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Synthesis of Enantioenriched γ-Amino-α,β-unsaturated Esters Utilizing Palladium-Catalyzed Rearrangement of Allylic Carbamates for Direct Application to Formal [3 + 2] Cycloaddition

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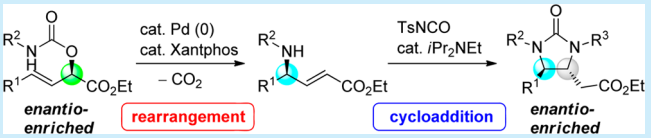
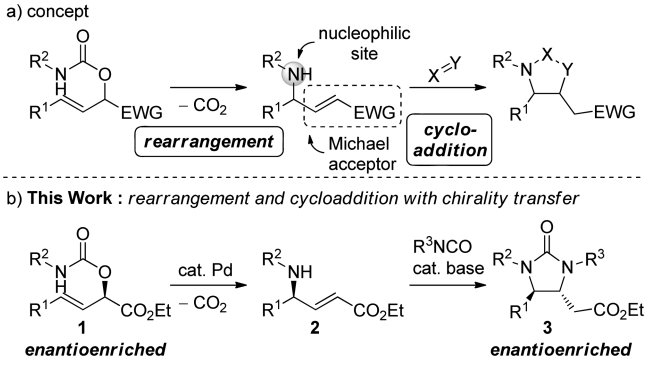
Supporting Information

ABSTRACT: An efficient synthesis of enantioenriched γ-amino-α,β-unsaturated esters was developed by utilizing the palladium-catalyzed decarboxylative rearrangement of enantioenriched allylic carbamates possessing an ester moiety at the allylic position. The reaction proceeded in good yield with a high degree of chirality transfer by making use of Xantphos as a superior ligand for the catalyst. The products directly participated in the formal [3 + 2] cycloaddition reaction with tosyl isocyanate under Brønsted base catalysis to afford enantioenriched β,γ-diamino acid derived imidazolidin-2-ones as versatile chiral building blocks.



The decarboxylative [3,3]-rearrangement of allylic carbamate is one of the most useful methods for the synthesis of allylic secondary amines, which are important building blocks in organic synthesis.[1] The starting allylic carbamates can be easily prepared by treating the corresponding allylic alcohols with isocyanates, and the reaction generally proceeds under mild conditions by using transition-metal catalysts such as Pd(II),[2] Pd(0),[3] Ir(I),[4] and Au(I) complexes.[5] Recently, as an application of this method to asymmetric synthesis, catalytic enantioselective reactions were developed in which achiral linear allylic carbamates were employed as substrates to provide chiral branched allylic amines having a monosubstituted alkene moiety.[2c,d,4] We envisioned that allylic carbamates possessing an electron-withdrawing group at the allylic position would be applicable to this transformation[3a] to provide allylic amines having an electron-deficient alkene moiety that can function as a Michael acceptor (Scheme 1a). We also expected that the products, which possess both a nucleophilic secondary amino group and an electrophilic alkene moiety, would directly participate in the formal [3 + 2] cycloaddition reaction with unsaturated compounds (X = Y) to afford nitrogen-containing heterocyclic compounds. In particular, we intended to develop a chirality transfer reaction of readily available enantioenriched allylic carbamate **1**, which has an ethoxycarbonyl group as an electron-withdrawing group, to provide enantioenriched γ-amino-α,β-unsaturated esters **2** for application to the synthesis of enantioenriched nitrogen-containing heterocyclic compounds by the formal [3 + 2] cycloaddition reaction (Scheme 1b). Conventionally, enantioenriched γ-amino-α,β-unsaturated esters **2** are prepared through the Wittig-type reaction of *N*-protected α-amino aldehydes, which are highly sensitive to the base-induced epimerization and require a tedious multistep synthesis.[6] Direct catalytic methods for the synthesis of those compounds with a broad scope are still limited.[7] Herein, we report that the decarboxylative rearrangement of enantioenriched allylic carbamates **1** proceeds under Pd(0) catalysis with good chirality transfer to afford enantioenriched γ-amino-α,β-unsaturated esters **2**. The formal [3 + 2] cycloaddition reaction of **2** with isocyanates under Brønsted base catalysis providing enantioenriched β,γ-diamino acid derived imidazolidin-2-ones **3** was also investigated.

