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Enantioselective Synthesis of Chiral Allenoates by Guanidine-Catalyzed Isomerization of 3-Alkynoates

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Isomerization is a chemical process in which an atom or group rearranges within a molecule, resulting in a structural reorganization without a change in the molecular formula. The Brønsted base catalyzed 1,3-proton shift reaction, proceeding through deprotonation and protonation sequences, allows allenes to be prepared directly from alkynes. While this is an often used and convenient preparation method for allenes,[1] only one previous attempt at catalytic asymmetric isomerization of alkynes was reported. It was carried out with a *Cinchona* alkaloid derivative under phase transfer conditions.[2] Propyne is ~2 kcal/mol more stable than propa-1,2-diene.[3] At equilibrium, the conversion for the isomerization reaction is dependent on the relative stabilities between the alkyne and allene.

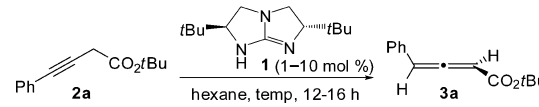
Allenes are present in many natural products and biologically active compounds;[4] they are also important intermediates in organic synthesis.[5] Due to the availability of enantiomerically pure propargyl alcohols, many chiral allenes are prepared through chirality transfer.[5a,6a] Relatively fewer examples are developed using enantioselective catalysts with pro-chiral starting materials.[5a,6a] Early examples include various palladium catalyzed reactions such as cross-coupling with allenyl-metal reagents,[6b] hydroboration,[6c] and substitution reactions.[6d] Breakthrough work was achieved by Hayashi and co-workers with hydrosilylation of 1-buten-3-ynes[6e,f] and rhodium-catalyzed 1,6-addition of aryltitanates to enynones.[6g] Recently, chiral allenic esters are prepared using iron porphyrin-catalyzed olefination of ketenes.[6h]

In previous studies, we established that guanidine **1** is an excellent catalyst in several highly enantioselective reactions.[7] In this communication, we demonstrate that chiral allenoates can be obtained *via* a Brønsted base catalyzed isomerization reaction of alkynes. We utilized a convenient preparation of functionalized 3-alkynoates reported by Fu.[8] In our optimization studies with allenoate **2a**, hexane was found to be the best solvent but only a moderate ee value was obtained (Table 1, entry 1). Both the conversion and ee value increased dramatically when the reaction temperature and concentration were lowered (entries 2−3). Interestingly, decreasing the catalyst loading led to even higher ee values (entries 4−5). The reaction conversion could not be raised substantially even after increasing the reaction time. The ee values were monitored over a time course (entry 4). At the start of the reaction, the ee value was 92%, and it rose briefly to 94% after 4 h. As the reaction progressed, it dropped and remained at 91%.

With the optimized conditions on hand, we examined the scope with different 4-aryl 3-alkynoates **2** (Table 2). Both electron-withdrawing and -donating substituents did not affect the reactivity and ee's (entries 2−4). Naphthyl and heteroaromatic groups also gave excellent ee's (entries 5−6). With the exceptions of allenoates **3g** and **3h**, the allenes were inseparable from the unreacted alkynes. The bulky ester group was a prerequisite for the reaction to proceed in high ee. The isomerization of alkyl alkynoates was too slow to be useful under current reaction conditions. The absolute configurations of the allenes were determined using the Lowe−Brewster rule.[9]

5-Hydroxyallenoates are versatile synthetic intermediates and particularly suitable for electrophilic cyclization.[10] Propargylic alcohol **4a** underwent isomerization smoothly to give allenic alcohol **5a** in good conversion and high ee values (Table 3, entry 1). When a tertiary propargylic alcohol **4b** or *O*-benzyl (Bn) protected propargylic alcohol **4c** was used, excellent ee's were also achieved (entries 2−3). *N*-Phthalimido (PhthN) protected propargylic amine **4e** was found to

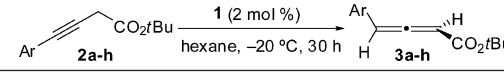
Table 1. Enantioselective Isomerization of 3-Alkynoates **2a** Catalyzed by Guanidine **1**



entry	**1** (mol %)	concn (M)	temp (°C)	yield (%)[a]	ee (%)[b]
1	10	0.20	rt	>99(65)	68
2	10	3.0×10^{-3}	rt	>99(56)	82
3	10	3.0×10^{-3}	−20	>99(75)	89
4	5	3.0×10^{-3}	−20	>99(75)	91
5	1	3.0×10^{-3}	−20	>99(59)	94

[a] Isolated combined yield of **2a** and **3a**; % of **3a** is in parentheses and was determined by ^{1}H NMR. [b] Chiral HPLC.

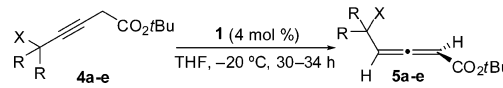
Table 2. Enantioselective Isomerization of 4-Aryl 3-Alkynoates **2**



entry	Ar (**2**)	**3**	yield (%)[a]	ee (%)[b]
1	Ph (**2a**)	**3a**	>99(70)	91
2[c]	4-*t*BuC$_6$H$_4$ (**2b**)	**3b**	>99(68)	94
3	3-MeC$_6$H$_4$ (**2c**)	**3c**	>99(62)	95
4	4-FC$_6$H$_4$ (**2d**)	**3d**	>99(70)	91
5[c,d]	6-MeO-naphth-2-yl (**2e**)	**3e**	>99(80)	93
6[c]	thiophen-2-yl (**2f**)	**3f**	>99(39)	89
7[d]	2-MeOC$_6$H$_4$ (**2g**)	**3g**	98(60)[e]	93
8	2-BrC$_6$H$_4$ (**2h**)	**3h**	99(76)[e]	79

[a] Isolated combined yield of **2** and **3**; % of **3** is in parentheses and was determined by ^{1}H NMR. [b] Chiral HPLC analysis. [c] 4 mol % of **1** was used. [d] THF was used as solvent. [e] Isolated yield of allenoate **3** in parentheses.

