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A New Strategy for the Synthesis of Chiral β -Alkynyl Esters via Sequential Palladium and Copper Catalysis

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Abstract

A new strategy for the synthesis of chiral β -alkynyl esters which relies on sequential Pd and Cu catalysis is reported. Terminal alkynes bearing aryl-, alkyl-, and silyl-groups can be employed without prior activation yielding a wide range of important chiral building blocks. The reaction sequence utilizes a robust Pd(II)-catalyzed hydroalkynylation of ynoates with terminal alkynes providing geometrically-pure ynoates which are readily reduced by CuH. In contrast to previous reports, where additions to ynoates proceed with marginal preference for the 1,6-pathway, this conjugate reduction occurs with high 1,4-selectivity yielding β -alkynyl esters with excellent levels of enantioselectivity. Importantly, the method tolerates a wide range of functionality, including allylic carbonates and carbamates, and thus allows for rapid elaboration of the β -alkynyl esters into a variety of chiral, substituted heterocycles.

In recent years, transition metal catalysis has increasingly established atom-economic, efficient processes for the construction of functional molecules. Nevertheless, many highly desirable chemical transformations still require the use of stoichiometric substrate activation. In this regard, the direct catalytic asymmetric conjugate addition of terminal alkynes to α , β -unsaturated esters, which exemplifies the ideals of atom and step economy,¹ has not been described. Due to the synthetic utility of alkynes and esters, these functional molecules are well regarded as valuable building blocks for further synthetic transformations. In addition, related chiral β -alkynyl acids have recently been identified as important pharmacophores in their own right.²

Despite the potential utility of direct catalytic asymmetric additions of terminal alkynes to activated olefins, progress in this area has been limited, largely due to the modest nucleophilicity of transition-metal acetylides.³ This problem has been addressed through the stoichiometric activation of terminal alkynes as their boron, aluminum, and zinc acetylides.⁴ However, such methods suffer from low functional group tolerance as well as increased downstream waste by virtue of poor atom economy.⁵ Recently, the direct catalytic asymmetric conjugate addition of terminal alkynes has been realized for a limited set of substrates. By using Cu catalysis, the Carreira and Shibasaki groups have demonstrated efficient asymmetric additions of terminal alkynes to Meldrum's acid alkylidenes and α , β -unsaturated thioamides, respectively.⁶ In addition, Hayashi and Fillion have established that Rh catalysis can promote the asymmetric addition of silyl acetylenes to enones, enals, and Meldrum's acid alkylidenes.⁷ While these reports stand out as pioneering efforts, each method is limited by either the required substitution on the alkyne or by the nature of the olefin wherein the activating group must subsequently be elaborated into an ester (Scheme

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Supporting Information Available. Experimental procedures and analytical data for all new compounds are available free of charge via the Internet at: <https://pubs.acs.org>.

1). Therefore, the direct synthesis of chiral β -alkynyl esters from readily accessible reagents remains an unmet challenge.

Herein, we describe a new, efficient strategy based on sequential Pd and Cu catalysis for the enantioselective synthesis of β -alkynyl esters that achieves this goal. The process takes place under mild, ambient conditions, occurs with high regio- and stereoselectivity, and tolerates a variety of substituents on the terminal alkyne (Scheme 1). Importantly, this method obviates the need to prepare and isolate geometrically pure enoates via traditional stereoselective olefination methods.

Since the late 1980's, our lab has been involved in the development of atom economical addition reactions that permit the cross-coupling of differentially substituted alkynes.⁸ Specifically, Pd(OAc)₂ ligated to an equimolar amount of tris(2,6-dimethoxy)phenylphosphine (TDMPP) catalyzes the hydroalkynylation of ynoates by terminal alkynes, affording a wide range of stereochemically defined ynenates in good yields. This reaction benefits from operational simplicity, as it is routinely performed with bench-top solvents under an ambient atmosphere at room temperature. While the ynenate products are suitable precursors to a variety of heterocycles,⁹ we questioned whether these substrates could also participate in an asymmetric CuH-catalyzed 1,4-reduction.¹⁰ The resulting two-step process, utilizing readily available alkyne starting materials, would yield chiral β -alkynyl esters and would provide an attractive alternative for the direct asymmetric conjugate addition of terminal alkynes to enoates (Scheme 1).

