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Synthesis of Chiral α,β-Unsaturated γ-Amino Esters via Pd-Catalyzed Asymmetric Allylic Amination

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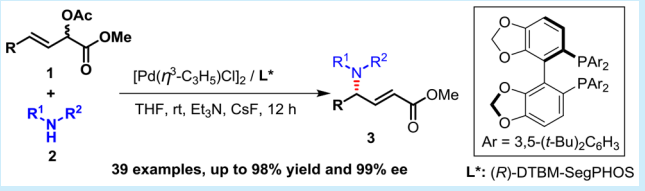
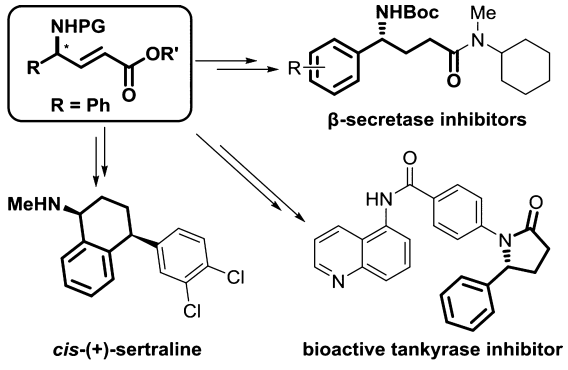
Supporting Information

ABSTRACT: A Pd-catalyzed asymmetric allylic amination of 4-substituted 2-acetoxybut-3-enoates with amines has been developed for the regiospecific synthesis of chiral α,β-unsaturated γ-amino esters. The desired chiral aminated products can be obtained in up to 98% yield, and 99% ee and can be conveniently transformed to chiral γ-amino acid/alcohol derivatives and chiral γ-lactams, which can then be subjected to the synthesis of several types of chiral drugs and drug candidates. The preferential formation of chiral γ-amino esters may be attributed to the bulky substituents on the right side of the allyl substrates. This work provides an efficient strategy for the synthesis of chiral α,β-unsaturated γ-amino esters and their derivatives.



Chiral α,β-unsaturated γ-amino esters are of considerable significance due to their use as versatile building blocks for chemical and biological synthesis.[1] They can be converted to chiral γ-amino amides (of which some are efficient β-secretase inhibitors),[2a] chiral γ-amino alcohols for the synthesis of the antidepressant drug *cis*-(+)-sertraline,[2b] or chiral γ-lactams for the synthesis of other biologically active compounds, such as a bioactive tankyrase inhibitor,[2c] etc. (Scheme 1).

Scheme 1. Chiral α,β-Unsaturated γ-Amino Esters as Drug (Intermediates) and Building Blocks



Generally, chiral α,β-unsaturated γ-amino esters can be prepared readily via a Wittig-type olefination of N-protected α-amino aldehydes. However, chiral aldehydes that are used in the reactions are sensitive to air, and their preparation requires a tedious multistep process. Few examples have emerged for the direct construction of chiral α,β-unsaturated γ-amino esters using chiral source-induced asymmetric synthesis (Scheme 1).[3]

By using enantioenriched allylic substrates, Lee synthesized two chiral α,β-unsaturated γ-amino esters via an Ir-catalyzed allylic amination.[3a] Norrby demonstrated an enantioconvergent synthesis of only one chiral α,β-unsaturated γ-amino ester by utilizing an asymmetric HWE reaction and a stereoselective Pd-catalyzed allylic substitution.[3b] Sharma[3c] and Ohshima[3d] independently reported a Pd- or Pt-catalyzed stereoselective opening of chiral vinyl epoxides with amine nucleophiles. Just recently, Terada employed an efficient Pd-catalyzed decarboxylative rearrangement of enantioenriched allylic carbamates for the synthesis of chiral γ-amino-α,β-unsaturated esters; slightly loss in enantioselectivities of aminated products was observed.[3e] Although several elegant methodologies have been developed, a direct catalytic asymmetric synthesis of chiral α,β-unsaturated γ-amino esters from various racemic allyl substrates and nucleophiles has yet to be explored.

