent fashion. The reaction proceeds with high atom economy and is conducted neat. The substituted glycolate products can be converted into useful alkene and alkane products. Studies aimed at the use of this reaction in the arena of total synthesis are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Determination of relative and absolute stereochemistries by X-ray crystallography.

A. Enantioconvergent Addition of Non-Stabilized Nucleophiles to α -Keto Esters (Only Example) **B. Jiang's Enantioselective Addition of Zinc Acetylides to α -Keto Esters** **C. This Work** **Scheme 1.**

Prior art relevant to the title reaction.

Scheme 2.

Chemical transformations of propargyl alcohol products and gram-scale reaction.

Conditions: a) TBAF (1 M solution in H₂O, 1.2 equiv), THF, 0°C, 15 minutes; b) Ni(OAc)₂ (30 mol%), NaBH₄ (60 mol%), ethylenediamine (1 equiv), H₂ (1 atm), EtOH, RT, 8 h; c) **E** (2 mol%), NaO^tBu (12 mol%), HBpin (1.5 equiv), toluene, 60°C, 16 h; d) Pd/C (10 wt.%), H₂ (1 atm).

Table 1

Optimization of alkynylation reaction conditions.^[a]

Entry	mol% Zn	L	T [°C]	Conv [%]	d ^[b]	e ^[c]
1	110	D ^[d]	RT	38	2.5:1	87:13
2	110	C ^[d]	RT	51	3.6:1	98:2
3	20	C	70	<5	–	–
4	110	C	70	70	3.7:1	64:36
5 ^[e]	20	C	70	94	3.8:1	96:4
6 ^[e]	20	C	40	99	8.7:1	99:1

ligands:

^[a]Unless otherwise noted, reactions conditions are as follows: 1.0 equiv of **1a**, 3.0 equiv of **2a**, variable amounts of Zn(OTf)₂, 50 mol% NEt₃, 22 mol% ligand, PhMe ([**1a**]₀=0.2 M), 24 h.^[b]Determined by ¹H NMR analysis of the crude reaction mixture.^[c]Determined by chiral HPLC analysis. Represents the enantiomeric ratio of the major diastereomer.^[d]₁₂₀ mol% ligand employed.^[e]Reactions were conducted using no solvent.

Table 2

Scope of alkynylation reaction.^[a]

^[a] Reaction conditions: 1.0 equiv **1**, 3.0 equiv **2**, 20 mol% Zn(OTf)₂, 22 mol% **C**, 50 mol% NEt₃, 24 h. All diastereomeric pairs were separated via column chromatography on silica gel. The reported enantiomeric ratio is of the major diastereomer.

^[b] Reaction conducted at 50 °C.

[c] Reaction conducted at 60°C.

[d] Reaction time of 48 h.

[e] Reaction conducted at 70°C.

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