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Organocatalytic Formation of Chiral Trisubstituted Allenes and Chiral Furan Derivatives

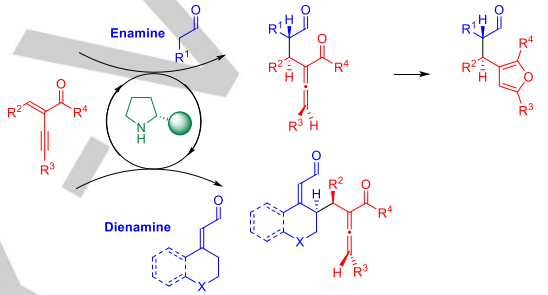
Pernille H. Poulsen, Yang Li, Vibeke H. Lauridsen, Danny K. B. Jørgensen, Teresa A. Palazzo, Marta Meazza, and Karl Anker Jørgensen*

Abstract: A novel reaction concept providing chiral allenes by amino catalytic activation of aldehydes or α,β-unsaturated aldehydes reacting with alkynyl-substituted enones is presented. The reaction forms a variety of trisubstituted allenes in high yields and excellent stereoselectivities. The utility of the reaction concept is demonstrated by the synthesis of chiral furan derivatives in high yields and stereoselectivities.

Allenes have attracted interest since their discovery by van't Hoff in 1875.[1] Their unique chemical structure is found in many bioactive natural products and pharmaceuticals,[2] and is of importance in organic synthesis and materials science as highly versatile intermediates.[3] A commonly highlighted characteristics is their potential to exhibit axial chirality, when appropriately substituted, as a result of the orthogonal relationship between the cumulated π-systems.

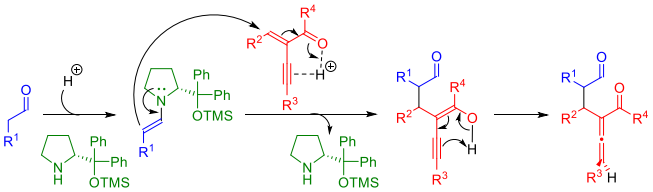
The development of asymmetric catalytic methods for the synthesis of chiral allenes has been an area of increased focus.[4] Traditional approaches rely on chirality transfer from enantioenriched propargylic alcohols or amines,[5] kinetic resolution of preformed racemic allenes[6] and the use of chiral ylide reagents in olefination of ketenes.[7] Contemporary endeavors have focused on the development of asymmetric catalytic strategies, particularly *via* metal-catalyzed reactions. Various metals, *e.g.* Pd, Cu, Rh, and Ni have been utilized in these asymmetric methodologies.[8] In comparison, organocatalytic approaches are underexplored, and a limited number of methodologies have been devised.[9] Marouka *et al*. presented a phase-transfer catalyzed alleno-Mannich reaction,[10] List *et al*. reported an enantioselective disulfonimide-catalyzed alkynylogous Mukaiyama aldol reaction,[11] and Sun *et al.* have disclosed an ion-pair catalyzed reaction of propargylic alcohols.[12] However, several of these methods are often limited to the formation of disubstituted allenes with higher substitution patterns largely being limited to allenoates.[13] Thus, the direct construction of chiral trisubstituted allenes from achiral or racemic starting materials *via* catalytic asymmetric strategies remains challenging. In the light of the limitations of the existing synthetic methodologies of chiral trisubstituted allenes and their attractive synthetic utility as intermediates in *e.g.* cycloisomerization reactions[3b,3f,14] in the construction of multi-substituted furans, we present a novel strategy for their synthesis. The synthetic utility of the chiral allenes is demonstrated by transforming them into chiral furan derivatives, which are important scaffolds in numerous natural products and pharmaceuticals.[15] Besides forming a challenging axially chiral trisubstituted allenic moiety, two additional point chiral centers are also formed.