Scheme 1. Reaction Design



The initial study was conducted with enantioenriched allylic carbamate (*R*)-**1a** (96% ee) having phenyl groups on both the nitrogen and the alkene terminus. The enantioenriched substrates **1** were synthesized from the enantioenriched α-hydroxy esters, which were easily prepared by palladium-catalyzed alkenylation of ethyl glyoxylate with vinylsilanes[8] or diastereoselective reduction of chiral β,γ-unsaturated α-oxo esters,[9] with isocyanate.[10] Compound **1a** was treated with a

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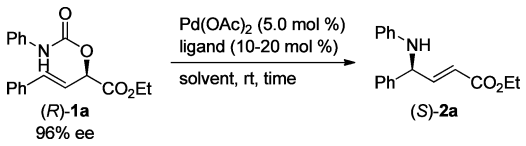
Table 1. Optimization of Reaction Conditions[a]



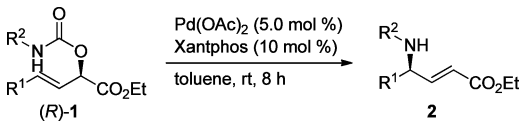
entry	ligand (mol %)	solvent	time (h)	yield[b] (%)	es[c] (%)
1	PPh_3 (20)	toluene	20	66	71
2	none	toluene	8	<1	
3	DPPE (10)	toluene	12	63	39
4	DPPB (10)	toluene	5	91	84
5	DPPF (10)	toluene	25	11	94
6	DPEPhos (10)	toluene	9	55	94
7	Xantphos (10)	toluene	8	86	95
8	$P(OEt)_3$ (20)	toluene	4	95	59
9	$P(OiPr)_3$ (20)	toluene	11	86	83
10	Xantphos (10)	THF	8	(49)	95
11	Xantphos (10)	1,4-dioxane	8	(46)	93
12	Xantphos (10)	CH_3CN	8	<1	
13[d]	Xantphos (10)	toluene	8	82	97

[a]Conditions: (*R*)-**1a** (0.20 mmol), $Pd(OAc)_2$ (0.010 mmol), ligand (0.020−0.040 mmol), solvent (2.0 mL). [b]Yields of isolated products. NMR yields are shown in parentheses. [c]Enantiomeric excess was determined by chiral stationary-phase HPLC analysis. es (enantiospecificity) = (ee % of product)/(ee % of substrate). [d]Toluene (3.0 mL) was used.

catalytic amount of $Pd(OAc)_2$ in the presence or absence of PPh_3 in toluene at room temperature for 20 h (Table 1, entries 1 and 2). Whereas no reaction occurred in the absence of PPh_3, the decarboxylative rearrangement proceeded in the presence of PPh_3 to provide γ-amino-α,β-unsaturated ester **2a** in 66% yield with 71% es (68% ee, es (enantiospecificity) = (ee % of product)/(ee % of substrate)). Ligand screening was carried out to increase both the chemical yield and the degree of chirality transfer (entries 3−9). A variety of bidentate phosphines as well as phosphites were examined, and Xantphos provided the best result; **2a** was obtained in 86% yield with 95% es (entry 7). The screening for the solvent revealed that toluene was the solvent of choice (entries 7 and 10−12). Decreasing the concentration of the reaction mixture improved the enantiospecificity (entry 13).[11] The absolute configuration of product **2a** was unambiguously determined to be *S* by single-crystal X-ray diffraction analysis after transformation through the formal [3 + 2] cycloaddition reaction (vide infra).[12]

