ChemPubSoc Europe

DOI: 10.1002/chem.201500397

CHEMISTRY
A European Journal
Communication

Asymmetric Synthesis

Intermolecular Asymmetric Carboesterification of Alkenes by Using Chiral Amine Auxiliaries under O_2: Synthesis of Enantioenriched α-Methylene-γ-Lactones through Chloropalladation of Alkynes

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Abstract: Herein, the first example of chloropalladation-initiated asymmetric intermolecular carboesterification of alkenes with alkynes by using chiral amine auxiliaries is reported. The use of (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine auxiliaries is essential for providing α-methylene-γ-lactones products in moderate to high yields and excellent enantioselectivities at room temperature. Moreover, the chiral amine auxiliaries can be readily removed by hydrolysis during the reaction process to keep the absolute configuration. This oxygen- and water-promoted asymmetric reaction opens a new window to study asymmetric processes in halopalladation reactions.

Over the past decade, nucleopalladation-initiated cross-coupling reactions of alkenes and alkynes have emerged as a powerful approach to construct C(sp^2)–C(sp^3) and carbon–heteroatom bonds in one step.[1,2] Since the initial studies in this area reported by Lu and co-workers,[3] different types of nucleopalladation-initiated cyclization reactions have been developed.[4,5] In particular, intermolecular and intramolecular carbocyclization of alkenes and alkynes have been explored and established as an effective method for constructing multimembered heterocyclic compounds.[6–8] Despite the numerous synthetic approaches for racemic products that have been developed, nucleopalladation-initiated asymmetric reactions remain highly desirable for the synthesis of optically active compounds. However, compared with the impressive development of oxypalladation-initiated asymmetric cyclization reactions,[9] halopalladation-initiated enantioselective transformations through chiral ligands and palladium complexes still remain a challenge, as the halide ions act as both a nucleophile and a ligand, which inhibits the coordination of the palladium species with other chiral ligands.[2d,9e]

To achieve an asymmetric version of the halopalladation-initiated reaction, a suitable strategy must be found. In our previous research, many different types of chiral ligands were tested in the palladium-catalyzed intermolecular asymmetric carboesterification of styrene with an alkylamide base;[10,11] however, no satisfactory results were obtained (see the Supporting Information for details). Using a chiral auxiliary in asymmetric synthesis is an effective tool for constructing optically active compounds in organic reactions,[12] such as in the Diels–Alder reaction,[13] in radical reactions,[14] and so on.[15] Thus, we reasoned that employment of a chiral auxiliary might prove suitable for halopalladation-initiated asymmetric reactions of alkenes with alkynes. Therefore, a palladium-catalyzed asymmetric intermolecular carboesterification of styrene with (*S*)-3-phenyl-*N*-(1-phenylethyl)propiolamide (**1a**, 97% *ee*) was designed, which used 5 mol% $PdCl_2$ and 2 equivalents of $CuCl_2{\cdot}2H_2O$ in MeCN at room temperature under an O_2 balloon (Scheme 1). To our delight, the cyclic product **3a** could be achieved in a good yield (81%) and moderate enantioselectivity (42% *ee*) with $Z/E > 98{:}2$ as determined by gas chromatography (GC). Moreover, the auxiliary (*R*)-1-phenylethanamine could be auto removed and kept the absolute configuration during the reaction process.

Inspired by these initial attempts, different chiral amine auxiliaries on the alkyne amide in the Pd-catalyzed intermolecular asymmetric carboesterification of styrene were investigated (Table 1). Intriguingly, the study demonstrated that the carboesterification occurred smoothly within a few hours. The desired cyclic product **3a** was obtained in good yields, but with moderate enantioselectivities when chiral α-arylamines (**1b** and **1c**) were used in the reactions (Table 1, entries 1 and 2). Examination of chiral amino-alcohols (**1d**–**1h**) gave lower yields of **3a**, but better enantioselectivity was obtained by increasing steric hindrance at the C3-position of the amino-alcohol (Table 1, entries 3–7). A good yield (77%) but poor enantioselectivity (12% *ee*) were achieved when (*S*)-methyl 2-amino-2-phenylacetate (**1i**) was employed in the reaction (Table 1, entry 8).