The present strategy is based on the reaction of aldehydes or α,β-unsaturated aldehydes, *via* enamine and dienamine intermediates, respectively, with alkynyl-substituted enones (Scheme 1). Furthermore, the chiral allene products, obtained from the enamine-mediated reactions, are converted into functionalized, chiral furan derivatives.



Scheme 1. Reaction concept for the formation of chiral trisubstituted allenes by the organocatalytic reaction of aldehydes or α,β-unsaturated aldehydes with alkynyl-substituted enones.

We envisioned that it might be possible to generate chiral trisubstituted allenes by applying secondary amine organocatalysis. In Scheme 2, this strategy is based on the formation of an enamine intermediate, formed by reaction of an aldehyde with the diphenylprolinol trimethylsilyl ether catalyst.[16] The nucleophilic chiral enamine intermediate attacks the α-alkynyl-substituted enone, thereby generating an enol intermediate, leaving the alkyne moiety untouched. In this step, a Brønsted acid is envisioned to be important for (i) stabilizing the enol intermediate, and (ii) providing the proton to be delivered in a stereoselective manner from the enol to the alkynyl moiety forming the trisubstituted allene. The stereoselective formation of the allene might also be influenced by the two stereocenters generated in the first step of the reaction.



Scheme 2. Envisioned reaction design for the generation of chiral trisubstituted allenes by the application of an organocatalytic strategy.

Optimization studies of the organocatalytic formation of the chiral trisubstituted allenes were initiated by reacting hydrocinnamaldehyde **1a** with the α-alkynyl-α,β-enone **2a** applying 20 mol% of the diphenylprolinol trimethylsilyl ether catalyst **3a** in the presence 20 mol% of benzoic acid in toluene at room temperature (Table 1, entry 1). We were pleased to observe that 80% conversion to the allene product **4a** was achieved. Although **2a** remained

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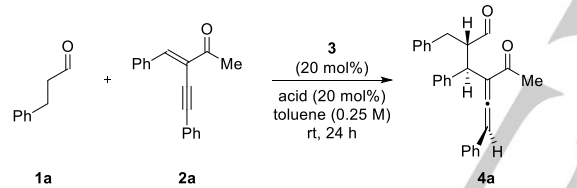
present in the reaction mixture, the two equivalents of **1a** were fully consumed. The unproductive consumption of **1a** was attributed to homo-aldol condensation of the aldehyde also catalyzed by **3a**. It is notable that <5% of allene **4a** was obtained in absence of benzoic acid. In order to improve conversion of **2a** to **4a** several reaction parameters were varied. Alternative Brønsted acid additives with varied pKa values were tested, unfortunately, without any improvement of the conversion of **2a** (Table 1, entries 2,3). Catalyst **3b** was unable to promote the reaction and no formation of product **4a** was observed (Table 1, entry 4). We also attempted to facilitate the conversion of **2a** by applying larger excess of **1a** and it was found that 3 equiv. of the aldehyde were optimal (Table 1, entries 5,6). In contrast, reversing the stoichiometry of **1a** and **2a** (1:2 or 1:3) did not improve the outcome of the reaction (Table 1, entries 7,8). By adding the aldehyde in two portions (2 equiv. from the beginning, followed by 1 equiv. 5 h later) the conversion was improved from 87% to 93% (Table 1, entry 5 *vs*. entry 9). A screening using hexanal as the aldehyde showed that the use of more polar solvents, such as $CHCl_3$ and CH_2Cl_2, resulted in lower diastereomeric ratios. Remarkably, no conversion was observed when performing the reaction in THF.[17] It was found in the screening that 3 equiv. of aromatic aldehyde **1a** was optimal, while for aliphatic aldehydes 2 equiv. was applied (*vide infra*).