With the optimum reaction conditions in hand, the scope of substrate **1** was investigated (Table 2). At first, the substituent at the alkene terminus was examined (entries 1−5). The reaction of 3-methoxyphenyl- and 4-chlorophenyl-substituted **1b** and **1c** proceeded with high degrees of chirality transfer (entries 1 and 2). 1-Naphthyl-substituted **1d** provided the desired product with a moderate degree of chirality transfer (entry 3). Whereas the reaction of 2-methyl-substituted **1e** proceeded smoothly to provide **2e** in good yield with a high degree of chirality transfer (entry 4), the reaction of 2-methoxy-substituted **1f** was sluggish and the ee value of **2f** was significantly decreased (39% ee) compared with that of starting **1f** (90% ee) (entry 5). Alkyl groups, such as the *n*-butyl group and methyl group, were applicable to this reaction. Compounds **1g** and **1h** underwent the reaction with high degrees of chirality transfer albeit in moderate yields (entries 6 and 7). Next, the substituent on the nitrogen was examined (entries 8−10). As a

Table 2. Substrate Scope[a]

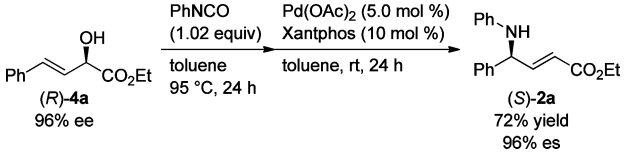


entry	R^1	R^2	ee of **1** (%)	**2**	yield[b] (%)	es[c] (%)
1	3-$MeOC_6H_4$	Ph	98	**2b**	75	94
2	4-ClC_6H_4	Ph	98	**2c**	60	96
3[d]	1-naphthyl	Ph	99	**2d**	78	82
4	2-MeC_6H_4	Ph	95	**2e**	65	94
5[e]	2-$MeOC_6H_4$	Ph	90	**2f**	35	43
6	*n*Bu	Ph	95	**2g**	44	98
7	Me	Ph	95	**2h**	52	93
8	Ph	4-$MeOC_6H_4$	96	**2i**	80	97
9	Ph	4-ClC_6H_4	96	**2j**	(48)	96
10	Ph	2-naphthyl	96	**2k**	82	95

[a]Conditions: (*R*)-**1** (0.20 mmol), $Pd(OAc)_2$ (0.010 mmol), Xantphos (0.020 mmol), toluene (3.0 mL). [b]Yields of isolated products. NMR yield is shown in parentheses. [c]Enantiomeric excess was determined by chiral stationary-phase HPLC analysis. es (enantiospecificity) = (ee % of product)/(ee % of substrate). [d]The reaction was conducted for 12 h. [e]The reaction was conducted for 24 h.

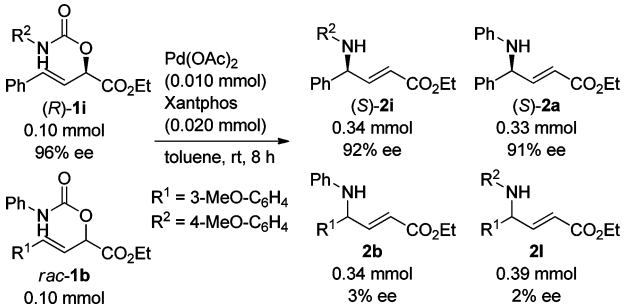
result, 4-methoxyphenyl- and 2-naphthyl-substituted **1i** and **1k** underwent the reaction without any problem to afford the corresponding products **2i** and **2k** in good yields, respectively. The reaction of 4-chlorophenyl-substituted **1j** proceeded with a high degree of chirality transfer, but the yield was moderate because of the instability of product **2j**. Substrates having an alkyl group on the nitrogen instead of an aryl group did not undergo the reaction. In addition, the reactions of tosyl- and benzoyl-substituted substrates resulted in complex mixtures of products. It is worth noting that the reaction could take place between allylic alcohol **4a** and phenyl isocyanate in a one-pot fashion without isolation of allylic carbamate **1a** (Scheme 2).