While attractive, this proposal is not without risk, given the complexities associated with regiochemical addition/reduction of extended π -systems. In particular, Cu-mediated conjugate additions to activated enyne substrates result in competitive 1,4- and 1,6-addition pathways, where literature precedent suggests a preference for the latter.¹¹ To our knowledge, there exists only one example of a copper-catalyzed, asymmetric 1,4-addition of an alkyl aluminium or zinc reagent to an ynenone that was recently reported by Hoveyda and co-workers.¹² To date, the catalytic asymmetric 1,4-reduction of an activated enyne has not been described.

To explore the feasibility of this strategy, ynenate **3aa** was prepared from ynoate **1a** and terminal alkyne **2a** using 3.0 mol % of Pd(OAc)₂ and mono-phosphine TDMPP at room temperature in 79% yield (Scheme 2). Importantly, only the (*E*)-isomer of **3aa** was produced in this Pd-catalyzed hydroalkynylation, as a mixture of olefin isomers would not be suitable for the ensuing asymmetric 1,4-reduction (*vide infra*).^{10k} We envisioned the asymmetric Cu-catalyzed 1,4-reduction of **3aa** taking place in the presence of the appropriate chiral bisphosphine and silane, yielding the corresponding ester **4aa**. Initial studies were carried out using ligands from the SEGPHOS family,^{10k} and while products resulting from 1,4-reduction were isolated in moderate yield, they were routinely accompanied by products arising from competitive 1,6-reduction. Upon screening various ligands, it was found that CuH ligated to the bis-phosphine (*R,R*)-WALPHOS (**L1**) promoted the 1,4-reduction with high regio- and enantioselectivity. Optimization of the catalyst loading, temperature, and reaction time provided satisfactory conditions to achieve complete 1,4-reduction of **3aa**. As such, the reduction was carried out using 5 mol % Cu(OAc)₂ · H₂O/**L1** in the presence of diethoxymethylsilane (DEMS) and *t*-BuOH at 4 °C, affording ester **4aa** in 90% isolated yield and with a 99% enantiomeric excess.

To demonstrate the synthetic scope of the process, substitution on both ynoate **1** and terminal alkyne **2** was examined and the results are summarized in Table 1. Ynenates **3aa**, **3ab**, and **3ac**, derived from **1a** and terminal alkynes bearing alkyl-, aryl-, and silyl-groups, were synthesized and subjected to the optimized 1,4-reduction conditions affording the

desired β -alkynyl esters **4aa**, **4ab**, and **4ac** (respectively) in excellent yield and enantioselectivity (entries 1-3). To our surprise, when an ynenote bearing a methyl group at the β -position (**3bb**) was prepared and subjected to the optimized reduction conditions, a less regioselective event occurred, affording the desired product **4bb** in 59% yield while maintaining high enantioselectivity (99% ee, entry 4).¹³ Ester **4bb** was subsequently converted to a known compound and the absolute stereochemistry was determined to be (*S*).¹⁴ Ynoate **1c** was coupled to alkynes **2a**, **2b**, and **2c** in a similar fashion affording ynenotes **3ca**, **3cb**, and **3cc** bearing allylic carbonates (entries 5-7). Successful Cu-catalyzed asymmetric 1,4-reduction of all three classes (alkyl, aryl, and silyl) of this activated enyne afforded β -alkynyl esters **4ca**, **4cb**, and **4cc** with additional functionality while maintaining outstanding regio- and enantioselectivity.¹⁵ Notably, both Pd and Cu-catalyzed events took place without competitive ionization or reduction of the allylic carbonate (**3ca**, **3cb**, and **3cc**) via a π -allyl type intermediate, further demonstrating the chemoselectivity of the process. Ynenotes with a pendant $-N(H)Boc$ group could also be prepared in excellent yield (**3da**, **3db**, and **3dc**), although when subjected to asymmetric 1,4-reduction using the combination of $Cu(OAc)_2 \cdot H_2O$ and ligand **L1**, the regioselectivity of the reduction dropped significantly. A further ligand screen revealed that 1,4-selectivity could be restored by switching to (*R,S*)-(*t*-Bu)₂-JOSIPHOS ligand **L2** and adding THF as a cosolvent, thus affording β -alkynyl esters **4da**, **4db**, and **4dc** in excellent yield and enantioselectivity (entries 8-10). Presumably, when ligand **L1** is employed, an internal coordination event by the $-N(H)Boc$ group with the catalyst disrupts the preference of copper to promote selective 1,4-reduction. In contrast, the catalyst generated from the more electron-rich and sterically-hindered ligand **L2** does not suffer from this phenomenon. It has been noted in prior work that Cu-catalyzed 1,4-reductions of α , β -unsaturated ketones carried out with **L1** and **L2** yield products with an opposite sense of chirality,^{10j} and therefore the esters in entries 8-10 have been assigned as (*R*) by analogy.

