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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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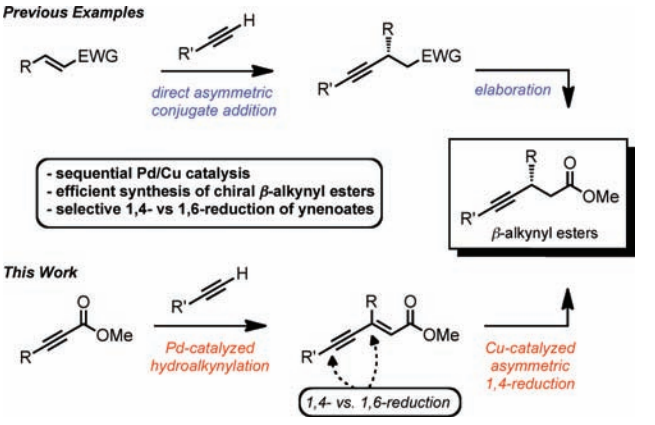
Supporting Information

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 ynenoates which are readily reduced by CuH. In contrast to previous reports, where additions to ynenoates 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 the nature of the olefin wherein the activating group must subsequently be elaborated into an ester (Scheme 1). Therefore, the direct synthesis of chiral β-alkynyl esters from readily accessible reagents remains an unmet challenge.

Scheme 1. Synthesis of Chiral β-Alkynyl Esters



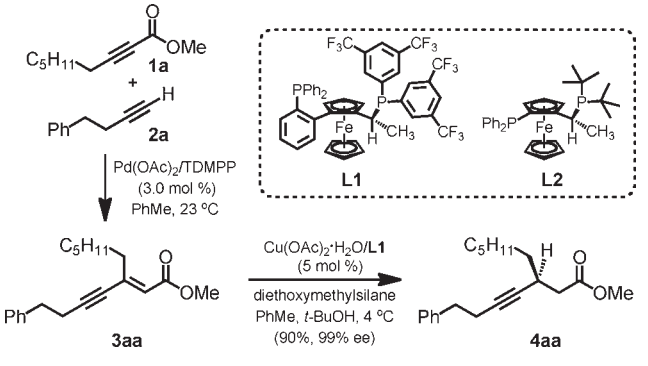
Herein, we describe a new, efficient strategy based on sequential Pd and Cu catalysis for the enantioselective synthesis of β-alkynyl esters that achieves this goal. The process takes place under mild, ambient conditions, occurs with high regio- and stereoselectivity, and tolerates a variety of substituents 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 1980s, 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 ynenoates in good yields. This reaction benefits from operational simplicity, as it is routinely performed with benchtop solvents under an ambient atmosphere at room temperature. While the ynenoate products are suitable precursors to a variety of heterocycles,[9] we questioned whether these substrates could also participate

Received: April 6, 2011
Published: May 11, 2011

dx.doi.org/10.1021/ja203171x | J. Am. Chem. Soc. 2011, 133, 8502–8505

Scheme 2. Sequential Pd/Cu Catalysis



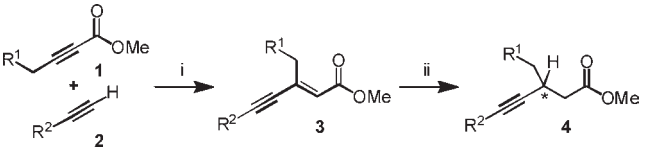
in an asymmetric CuH-catalyzed 1,4-reduction.[10] The resulting two-step process, utilizing readily available alkyne starting materials, would yield chiral β-alkynyl esters and would provide an attractive alternative for the direct asymmetric conjugate addition of terminal alkynes to enoates (Scheme 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 aluminum 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, ynenoate **3aa** was prepared from ynoate **1a** and terminal alkyne **2a** using 3.0 mol % of $Pd(OAc)_2$ and monophosphine 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 bis-phosphine 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 % $Cu(OAc)_2 \cdot H_2O$/**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. Ynenoates **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 ynenoate bearing a methyl group at the β-position (**3bb**) was

Table 1. Synthetic Scope[a]



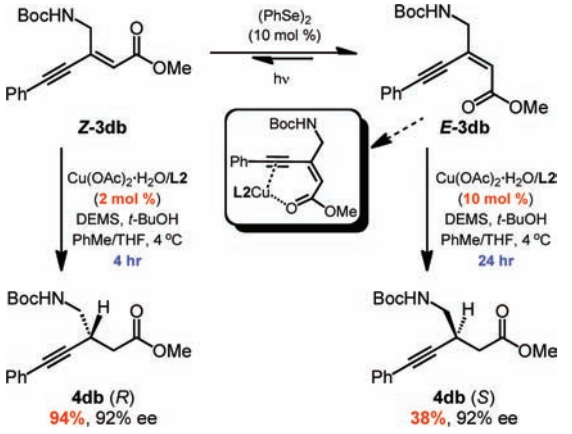
entry	1	R^1	2	R^2	3	yield (%)[c]	L	4	yield (%)[d]	ee (%)[e]
1	**1a**	C_5H_{11}	**2a**	$(CH_2)_2Ph$	**3aa**	79	**L1**	**4aa**	90	99 (*S*)
2	**1a**	C_5H_{11}	**2b**	Ph	**3ab**	84	**L1**	**4ab**	90	99 (*S*)
3	**1a**	C_5H_{11}	**2c**	BDMS	**3ac**	92	**L1**	**4ac**	87	99 (*S*)
4	**1b**	H	**2b**	Ph	**3bb**	95	**L1**	**4bb**	59	99 (*S*)
5	**1c**	OCO_2Me	**2a**	$(CH_2)_2Ph$	**3ca**	77	**L1**	**4ca**	98	99 (*S*)
6	**1c**	OCO_2Me	**2b**	Ph	**3cb**	77	**L1**	**4cb**	92	99 (*S*)
7	**1c**	OCO_2Me	**2c**	BDMS	**3cc**	67	**L1**	**4cc**	81	99 (*S*)
8[b]	**1d**	N(H)Boc	**2a**	$(CH_2)_2Ph$	**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 % $Cu(OAc)_2 \cdot H_2O$/**L1**, DEMS (2 equiv), *t*-BuOH (2 equiv), 0.2 M in PhMe at 4 °C, 14−20 h. [b] Conditions (ii) changed to 2 mol % $Cu(OAc)_2 \cdot H_2O$/**L2**, DEMS (1.5 equiv), *t*-BuOH (1.5 equiv), 0.2 M in PhMe/THF (4:1) at 4 °C, 4 h. [c] Isolated yield. [d] Isolated yield based on **3**. [e] Enantiomeric excess determined by chiral HPLC using a Daicel CHIRALPAK IB column. **L1** = (*R*,*R*)-WALPHOS, **L2** = (*R*,*S*)-(*t*-Bu)$_2$-JOSIPHOS.