Next, various chiral cyclohexane amines were examined. Only moderate yield (45%) but high enantioselectivity (78% *ee*) was observed when (1*S*,2*S*)-cyclohexane-1,2-diamine (**1k**) was employed (Table 1, entry 10 in parentheses). To improve

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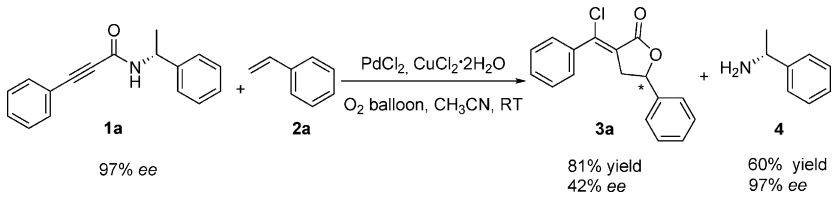
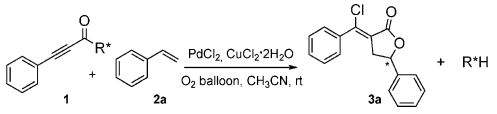
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500397.

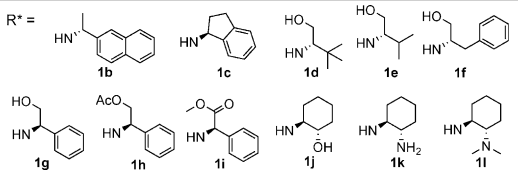


Scheme 1. Pd-catalyzed intermolecular asymmetric carboesterification of styrene with (*S*)-3-phenyl-*N*-(1-phenylethyl)propiolamide (**1a**).

thoxy groups on the styrene, were well-tolerated, and the reaction was also applicable to aryl moieties with different substitution patterns (Table 2, **3a**–**m**). Pleasingly, 99.2% *ee* was obtained after recrystallization of the product **3h** from isopropa-

Table 1. Pd-catalyzed intermolecular asymmetric carboesterification of styrene with a chiral alkyne amide.[a]

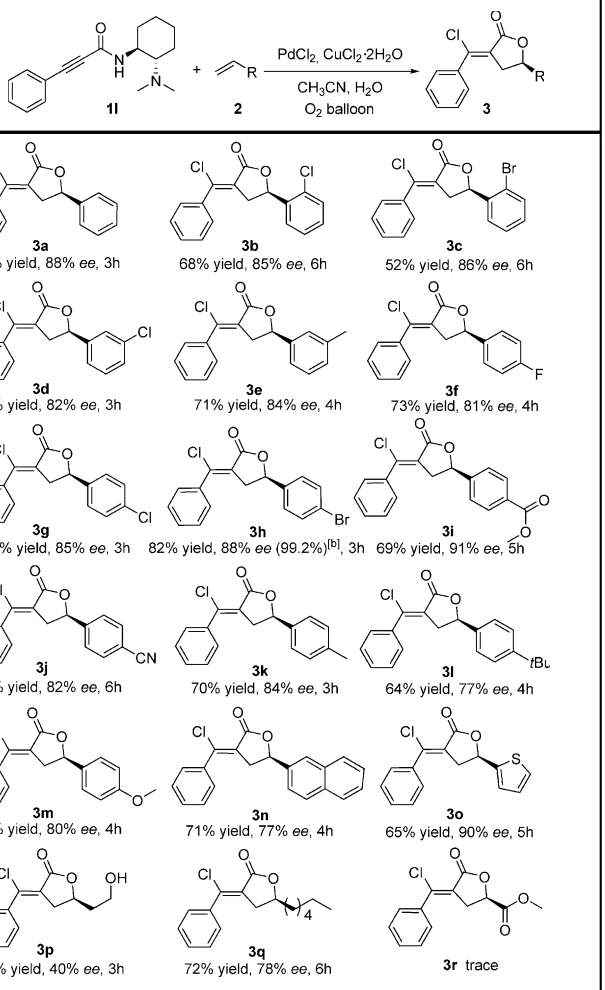




Entry	Substrates	Time	**3a** Yield [%][b]	**3a** *ee* [%][c]
1	**1b**	3 h	73	58
2	**1c**	3 h	74	24
3	**1d**	6 h	33	68
4	**1e**	6 h	46	40
5	**1f**	6 h	46	12
6	**1g**	6 h	39	66
7	**1h**	3 h	49	28
8	**1i**	3 h	77	12
9	**1j**	6 h	51	30
10[d]	**1k**	3 h	72 (45)	82 (78)
11[d]	**1l**	3 h	77	88