In order to investigate the significance of olefin geometry in the asymmetric CuH 1,4-reduction, ynenote (*Z*)-**3db** was converted to its geometric isomer (*E*)-**3db** by irradiation in the presence of diphenyldiselenide.¹⁶ As previously described, using 2 mol % $Cu(OAc)_2 \cdot H_2O/L2$, ynenote (*Z*)-**3db** was reduced with complete 1,4-selectivity to provide **4db** in 94% yield and with 92% enantioselectivity as the (*R*)-enantiomer (Scheme 3). However, reduction of (*E*)-**3db** was distinctly slower and required an increase in the catalyst loading and reaction time. Even in the presence of 10 mol % $Cu(OAc)_2 \cdot H_2O/L2$ for 24 hours, only 38% conversion to β -alkynyl ester **4db** was observed. Although the reaction cleanly afforded the complimentary (*S*)-antipode with 92% enantioselectivity as expected, we were surprised to find such a dramatic drop in the rate of 1,4-reduction. We speculate that the proximity of the ester to the alkyne in (*E*)-**3db** allows a bidentate chelation with Cu and serves to obstruct the desired 1,4-reduction pathway. Experiments are currently ongoing to fully elucidate this interesting observation.

To highlight the robust nature and operational simplicity of these two catalytic events, a one-pot hydroalkynylation/1,4-reduction protocol was developed. It quickly became clear that excess terminal alkyne remaining in solution upon completion of the Pd-catalyzed hydroalkynylation resulted in attenuated reactivity during the subsequent Cu-catalyzed 1,4-reduction. To circumvent this problem, a slight excess (1.2 equiv) of ynoate **1d** was employed in the hydroalkynylation with terminal alkyne **2a**. Upon complete consumption of **2a**, the reaction was cooled to 0 °C and a solution of $Cu(OAc)_2 \cdot H_2O/L2$ was introduced followed by DEMS and *t*-BuOH. The ensuing Cu-catalyzed asymmetric 1,4-reduction took place smoothly and the β -alkynyl ester **4da** was isolated in 78% yield and 92% enantiomeric excess from terminal alkyne **2a** (Scheme 4).

An important aspect of this method is that both C–C and C–H bond forming events occur chemoselectively in the presence of additional functional groups. As a result, functionalized β -alkynyl esters (**4**) are produced efficiently and provide an ideal platform from which to construct a variety of valuable, chiral heterocycles (Scheme 5). For example, carbonate **4ca** is hydrolyzed selectively to reveal an –OH group that can be differentially cyclized to yield either chiral lactone **5** or chiral tetrahydrofuran **6**.^{17,18} Similarly, chiral pyrrolidinone **7** and tetrasubstituted chiral dihydro-pyrrole **8** can be prepared from the corresponding β -alkynyl ester **4db** bearing an –NHBoc group.^{9a} The asymmetric synthesis of **8** in good yield and with high enantioselectivity, utilizing only three transition-metalcatalyzed steps (in two pots) from phenylacetylene is particularly noteworthy.

In summary, a new strategy for the synthesis of chiral β -alkynyl esters from readily available alkyne starting materials has been developed. We believe that this methodology represents an attractive alternative to traditional additions of terminal alkynes to activated olefins. Construction of the chiral propargylic center is carried out by an initial Pd-catalyzed hydroalkynylation of an ynoate with a terminal alkyne (*C–C bond*) and subsequently an asymmetric, Cu-catalyzed 1,4-addition of hydride (*C–H bond*). Both steps occur under mild, practical conditions and the 1,4- vs. 1,6-regioselectivity in the asymmetric CuH-reduction is unprecedented. The robust nature of each catalytic step is highlighted by the development of an efficient one-pot protocol. The method is highly chemoselective and tolerant of numerous functional groups, allowing for the rapid construction of chiral functionalized β -alkynyl esters. These substrates can be selectively cyclized, providing rapid syntheses of chiral lactones, tetrahydrofurans, pyrrolidinones, and dihydropyrroles. Finally, we note that both Pd-catalyzed hydroalkynylation and Cu-catalyzed asymmetric 1,4-reduction tolerate a wide variety of electron withdrawing groups in addition to esters. Therefore, we are optimistic that future efforts to extend the scope of this new strategy beyond ynoates will be realized in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. In addition to the formation of **4bb** in 59% isolated yield, reduction of ynenolate **3bb** produced complex, inseparable mixtures of by-products consistent with 1,6-reduction that represent the remaining mass balance.
14. Alkyne (*S*)-**4bb** was readily reduced to ester (*R*)-**SI-3**, the antipode of which has previously been prepared in 87% ee: Lopez F, Harutyunyan SR, Meetsma A, Minnaard AJ, Feringa BL. *Angew Chem Int Ed.* 2005; 44:2752.. The absolute stereochemistry of the current CuH reduction is assigned by analogy.