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 ynenoates **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. Ynenoates 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

dx.doi.org/10.1021/ja203171x |*J. Am. Chem. Soc.* 2011, 133, 8502–8505

Scheme 3. Olefin Isomerization and 1,4-Reduction



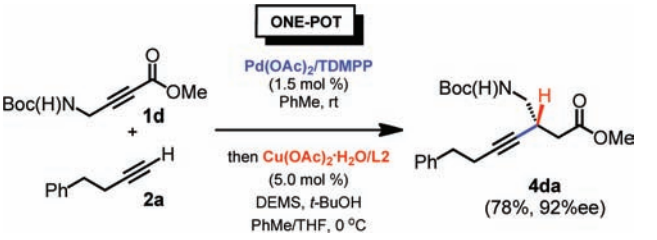
products with an opposite sense of chirality,[10n] and therefore the esters in entries 8−10 have been assigned as (*R*) by analogy.

To investigate the significance of olefin geometry in the asymmetric CuH 1,4-reduction, ynenoate (*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**, ynenoate (*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 h, only 38% conversion to *β*-alkynyl ester **4db** was observed. Although the reaction cleanly afforded the complementary (*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.

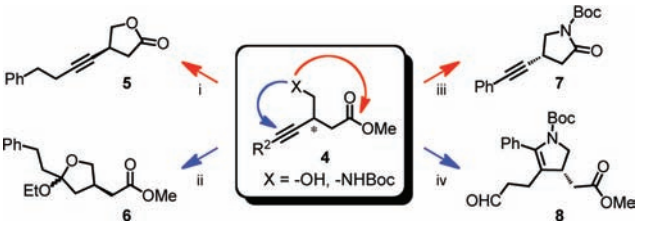
To highlight the robust nature and operational simplicity of these two catalytic events, a one-pot hydroalkynylation/1,4-reduction protocol was developed. It quickly became clear that excess terminal alkyne remaining in solution upon completion of the Pd-catalyzed hydroalkynylation resulted in attenuated 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

Scheme 4. One-Pot Sequential Pd/Cu Catalysis



Scheme 5. Chiral Heterocycle Synthesis[a]



[a] Conditions: (i) Otera's catalyst (10 mol %), PhMe, 85 °C, 78%. (ii) AuCl (10 mol %), PPTS (10 mol %), EtOH, 0 °C, 50%. (iii) $AlMe_3$ (1.5 equiv), PhMe, −20 °C, 81%. (iv) $Pd(OAc)_2$ (7.5 mol %), acrolein, LiBr, THF, rt, 64%.

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-metal-catalyzed 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 ynenoates will be realized in due course.

■ ASSOCIATED CONTENT

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

dx.doi.org/10.1021/ja203171x |*J. Am. Chem. Soc.* 2011, 133, 8502–8505

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ACKNOWLEDGMENT

We thank the National Science Foundation (CHE 0948222) and the National Institutes of Health (GM33049) for their generous support of our programs. B.R.T. and J.-P. L. are grateful for NIH postdoctoral fellowships (CA137999 and GM083428 respectively). We thank Johnson-Matthey for generously providing us with palladium salts and Solvias for providing chiral phosphine ligands.

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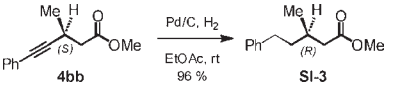
(13) In addition to the formation of **4bb** in 59% isolated yield, reduction of ynenoate **3bb** produced complex, inseparable mixtures of byproducts consistent with 1,6-reduction that represent the remaining mass balance.

(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, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *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 a 1.0 mmol scale, the CuH reductions were typically performed on a 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).

(16) Trost, B. M.; Hachiya, I.; McIntosh, M. C. *Tetrahedron Lett.* **1998**, *39*, 6445.

(17) Lactone **5** was synthesized using Otera's catalyst (1,3-diisothiocyanatotetrabutyldistannoxane): Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. For a review of transesterification catalysts, see: Otera, J. *Chem. Rev.* **1993**, *93*, 1449.

(18) For a related gold-catalyzed synthesis of tetrahydrofurans, see: Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489.