Scheme 2. One-pot Synthesis from (*R*)-4a



At this point, in order to acquire information on the reaction mechanism, a crossover experiment was carried out (Scheme 3). Equimolar amounts of enantioenriched (*R*)-**1i** (96% ee) and

Scheme 3. Crossover Experiment



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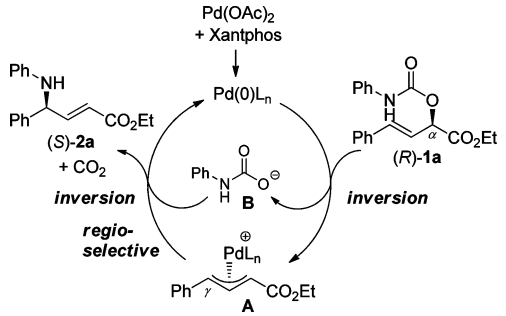
racemic **1b** were treated with catalytic amounts of $Pd(OAc)_2$ and Xantphos. As a result, four products, including normal products **2i** and **2b** and crossover products **2a** and **2l**, were obtained in almost equal amounts. In addition, **2i** and **2a**, which have an allyl moiety derived from enantioenriched **1i**, were obtained with high ee values, whereas **2b** and **2l** were obtained in an almost racemic fashion. This result clearly indicates that the reaction involves the intermolecular addition to a π-allyl palladium intermediate.

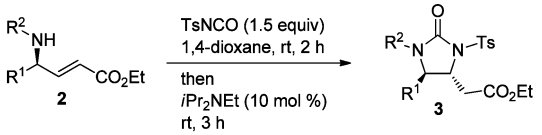
Scheme 4. Plausible Catalytic Cycle



On the basis of this result, a plausible catalytic cycle for the rearrangement is depicted in Scheme 4. The catalytic cycle is initiated by the oxidative addition of an allylic carbamate to Pd(0) generated in situ via the reduction of $Pd(OAc)_2$, providing cationic π-allyl palladium intermediate **A** and anionic species **B**. Then, the external nucleophilic attack of **B** on **A** at the γ-position of the ester moiety occurs with concomitant decarboxylation to afford the product and regenerated Pd(0).[13] The regiospecificity of this reaction is consistent with the common feature of the nucleophilic attack on π-allyl palladium intermediate having an electron-withdrawing group.[14] In this chirality transfer reaction, (*R*)-**1a** is transformed into (*S*)-**2a**. This stereochemical outcome is rationalized as follows. The oxidative addition occurs with the inversion of configuration at the α-position of the ester moiety. The following nucleophilic addition to cationic π-allyl palladium intermediate **A** proceeds with the inversion of configuration at the γ-position of the ester moiety prior to the competing racemization of **A**.

Next, the formal [3 + 2] cycloaddition reaction of γ-amino-α,β-unsaturated esters with isocyanates, which directly provides enantioenriched β,γ-diamino acid derived imidazolidin-2-ones, was investigated (Scheme 5).[15,16] As a result, tosyl isocyanate was a suitable partner, and the reaction proceeded smoothly under Brønsted base catalysis.[17] Treatment of **2a** with 1.5 equiv of tosyl isocyanate in 1,4-dioxane at room temperature followed by addition of a catalytic amount of *N*,*N*-diisopropylethylamine provided **3a** in good yield with perfect diastereoselectivity.[12] During the reaction, erosion of enantiomeric purity did not occur. The reactions of **2g** and **2i** also proceeded without any problem to afford the corresponding enantioenriched imidazolidin-2-ones.

Scheme 5. Formal [3 + 2] Cycloaddition

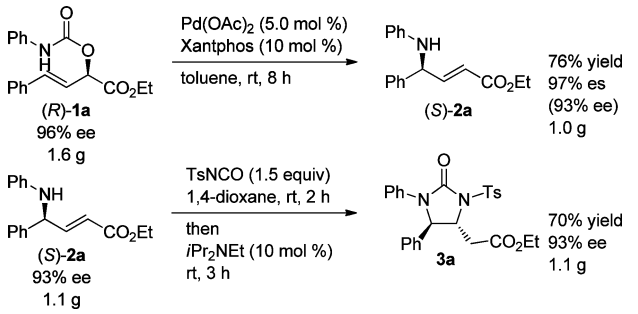


2a : $R^1 = R^2$ = Ph, 93% ee
2g : R^1 = *n*Bu, R^2 = Ph, 93% ee
2i : R^1 = Ph, R^2 = 4-MeO-C_6H_4, 92% ee