We also note that the synthesis of (*R*)-**SI-3**, constitutes the formal addition an alkyl group to an α , β -unsaturated ester. We believe that this 3-step sequence, comprised entirely of catalytic reactions, compares favorably to other known, asymmetric, alkyl conjugate addition reactions.

15. While the hydroalkynylations were routinely performed on 1.0 mmol scale, the CuH reductions were typically performed on 0.15-0.30 mmol scale. As a preliminary indication of scalability, the synthesis of alkyne **4ca** was performed on a 0.75 mmol scale, and the reaction maintained excellent yield and enantioselectivity (98% yield, 99% ee).
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Scheme 1. Synthesis of chiral β-alkynyl esters

Scheme 2. Sequential Pd/Cu Catalysis

Scheme 3. Olefin Isomerization and 1,4-Reduction

Scheme 4. One-Pot Sequential Pd/Cu Catalysis

Scheme 5. Chiral Heterocycle Synthesis

Conditions: (i) Otera's catalyst (10 mol %), PhMe, 85 °C, 78%. (ii) AuCl (10 mol %), PPTS (10 mol %), EtOH, 0 °C, 50%. (iii) AlMe₃ (1.5 equiv), PhMe, -20 °C, 81%. (iv) Pd(OAc)₂ (7.5 mol %), acrolein, LiBr, THF, rt, 64%.

Table 1

Synthetic Scope^a

entry	1	R ¹	2	R ²	3	yield (%) ^c	L	4	yield (%) ^d	ee (%) ^e
1	1a	C ₃ H ₁₁	2a	(CH ₂) ₂ Ph	3aa	79	L1	4aa	90	99 (S)
2	1a	C ₅ H ₁₁	2b	Ph	3ab	84	L1	4ab	90	99 (S)
3	1a	C ₃ H ₁₁	2c	BDMS	3ac	92	L1	4ac	87	99 (S)
4	1b	H	2b	Ph	3bb	95	L1	4bb	59	99 (S)
5	1c	OCO ₂ Me	2a	(CH ₂) ₂ Ph	3ca	77	L1	4ca	98	99 (S)
6	1c	OCO ₂ Me	2b	Ph	3cb	77	L1	4cb	92	99 (S)
7	1c	OCO ₂ Me	2c	BDMS	3cc	67	L1	4cc	81	99 (S)
8 ^b	1d	N(H)Boc	2a	(CH ₂) ₂ Ph	3da	91	L2	4da	90	94 (R)
9 ^b	1d	N(H)Boc	2b	Ph	3db	94	L2	4db	94	92 (R)
10 ^b	1d	N(H)Boc	2c	BDMS	3dc	93	L2	4dc	85	97 (R)

^a Conditions: (i) **1/2** = 1:1.25-1.75, 1.5-3.0 mol% Pd(OAc)₂/TDMPP, 1.0 M in PhMe at 23 °C for 1-18 h. (ii) 5 mol % Cu(OAc)₂·H₂O/**L1**, DEMS (2 equiv), *t*-BuOH (2 equiv), 0.2M in PhMe at 4 °C, 14-20 h.

^b (ii) with 2 mol % Cu(OAc)₂·H₂O/**L2**, DEMS (1.5 equiv), *t*-BuOH (1.5 equiv), 0.2M in PhMe/THF (4:1) at 4 °C, 4 h.

^c Isolated yield.

^d Isolated yield based on **3**.

^e ee determined by chiral HPLC using a Daicel CHIRALPAK® IB column. **L1** = (*R*, *R*)-WALPHOS, **L2** = (*R*, *S*)-(*t*-Bu)₂-JOSIPHOS.