Pd-catalyzed allylic substitution is a powerful synthetic tool for the formation of C−C and C−X bonds (X = N, O, S, etc.).[4] Recently, we have developed several metal-catalyzed asymmetric allylic alkylations for the construction of biologically active chiral molecules which possess excellent catalytic behavior.[5] Among them, a hydrogen-bond-directed regioselective Pd-catalyzed asymmetric allylic alkylation has been developed, providing "branched" chiral α-amino acids in high yields and excellent selectivities.[5e]

Herein, we disclose an efficient pathway for the preparation of α,β-unsaturated γ-amino esters via a Pd-catalyzed asymmetric allylic amination of functionalized allyl substrates and amine nucleophiles (Scheme 2).

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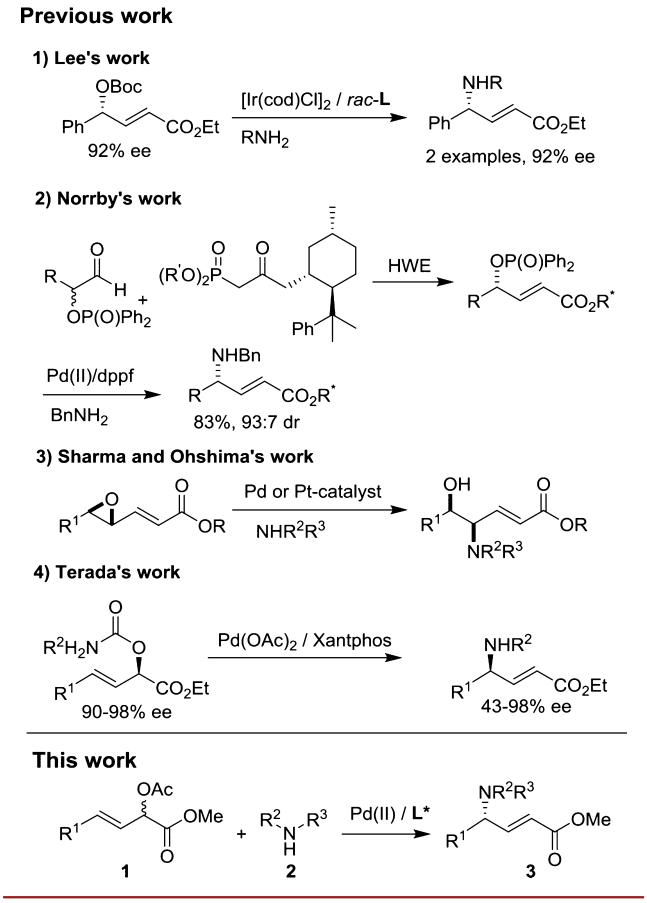
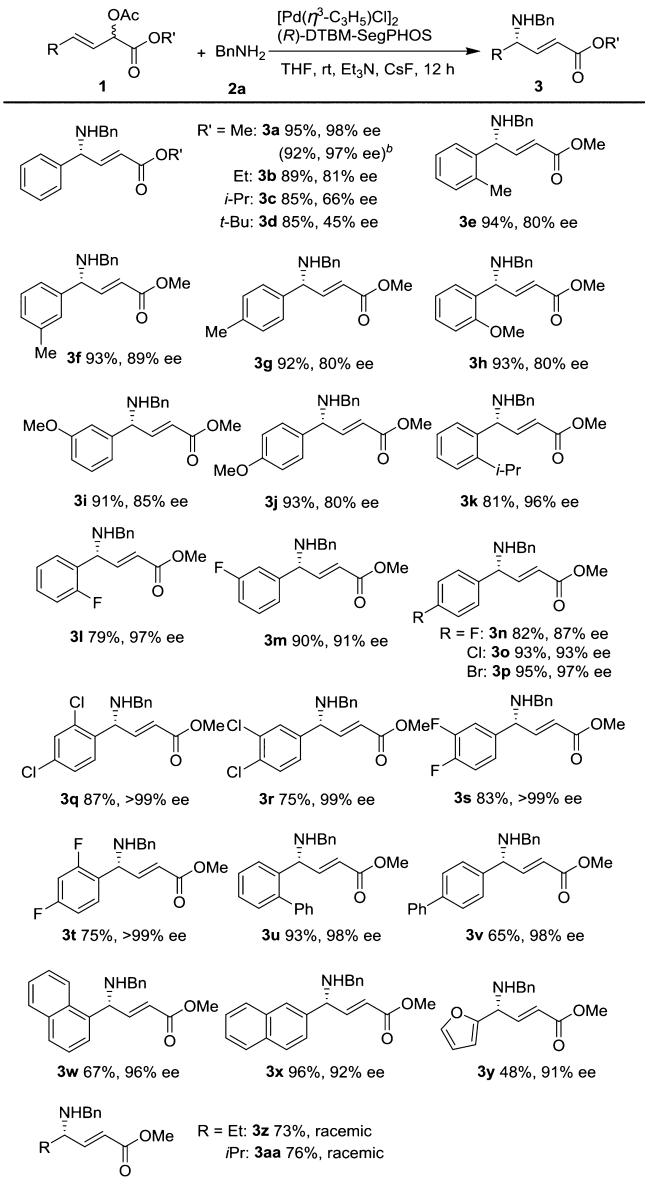
Scheme 2. Reported Examples and Our Project