3a 80% yield, dr >99:1, 93% ee
3g 75% yield, dr >99:1, 93% ee
3i 70% yield, dr >99:1, 92% ee

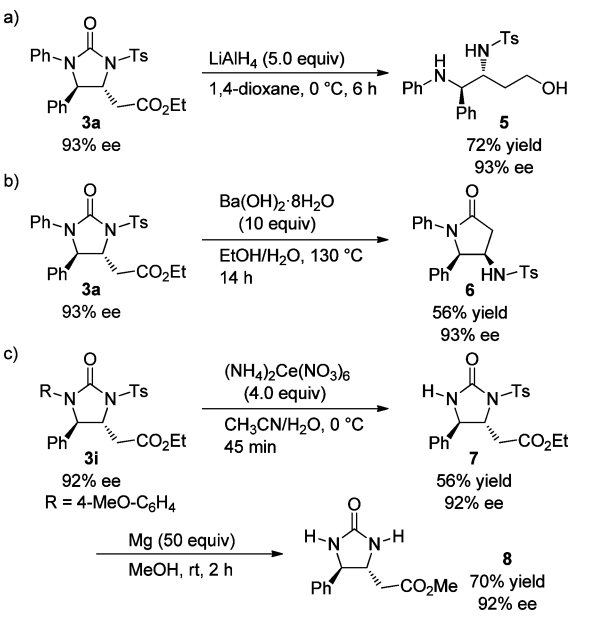
Both decarboxylative rearrangement and the formal [3 + 2] cycloaddition were sufficiently reliable to perform in gram scale (Scheme 6).

Scheme 6. Gram-Scale Synthesis of 2a and 3a



Finally, the transformation of the products of the formal [3 + 2] cycloaddition reaction was conducted (Scheme 7). Treatment of **3a** with an excess amount of $LiAlH_4$ resulted in the reduction of both the urea moiety and the ester moiety to provide diamino alcohol **5** in good yield (Scheme 7a). Hydrolysis under basic conditions provided lactam **6** (Scheme 7b). Both substituents on the nitrogens of **3i** were removable. The 4-methoxyphenyl group could be removed by treatment with ceric ammonium nitrite in acetonitrile/H_2O. The tosyl group of **7** could be cleaved by treatment with magnesium in methanol to afford **8**. In all cases, erosion of enantiomeric purity did not occur.

Scheme 7. Transformation of Products



In conclusion, we have newly developed an efficient synthesis of enantioenriched γ-amino-α,β-unsaturated esters by utilizing the palladium-catalyzed decarboxylative rearrangement of enantioenriched allylic carbamates possessing an ester moiety at the allylic position. The reaction proceeded in good yield with a high degree of chirality transfer by making use of Xantphos as a superior ligand for the catalyst. The products,

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which possess both a nucleophilic secondary amino group and an electrophilic alkene moiety, directly participated in the formal [3 + 2] cycloaddition reaction with tosyl isocyanate under Brønsted base catalysis to afford enantioenriched β,γ-diamino acid derived imidazolidin-2-ones. The newly developed sequential methodology offers facile access to versatile chiral building blocks. Research on further applications of this methodology is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00471.

Experimental procedures, screening of reaction conditions, and characterization data (PDF)
Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for details.

(11) Screening of other conditions, such as palladium precatalysts and the amount of Xantphos, was also conducted. See the Supporting Information for details.

(12) CCDC no. 1526561 for **3a**. See the Supporting Information for details.

(13) At this stage, the timing of decarboxylation is not clear. According to the literature (ref 3b), generation of anilide through decarboxylation prior to nucleophilic attack seems to be feasible. However, an alternative mechanism, in which the nucleophilic attack occurs prior to decarboxylation, cannot be ruled out. See ref 4.

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(17) A preliminary study was conducted with racemic **2a**. See the Supporting Information for details.

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