[a] Reactions were carried out at 20 °C under an O_2 balloon with **1** (0.20 mmol), **2a** (0.24 mmol), $PdCl_2$ (5 mol%), and $CuCl_2{\cdot}2H_2O$ (0.4 mmol) in acetonitrile (0.5 mL) for 3–6 h. [b] Isolated yield. [c] Determined by HPLC. [d] 5 equiv of water was used.

Table 2. Substrate scope of alkenes.[a]



[a] Reaction conditions: **1l** (0.20 mmol), alkenes (0.24 mmol), $PdCl_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (0.4 mmol), and H_2O (1 mmol) in acetonitrile (0.5 mL) for 3–6 h at20 °C under an O_2 balloon. The *ee* values were determined by HPLC. [b] The *ee* value determined after recrystallization is shown in parentheses, yield: 68%.

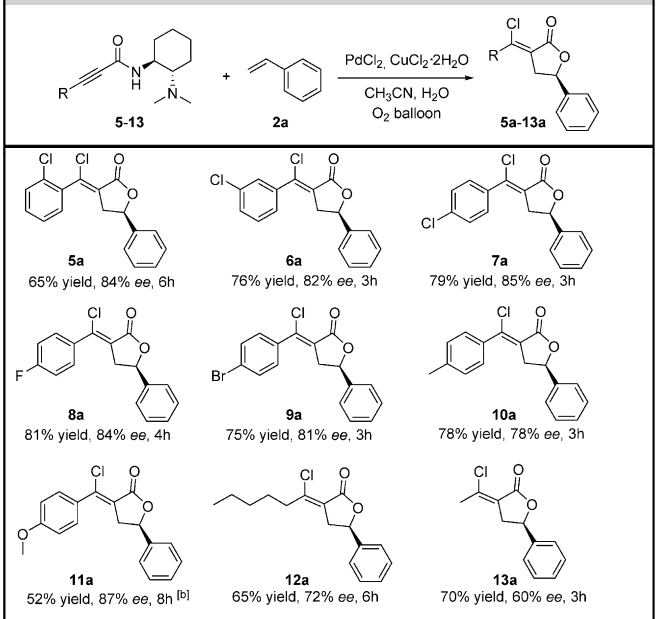
the reactivity, optimization of the reaction conditions was undertaken (see the Supporting Information for details). Fortunately, a good yield (72%) and high enantioselectivity (82% *ee*) was achieved when an additional 5 equivalents of H_2O were used (Table 1, entry 10), a result that might be due to the ability of water to promote the amide hydrolysis. Further exploration of auxiliary in the carboesterification reaction indicated that the (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine (**1l**) auxiliary gave the cyclic product in good yield (78%) with excellent enantioselectivity (88% *ee*; Table 1, entry 11).

With the optimized reaction conditions in hand, we next established the substrate scope of this intermolecular asymmetric carboesterification of alkenes with *N*-((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)-3-phenylpropiolamide (**1l**). It was found that moderate to good yields and high enantioselectivities were achieved with aryl alkenes and alkyl alkenes as the substrates (Table 2). Both electron-deficient substituents, such as fluoro and CN groups, and electron-rich substituents, such as methoxy groups on the styrene, were well-tolerated, and the reaction was also applicable to aryl moieties with different substitution patterns (Table 2, **3a**–**m**). Pleasingly, 99.2% *ee* was obtained after recrystallization of the product **3h** from isopropanol (IPA). The absolute configurations of the products were confirmed based on a single-crystal X-ray analysis of **3h** (see the Supporting Information for details). Slightly lower yield and enantioselectivity (71% yield, 77% *ee*) were observed when 2-vinylnaphthalene was employed in this reaction (Table 2, **3n**), but the thiophene heteroaryl substrate afforded the corresponding product **3o** with good results (65% yield, 90% *ee*). Linear olefins can be used in the reaction to give the

desired products, **3p** and **3q**, in high yields with good enantioselectivities (40% *ee* and 78% *ee*, respectively) (Table 2). Unfortunately, for activated alkenes, such as methyl acrylate, the asymmetric process did not occur (Table 2, **3r**).