Table 1. Asymmetric catalytic synthesis of chiral trisubstituted allenes. Screening results.[a]

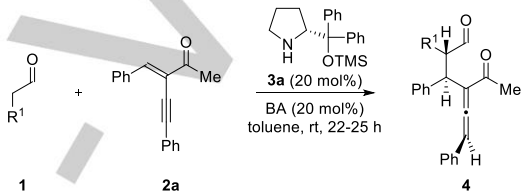


entry	**1a**:**2a**	**3**	acid	conv. (%)[b]
1	2:1	**3a**	BA	80
2	2:1	**3a**	CH_3CO_2H	78
3	2:1	**3a**	*o*-NBA	72
4	2:1	**3b**	BA	nr
5	3:1	**3a**	BA	87
6	4:1	**3a**	BA	88
7	1:2	**3a**	BA	83
8	1:3	**3a**	BA	83
9[c]	3:1	**3a**	BA	93

[a] Reactions performed on a 0.05 mmol scale. [b] Determined by ^{1}H NMR of the crude reaction mixture at full consumption of **1a**. [c] Aldehyde **1a** was added in two portions (2 equiv. from the beginning followed by 1 equiv. 5 h later). BA: Benzoic acid; *o*-NBA: *ortho*-Nitrobenzoic acid.

Aminocatalysis combined with Brønsted acid activation allowed us to develop a protocol for the direct synthesis of trisubstituted chiral allenes. The generality of the reaction was explored by reacting a series of aldehydes **1a**-**g** with α-alkynyl-α,β-enone **2a** and the results are outlined in Table 2. Performing the reaction with hydrocinnamaldehydes bearing electron-neutral, electron-donating, and electron-withdrawing groups on the aromatic ring afforded the allenes **4a**-**c** in high yields and excellent stereocontrol (Table 2, entries 1-3). Homologated aldehyde **1d** also reacted smoothly to provide allene **4d** in high yield and excellent enantiomeric excess, although a small amount of a second diastereoisomer was observed (Table 2, entry 4). Reactions of both linear and cyclic aliphatic aldehydes proceeded with the same excellent enantioselectivity (96-99% *ee*) and afforded the allene adducts **4e**-**g** in 87-95% yield (Table 2, entries 5-7).

Table 2. Asymmetric catalytic synthesis of chiral trisubstituted allenes from aldehydes. Scope of aldehydes **1**.[a]



entry	R^1	yield (%)	dr[b,c]	*ee* (%)[d]
1[e]	$PhCH_2$ (**1a**)	**4a**-95	>20:1 (>20:1)	>99
2[e]	*p*-MeO-C_6H_4-CH_2 (**1b**)	**4b**-83	>20:1 (>20:1)	>99
3[e]	*p*-MeO_2C-C_6H_4-CH_2 (**1c**)	**4c**-77	>20:1 (>20:1)	>99
4[e]	$PhCH_2CH_2$ (**1d**)	**4d**-82	14:1 (12:1)	99
5	Me (**1e**)	**4e**-87	15:1 (10:1)	96
6	*n*-Bu (**1f**)	**4f**-95	>20:1 (16:1)	99
7	cyclohexyl-CH_2 (**1g**)	**4g**-95	>20:1 (12:1)	98

[a] Reactions performed with **1** (0.2 mmol) and **2a** (0.1 mmol) in toluene (0.4 mL). [b] Diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture. [c] Ratio in parentheses refers to the diastereomeric ratio determined by ^{1}H NMR of the isolated product. [d] Enantiomeric excess determined by UPC^2 (see Supporting Information). [e] Reactions performed with 0.3 mmol of **1** added in two portions (0.2 mmol from the beginning followed by 0.1 mmol 5 h later). BA: Benzoic acid.