Scheme 3. Scope of Substrates 1[a]



[a]Reactions of **1** (0.1 mmol) and **2a** (2 equiv) were carried out using a catalyst system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %) and (*R*)-DTBM-SegPHOS (10 mol %) in the presence of Et_3N (2 equiv) and CsF (1.2 equiv) in THF (2 mL) at rt for 12 h; isolated yields and ee's were determined by chiral HPLC using a chiral OJ-H or OD-H column; the absolute configuration of products was determined by the NOESY spectrum of **3a**[6] and transforming **3a** to its corresponding chiral γ-lactam derivative and comparing the sign of its optical rotation with reported data.[7] [b]The reaction was carried out on a large scale with 1 mmol of **1a**.

The effect of solvent, base, additive, and ligand on the Pd-catalyzed asymmetric allylic amination of methyl (*E*)-2-acetoxy-4-phenylbut-3-enoate (**1a**) with benzylamine (**2a**) was examined in details, and the optimal reaction conditions are as follows: using a catalyst system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (*R*)-DTBM-SegPHOS in the presence of Et_3N and CsF in THF at rt for 12 h.[6]

With the optimized reaction conditions in hand, reaction scope with regard to the allylic substrates **1** was investigated (Scheme 3). First, substrates bearing different ester groups were investigated and **3a** with a Me group gave the best result (**3a–d**). Next, **1** bearing different substituted Ar groups was examined. The ee of the desired products decreased for substrates bearing electron-donating groups on the phenyl rings (**3e–j**). However, **3k** bearing a bulky *ortho*-substituted *i*-Pr group was obtained in 96% ee. Both good to high yields and excellent enantioselectivities were obtained for substrates with electron-withdrawing groups on phenyl groups (**3l–p**). Substrates bearing two electron-withdrawing groups on the phenyl rings all gave their corresponding products with good yields and excellent enantioselectivities (with >99% ee in several cases, **3q–t**). Excellent enantioselectivities were retained when the electron-withdrawing groups were replaced by phenyl rings (**3u** and **3v**). Replacing the phenyl ring with naphthalene groups had little influence on the reaction outcomes (**3w** and **3x**). A substrate bearing a furyl ring was used in the reaction, with the desired product also being obtained in excellent enanioselectivity but only moderate yields (**3y**). Finally, the reactions were carried out with substrates by replacing Ar groups with aliphatic substituents. However, only racemic products **3z** and **3aa** were obtained in moderate yields.

Subsequently, a number of different amines (**2**) were investigated in the asymmetric amination (Scheme 4). Primary amines provided good to excellent yields and excellent enantioselectivities (**3ab–af**). As a comparison, secondary amines, both cyclic and acyclic, gave their respective products in excellent yields with moderate to good enantioselectivities (**3ag–am**).