Next, we screened a series of alkyne amides with (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine as the auxiliary and found that both electron-rich and electron-poor aryl groups were also well tolerated (Table 3, **5a**–**11a**). A wide range of

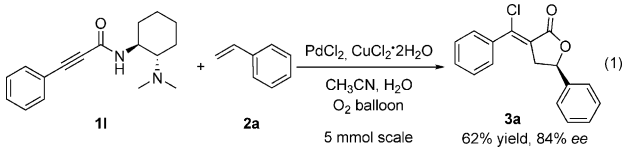
Table 3. Substrate scope of alkyne amide.[a]

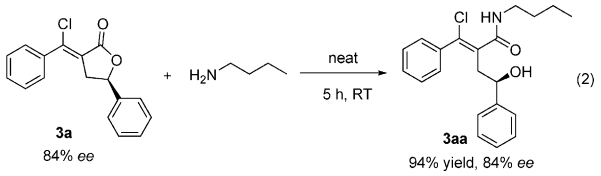


[a] Reaction conditions: alkyne amides (0.20 mmol), **2a** (0.24 mmol), $PdCl_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (0.4 mmol), and H_2O (1 mmol) in acetonitrile (0.5 mL) for 3–6 h at 20 °C under an O_2 balloon. The *ee* values were determined by HPLC. [b] With an ice-water bath.

substrates with different substituents on the aryl group provided the desired products with high enantioselectivities of 78–87% *ee* (Table 3, **5a**–**7a**). To our delight, this reaction was successfully applied to 3-alkyl substituted alkyne amides, and these substrates were smoothly converted to the asymmetric carboesterification products in good yields with good enantioselectivities (Table 3, **12a** and **13a**).

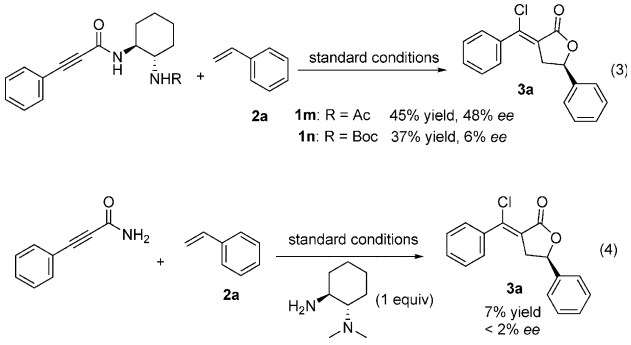
Under the standard conditions, a satisfactory result (62% yield, 84% *ee*) was obtained when the reaction was performed on a 5-mmol scale [Eq. (1)]. The newly formed γ-lactones were easily transformed to more useful frameworks of biologically active natural products. For example, a simple aminolysis of **3a** was achieved with *n*-butylamine to give chiral γ-hydroxy amide **3aa** in 94% yield and kept the absolute configurations under mild reaction conditions [Eq. (2)].