With the positive results obtained for the variation of aldehydes **1,** attention was turned to the reactivity of different α-alkynyl-α,β-enones **2**. We set out to vary all three substituents of the α-alkynyl-α,β-enone and commenced by reacting **2b**-**d** carrying aromatic and aliphatic groups, at the alkene moiety with hexanal **1f** (Table 3, entries 1-3). Satisfyingly, all three α-alkynyl-α,β-enones were tolerated under the optimized reaction conditions and the corresponding chiral allenes **4h-j** were obtained in high yields and excellent enantioselectivities. Excellent results were obtained with α-alkynyl-α,β-enones **2e**-**h** having electronically varied alkynyl aromatic rings providing allenes **4k**-**n** in 85-99% yield (Table 3, entries 4-7). In the case of strong electron-withdrawing substituents, such as trifluoromethyl and nitro groups, the reaction times were reduced to 4 and 2 h, respectively. When an

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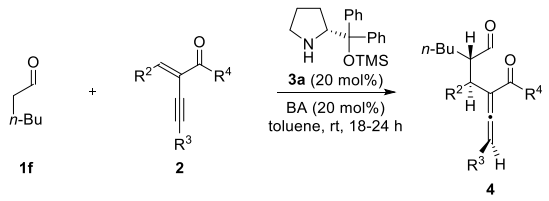
aliphatic substituent is introduced, the allene **4o** is formed as a single stereoisomer, however, with decreased yield (40%, Table 3, entry 8). Replacement of the methyl at the ketone with a phenyl substituent also afforded allene **4p** with similar results (entry 9).

Table 3. Asymmetric catalytic synthesis of chiral trisubstituted allenes from aldehydes. Scope of α-alkynyl-α,β-enones **2**.[a]



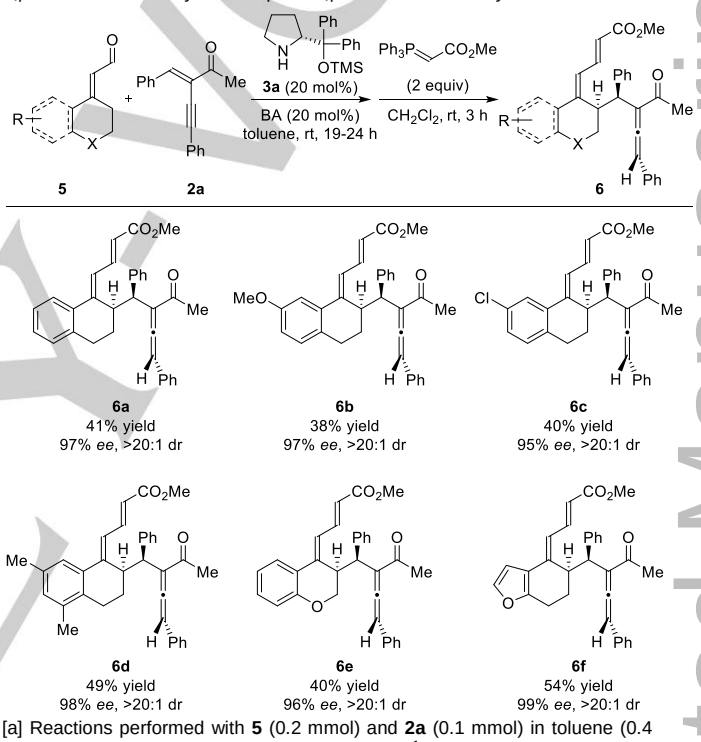
entry	R^2, R^3, R^4	yield (%)	dr[b,c]	*ee* (%)[d]
1	*p*-Me-C_6H_4, Ph, Me (**2b**)	**4h**-88	>20:1 (>20:1)	>99
2	*p*-Cl-C_6H_4, Ph, Me (**2c**)	**4i**-94	16:1 (11:1)	>99
3	Me, Ph, Me (**2d**)	**4j**-85	14:1 (7:1)	84
4[e]	Ph, *p*-Me-C_6H_4, Me (**2e**)	**4k**-99	>20:1 (16:1)	98
5	Ph, *p*-Br-C_6H_4, Me (**2f**)	**4l**-85	>20:1 (>20:1)	99
6[f]	Ph, *p*-CF_3-C_6H_4, Me (**2g**)	**4m**-92	>20:1 (8:1)	>99
7[g]	Ph, *p*-NO_2-C_6H_4, Me (**2h**)	**4n**-91	16:1 (4:1)	>99
8[e,h]	Ph, *n*-Bu, Me (**2i**)	**4o**-40	>20:1 (12:1)	>99
9[e,h]	Ph, Ph, Ph (**2j**)	**4p**-80	16:1 (12:1)	96