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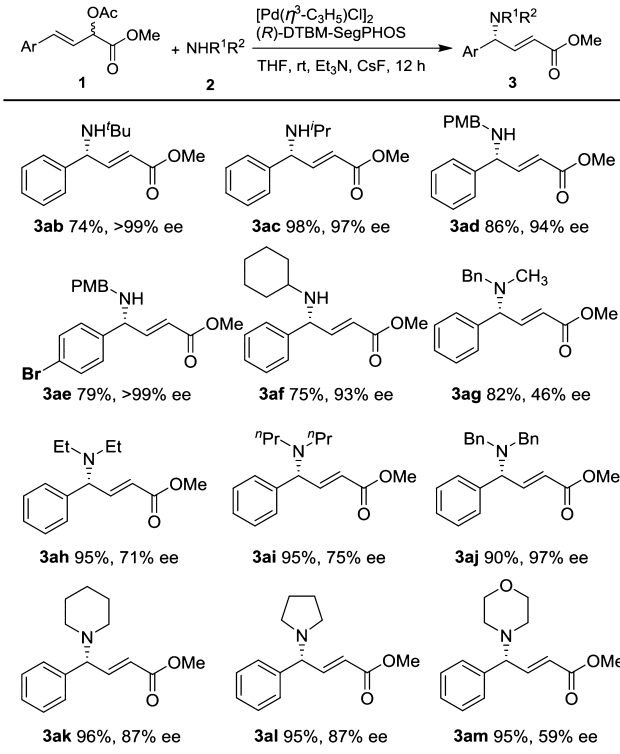
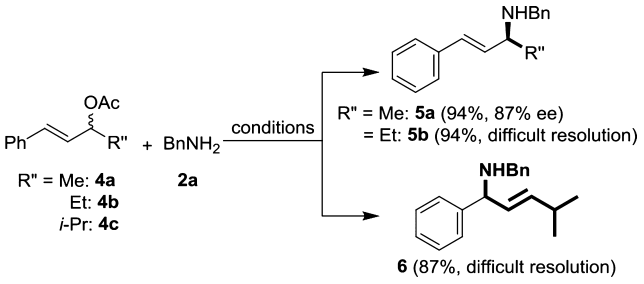
Scheme 4. Scope of Nucleophilic Amines 2[a]



[a]Using the optimal reaction conditions shown in Scheme 3; isolated yields and ee's were determined by chiral HPLC using a chiral OJ-H or OD-H column; the absolute configuration of products was determined by comparing the sign of the optical rotations with **3a**.

In order to determine the origin for the preferential formation of γ-aminated products over α-aminated products, substrates **4** bearing Me, Et and *i*-Pr groups, respectively, instead of ester groups, were subjected to the above reaction conditions (Scheme 5). When **4c** bearing a bulky *i*-Pr group

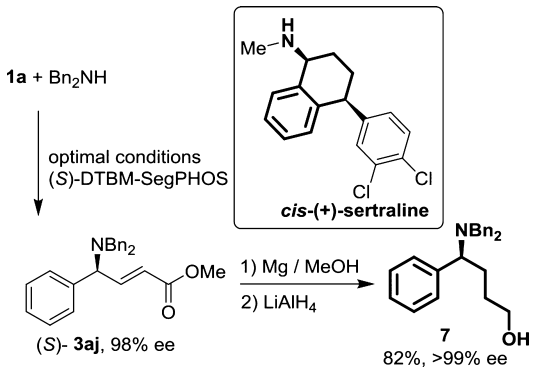
Scheme 5. Control Experiments



was used in the above reaction under the optimal reaction conditions, the corresponding aminated product **6** was obtained in high yield. However, substrates **4a** and **4b** bearing the less bulky groups, gave the unexpected "α-substituted" products in 94% yields. Obviously, the steric hindrance of the left aryl groups have no effect on the regioselectivity of the reaction (see the data in Scheme 3). The bulky substituents on the right side of the allyl substrates (ester groups and *i*-Pr versus Me and Et) may be responsible for the preferential formation of the γ-substituted products.

