γ-Substituted Allenic Amides in the Phosphine-Catalyzed Enantioselective Higher Order Cycloaddition with Azaheptafulvenes

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γ-Substituted allenic amides in the phosphine-catalyzed enantioselective higher order cycloaddition with azaheptafulvenes

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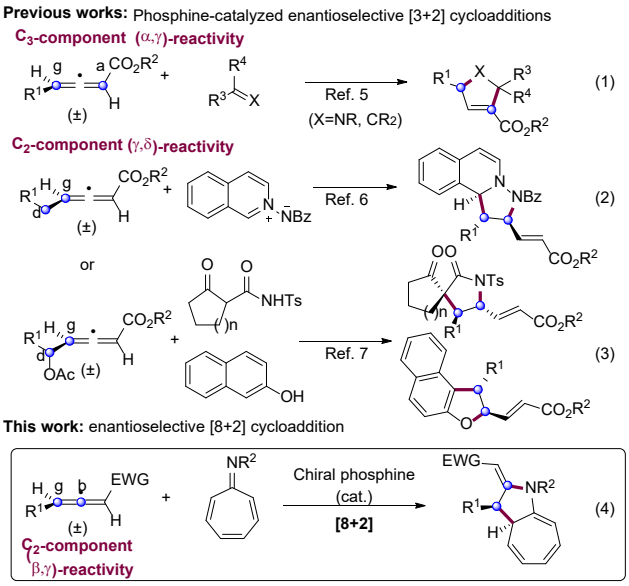
ABSTRACT: Racemic γ-substituted allenes undergo enantioselective higher order [8+2]-cycloaddition with azaheptafulvenes using a chiral amino acid-derived amidophosphine as catalyst, providing the corresponding azaazulenoid cycloadducts with excellent levels of regio-, diastereo- and enantioselectivities. In this reaction, the activated allylic phosphonium ylide intermediate participates as the C_2-component of the reaction, in contrast to the conventional reactivity of this type of zwitterionic intermediates as C_3-components in cycloaddition reactions.

The ability of electrophilic allenes to form 1,3-dipoles upon activation with a Lewis base catalyst has become a landmark for the development of a wide variety of annulation reactions. Since the pioneering reports by the groups of Lu and Kwon,[1] many examples of enantioselective cycloaddition reactions involving electron-deficient allenes have been disclosed,[2] in parallel with the development of chiral tertiary phosphines as nucleophilic organocatalysts.[3] However, most of the examples reported in the literature are typically limited to the use of (achiral) allenes that do not contain any substituent at the γ-position.[4] There are some particular examples in which racemic γ-substituted allenes have been employed as C_3-scaffolds in asymmetric (3+2) cycloadditions (Scheme 1, Eq. 1).[5] However, their use as C_2-components has been scarce and it is restricted to their reactivity at the γ,δ-positions, which requires either an enolizable γ-substituted allenoate[6] or a particularly functionalized substrate that incorporates a leaving group at the δ-position (Scheme 1, Eqs. 2 and 3 respectively).[7]

In view of the state of the art, and in connection with our research program devoted to the development of enantioselective transformations catalyzed by chiral tertiary phosphines,[8] we envisaged the potential use of racemic γ-substituted allenes as 2π-components in catalytic and enantioselective higher order [8+2]-cycloaddition with azaheptafulvenes under phosphine catalysis (see Scheme 1, Eq. 4). This type of cycloadditions, that involve more than 6π-electrons, are currently experiencing a renaissance.[9] In particular, and despite pioneering non-asymmetric precedents on [8+2]-cycloadditions by Doering and Houk,[10] that were followed by several reports afterwards,[11] enantioselective variants of higher order cycloadditions have only been successfully accomplished in the last few years.[12] On the other hand, there are two precedents on enantioselective [4+3][12i,n] and [4+4][12l] higher-order cycloadditions using allenes as the 1,3-dipole source, but both cases involve the participation of the allene reagent as a C_4-component and therefore as the source of the 4π-partner of the reaction.

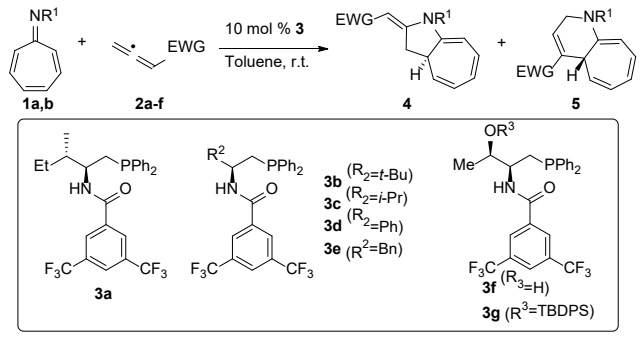
Scheme 1. γ-Substituted allenes in phosphine-catalyzed enantioselective cycloadditions.