[a] Reactions performed with **1f** (0.2 mmol) and **2** (0.1 mmol) in toluene (0.4 mL). [b] Diastereomeric ratio was determined by ^{1}H NMR of the crude reaction mixture. [c] Ratio in parentheses refers to the diastereomeric ratio determined by ^{1}H NMR of the isolated product. [d] Enantiomeric excess determined by UPC^2 (see Supporting Information). [e] Reactions performed with 0.3 mmol of **1f** added in two portions (0.2 mmol from the beginning followed by 0.1 mmol 5 h later). [f] Reaction time 4 h. [g] Reaction time 2 h. [h] Reaction time 30 h. BA: Benzoic acid.

Encouraged by the successful synthesis of chiral trisubstituted allenes bearing a range of substituents in a highly stereoselective fashion, we decided to explore the possibility of applying the methodology to α,β-unsaturated aldehydes. α,β-Unsaturated aldehydes **5** can condense with organocatalyst **3a** and generate reactive dienamine intermediates[18] which react as nucleophiles with the α-alkynyl-α,β-enone **2a**. A challenge of applying dienamines is that they contain an additional nucleophilic center. Thus, the reaction could potentially take place at both the α- and γ-carbon atoms yielding two regioisomeric products.

We initiated our investigations by reacting the cyclic α,β-unsaturated aldehyde **5a** with α-alkynyl-α,β-enone **2a** (Scheme 3). We were pleased to find that only a single regioisomeric product **6a** was formed, which corresponds to nucleophilic attack of the γ-carbon of the α,β-unsaturated aldehyde at the alkene moiety of **2a**. The excellent stereocontrol found in the reactions of aldehydes was maintained for this class of α,β-unsaturated aldehydes, despite the increased distance between the catalyst and the reactive center of the dienamines. Allene **6a** was isolated as a single stereoisomer in 41% yield after *in-situ* Wittig reaction. Similar results were obtained for α,β-unsaturated aldehydes fused with both electron-rich, electron-poor, and multi-substituted aromatic systems providing allenes **6b**-**d** with excellent stereoselectivities and moderate yields. We were pleased to observe that a dihydrochromone derived α,β-unsaturated aldehyde and a fused heterocyclic furan reacted smoothly providing chiral allenes **6e**,**f**. The α,β-unsaturated aldehydes obtained by the organocatalytic reactions were difficult to purify, therefore a Wittig transformation was performed affording **6a**-**f** to ease purification.

Scheme 3. Asymmetric catalytic synthesis of chiral trisubstituted allenes from α,β-unsaturated aldehydes. Scope of α,β-unsaturated aldehydes **5**.[a]



[a] Reactions performed with **5** (0.2 mmol) and **2a** (0.1 mmol) in toluene (0.4 mL) at rt. The diastereomeric ratio determined by ^{1}H NMR of the isolated products. Enantiomeric excess determined by UPC^2 (see Supporting Information). BA: Benzoic acid.

Additionally, we have demonstrated that the chiral trisubstituted allenes, obtained *via* enamine intermediates, can be used for the synthesis of chiral furan derivatives. Scheme 4 shows the results for the one-pot transformation of the allenes **4** into chiral furan derivatives **7** catalyzed by a combination of AgOTf (10 mol%) and Ph_3PAuCl (10 mol%). The functionalized furans were obtained in high yields and excellent stereoselectivities.

The absolute configuration of allenes **4** obtained by the stereoselective reaction of the aldehydes **1** has been assigned by X-ray analysis of furan derivative **7b** combined with CD (both experimentally and computationally).[17] For proposed assignment of minor diastereoisomer (in select cases), see Supporting Information.