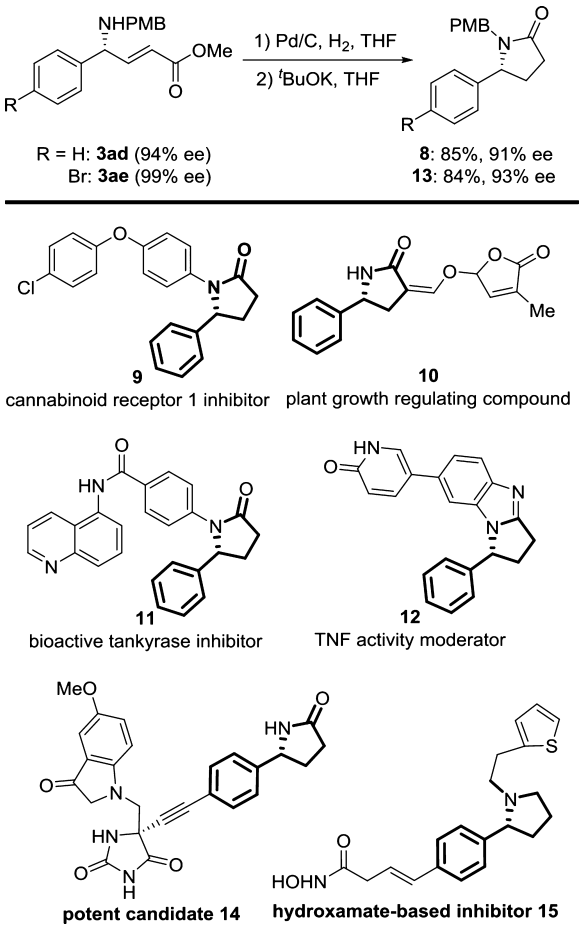
To prove the usefulness of the chiral aminated products, the product (*S*)-**3aj** produced using (*S*)-DTBM-SegPHOS as the chiral ligand, was treated with magnesium in MeOH and then with $LiAlH_4$, to afford the corresponding alcohol **7** in high yield without loss in enantioselectivity. Compound **7** is a key intermediate for the synthesis of chiral drug *cis*-(+)-sertraline, an effective antidepressant (Scheme 6).[2b]

Scheme 6. Synthesis of Chiral γ-Amino Alcohol 7



The chiral α,β-unsaturated γ-amino esters can also be converted to chiral γ-lactams, which are challenging to synthesize via conventional means but are widely used for the synthesis of both drugs and natural products.[8] Thus, the chiral γ-lactam **8** can be obtained readily in good yield and with excellent enantioselectivity from **3ad** via a Pd/C-catalyzed hydrogenation and subsequent cyclization (Scheme 7).

Scheme 7. Synthesis of Chiral γ-Lactam 8 and 13



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Compound **8** can be used as a key intermediate for the construction of several biologically active compounds, such as the cannabinoid receptor 1 inhibitor **9**,[9a] the TNF activity moderator **10**,[9b] the bioactive tankyrase inhibitor **11**,[2c] and the plant growth regulating compound **12**.[9c]

To further explore the utility of chiral γ-lactams in organic synthesis, **3ae** bearing a *para*-substituted bromine atom on the phenyl ring was converted to its corresponding chiral γ-lactam **13** in high yield (Scheme 7). Compound **13** could be further transformed to **14** (a candidate for the treatment of inflammatory disorders)[10a] or a hydroxamate-based inhibitor of deacetylases B **15** following literature procedures.[10b]

In summary, we have developed a Pd-catalyzed asymmetric allylic amination of 4-substituted 2-acetoxybut-3-enoates with different amines for the synthesis of chiral α,β-unsaturated γ-amino esters. The desired products can be obtained in up to 98% yield and with more than 99% ee and can be transformed to chiral γ-amino acid/alcohol derivatives and chiral γ-lactams, which can be further applied to the synthesis of several types of chiral drugs and drug candidates. The preferential formation of γ-amino esters over α-amino esters has been discussed. This work provides an efficient strategy for the synthesis of chiral γ-substituted α,β-unsaturated γ-amino esters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01904.

Experimental procedures, characterization details, and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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