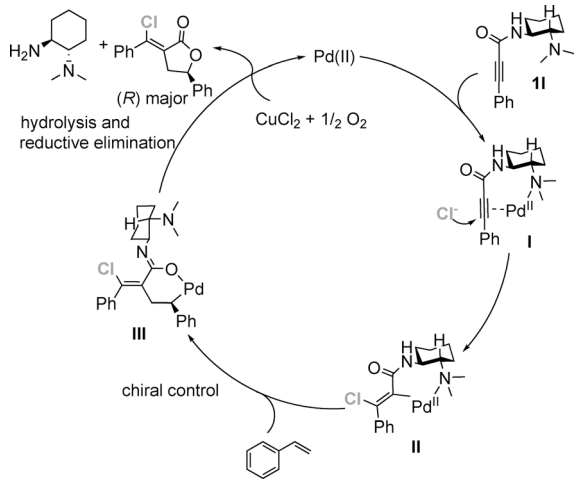


To gain insight into the mechanism of the asymmetric carboesterification process, several control experiments were conducted. Under the standard conditions, a clear decrease in yields and enantioselectivities was observed when substitutions such as acetyl (Ac) and *tert*-butyloxycarbonyl (Boc) groups were employed on the nitrogen atom of the substrates, an observation that indicated coordination between the palladium species and N atom of substrates occurred [Eq. (3)]. In addition, 3-phenylpropiolamide was transferred to the racemic product **3a** when 1 equivalent of (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine was used, suggesting that the enantioselectivity was determined by the chiral substrate, rather than the chiral amine removed from the substrate [Eq. (4)].

Base on the above observations and previous reports,[7,8,10]



a tentative mechanism for this intermolecular asymmetric alkene carboesterification is proposed (Scheme 2). Firstly, Pd^{II} coordinates with nitrogen and the carbon–carbon triple bond of the substrate to generate intermediate **I**. Subsequently, the



Scheme 2. Plausible reaction mechanism.

vinylpalladium species **II** is formed by *trans*-chloropalladation of alkyne amide. Then, a *syn*-insertion occurs via coordination of the alkene and the enantioselectivity is achieved by steric repulsion between the alkene substituent and the chiral auxiliary. Intermediate **III**, which is obtained by the isomerization of the chiral *syn*-insertion intermediate, then undergoes hydrolysis and reductive elimination to afford the target product and Pd^0. Simultaneously, the active Pd^{II} species is regenerated by oxidation with $CuCl_2$ and O_2, and the catalytic cycle is completed. This stereochemical model is also in accordance with the absolute configuration observed in the carboesterification product **3 h**.

In summary, we have developed a chloropalladation-initiated intermolecular asymmetric carboesterification of alkenes under O_2 for the first time with a chiral diamine auxiliary, providing optically enriched α-methylene-γ-lactones in good yields and enantioselectivities. The chiral diamine auxiliary not only gave the cyclization products in moderate to excellent enantioselectivities through chirality transfer, but also was readily removed through hydrolysis during the reaction process and could be recovered in good yield with the original enantioselectivity. This work could provide a guide for further asymmetric synthesis through halopalladation reactions. Continuing efforts to clarify the mechanism of this novel asymmetric reaction and develop applications for the enantioenriched products are currently underway in our laboratory.

Acknowledgements

We thank the National Natural Science Foundation of China (21202046 and 21472051), National Basic Research Program of China (973 Program) (2011CB808600), and the Fundamental Research Funds for the Central Universities (2014ZP0004 and 2014ZZ0046) for financial support.

Keywords: asymmetric synthesis · carboesterification · chiral auxiliary · chloropalladation · γ-lactones

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[16] CCDC-1009702 (**3 h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: January 30, 2015
Published online on ■■ ■■, 0000

COMMUNICATION

Asymmetric Synthesis

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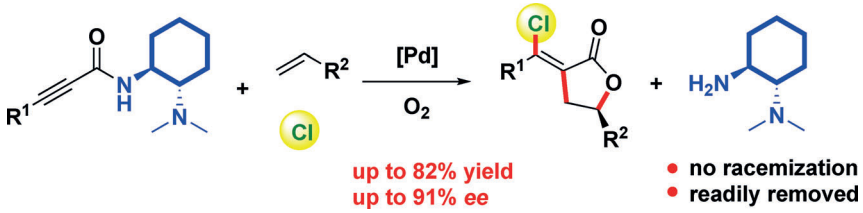
Intermolecular Asymmetric Carboesterification of Alkenes by Using Chiral Amine Auxiliaries under O_2: Synthesis of Enantioenriched α-Methylene-γ-Lactones through Chloropalladation of Alkynes



Chiral auxiliary: The first example of asymmetric intermolecular carboesterification of alkenes with alkyne amides initiated by chloropalladation is achieved. The use of (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine auxiliary is essential for providing the cyclization products in moderate to high yields with excellent enantioselectivities, and can be readily removed by hydrolysis to maintain the absolute configuration. This oxygen- and water-promoted reaction also gives a novel route to enantioenriched α-methylene-γ-lactones under mild conditions.