Scheme 4. Au/Ag-Catalyzed transformation of chiral trisubstituted allene intermediates into chiral furan derivatives **7**.[a]

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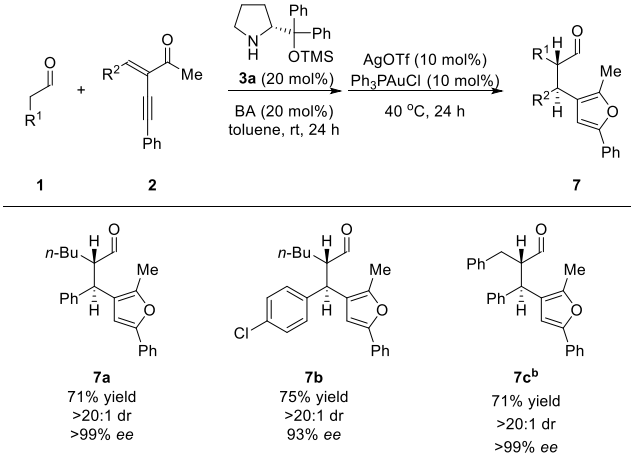
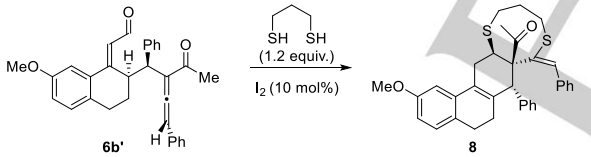


[a] Reactions performed with **1** (0.2 mmol) and **2** (0.1 mmol) in toluene (0.4 mL) at rt for 24 h. The crude reaction mixture was flushed with argon, and Ph_3PAuCl (10 mol%) and AgOTf (10 mol%) were sequentially added. The mixture was heated to 40 ^{0}C for 24 h. The diastereomeric ratio determined by ^{1}H NMR of the isolated products. Enantiomeric excess determined by UPC^2 (see Supporting Information). [b] The reaction performed with 0.3 mmol of **1** added in two portions (0.2 mmol from the beginning followed by 0.1 mmol 5 h later). BA: Benzoic acid

In an attempt to obtain crystals suitable for X-ray analysis of chiral allenes **6**, a transformation was performed as shown in Scheme 5. Allene **6b'** was isolated[19] and reacted with 1,3-propanedithiol in the presence of I_2 as catalyst, and product **8** was obtained in 30% yield over two steps in excellent stereoselectivity. Based on X-ray analysis of **8** combined with experimental/computational CD,[17] and comparison with previous publications[18] the absolute configuration of the allenes **6** in Scheme 3 have been assigned.

Scheme 5. Formation of a complex tetracyclic compound.



In conclusion, a novel reaction concept affording chiral trisubstituted allenes *via* aminocatalytic activation of aldehydes or α,β-unsaturated aldehydes has been demonstrated. The methodology allows for formation of axially chiral trisubstituted allenes in high yields and excellent stereoselectivities. The utility of this procedure has been demonstrated *via* one-pot synthesis of densely functionalized chiral furan derivatives maintaining the high stereoselectivities. In addition, the formation of a complex tetracyclic compound has been demonstrated.

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Keywords: asymmetric catalysis • chiral allenes • chiral furans • organocatalysis

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[19] Aldehyde **6'** was difficult to purify *via* FC and was isolated with other side products. This mixture was used directly in the transformation. The reported yield is the overall yield for two steps.

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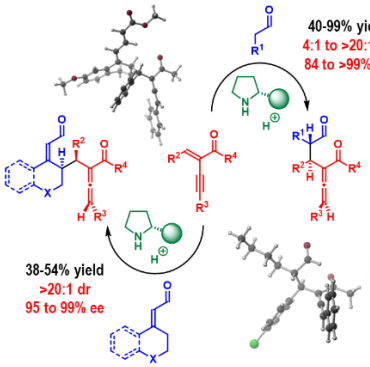

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Organocatalytic formation of chiral trisubstituted allenes and chiral furan derivatives