Table 3. Asymmetric Synthesis of 5-Functionalized Allenoates **5**



entry	**4** [X, R]	**5**	yield (%)[a]	ee (%)[b]
1[c]	**4a** [HO, H]	**5a**	98(57)	86
2	**4b** [HO, Me]	**5b**	94(59)	94
3[c]	**4c** [BnO, Me]	**5c**	98(79)	95
4	**4d** [CbzNH, H]	**5d**	99(65)	91
5	**4e** [PhthN, H] [d]	**5e**	99(94)	94

[a] Isolated combined yield of **4** and **5**; % of **5** as determined by ^{1}H NMR in parentheses. [b] Chiral HPLC analysis. [c] 2 mol % of catalyst **1** was used. [d] PhthN = phthalimido.

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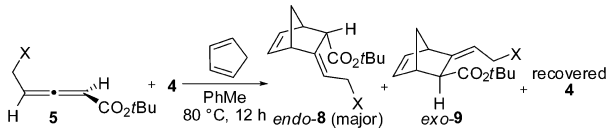
Table 4. Relative Stabilities of Alkyne/Allene Isomer Pairs at −20 °C

entry	alkyne	allene	ΔH (kcal/mol)	ΔS (eu)	ΔG (kcal/mol)	yield (%)
1	**2a**	**3a**	−5.1	−5.8	−3.7	70
2	**2e**	**3e**	−5.5	−5.0	−4.3	80
3	**2f**	**3f**	−4.6	−6.2	−3.0	39
4	**4e**	**5e**	−7.4	−3.4	−6.5	94

Table 5. Cycloadditions of Allenoates **5** with Cyclopentadiene



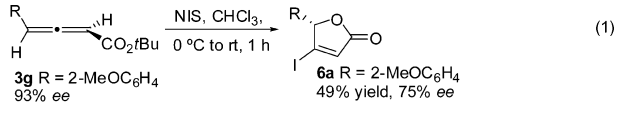
entry	X	**5** (**5**:**4**, ee of **5**)	yield (%)[a]	dr[b]	ee (%)[c]
1	OH	**5a** (57:43, 86)	85(70)	4:1	85(**8a**), 89(**9a**)
2	NHCbz	**5d** (65:35, 91)	98(60)	3:1	87(**8b**), 85(**9b**)
3	PhthN	**5e** (94:6, 94)	99(−)	2:1	93(**8c**), 93(**9c**)

[a] Isolated yield of *endo*-**8** + *exo*-**9** based on amount of allene used; % recovery of **4** in parentheses. [b] Determined by ^{1}H NMR. [c] Chiral HPLC.

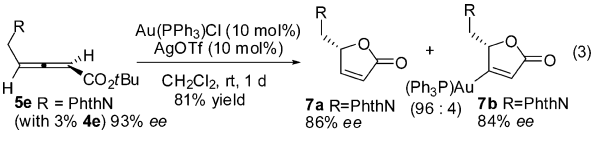
give a much better conversion than the *N*-Cbz protected amine **4d** (entries 4−5). When the allene *rac*-**5e** was subjected to the optimized reaction condition, no change in ee was observed.

The relative stabilities between selected alkyne/allene isomer pairs were evaluated using DFT calculations (B3LYP, Table 4). All allenes evaluated are found to be more stable than the corresponding alkynes. The calculated ΔG values correlate well with the observed yields. While the ΔG values suggest that all the isomerizations could go to high reaction conversion, prolonged reaction times may be required.

An important application of chiral allenes is the preparation of functionalized chiral lactones such as β-halobutenolides.[11] The iodolactonization of allenoate **3g** with *N*-iodosuccinimide (NIS) occurred with some loss of ee (eq 1). When a mixture of **2b** and **3b** was cyclized with pyridinium tribromide ($PyHBr_3$), good chirality transfer was observed and alkyne **2b** was recovered quantitatively (eq 2).



Cationic gold complexes are shown to be effective catalysts in alkyne-carbonyl cyclizations.[12] Using a stoichiometric amount of $Au(PPh_3)Cl$, **7b** was obtained in 97% yield and 85% ee with variable amounts of lactone **7a**, depending on the reaction time. Since cationic gold species were released during the reaction, the reaction can be conducted using 10 mol % of the Au(I) complex. Allenoate **5e** was converted to butenolide **7a** in 81% yield and 86% ee and with 4% of Au(I) complex **7b** (eq 3).



The cycloaddition of allenoates with dienes are of great interest to natural products chemists.[13] The Diels−Alder reaction of allenoates and cyclopentadiene gave the *endo* diastereomer **8** (olefin in *Z* configuration) as the major isomer (Table 5). The yields and chirality transfer were excellent. The relative stereochemistry was determined by NOE experiments. Absolute stereochemistry was proposed using a model in which the diene approached the allenoate from the less hindered side (see Supporting Information).

In summary, chiral bicyclic guanidine **1** is found to catalyze the isomerization of alkynes to chiral allenes with high ee's. The axial chirality is efficiently transferred to functionalized butenolides and cycloaddition products. We also successfully demonstrate the stereospecific synthesis of butenolide through allenoate cyclization with a catalytic cationic Au(I) complex.

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Supporting Information Available: Experimental procedures, computational and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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