As a proof of concept (see Table 1, entry 1), we reacted *N*-sulfonyl derivative **1a** with commercially available ethyl 2,3-butadienoate (**2a**) in the presence of a catalytic amount of isoleucine-derived amidophosphine **3a**, which has demonstrated its proficiency for the activation of allenoates in other examples of enantioselective reactions.[3e] Two cycloadducts (**4a** and **5a**) derived from the 2π- and 4π-reactivity of the allenoate were isolated from this initial experiment, but the target cyclohepta[*b*]pyrrole product **4a** was the minor one and the enan-

tioselectivity was poor. When *tert*-butyl allenoate (**2b**) was employed, the enantiocontrol was improved, but the [8+2]-cycloadduct was still the minor product (entry 2). This tendency was reversed when phenyl ester **2c** was used, isolating cycloadduct **4c** as the major product, but with very poor enantiocontrol (entry 3). Interestingly, phenyl thioester **2d** and phenyl ketone **2e** behaved exclusively as 2π components (entries 4 and 5), and the corresponding cycloadducts **4d** and **4e** were obtained as single isomers, still with poor enantiocontrol, but in a good yield in the latter case. Strikingly, allenic amide **2f** turned out to be an excellent 2π component in this reaction, since the corresponding [8+2]-cycloadduct **4f** was formed as a single regioisomer, with high yield and with excellent enantiocontrol (entry 6).

Table 1. Preliminary results and catalyst screening[a]



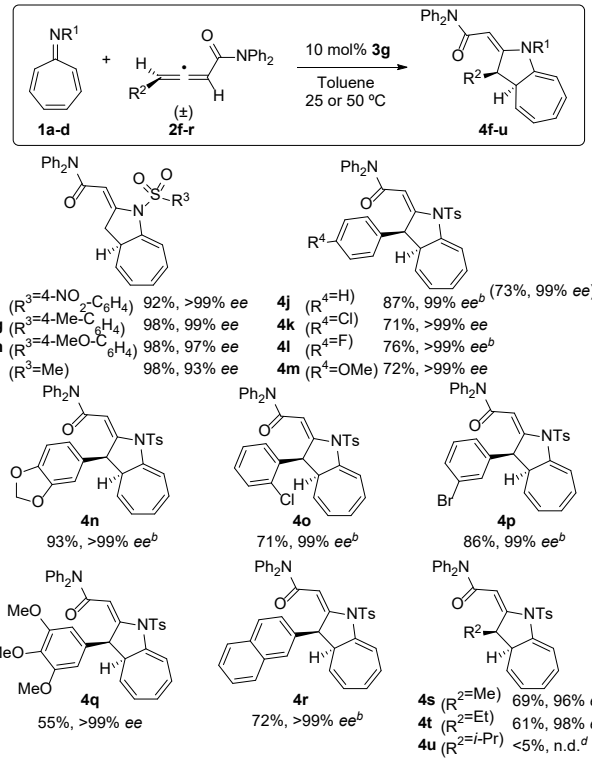
Entry	R[1]	EWG	Cat.	**4**/**5**[b]	Yield (%)[c]	ee (%)[d]
1	Ns (**1a**)	CO_2Et (**2a**)	**3a**	0.3:1	29[e]	28[f]
2	Ns (**1a**)	CO_2t-Bu (**2b**)	**3a**	0.2:1	47[e]	53[g]
3	Ns (**1a**)	CO_2Ph (**2c**)	**3a**	2.4:1	37[e]	20[h]
4	Ns (**1a**)	C(O)SPh (**2d**)	**3a**	>20:1	22 (**4d**)	17
5	Ns (**1a**)	C(O)Ph (**2e**)	**3a**	>20:1	72 (**4e**)	22
6	Ns (**1a**)	$C(O)NPh_2$ (**2f**)	**3a**	>20:1	88 (**4f**)	96
7	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3a**	>20:1	96 (**4g**)	95
8	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3b**	>20:1	98 (**4g**)	87
9	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3c**	>20:1	99 (**4g**)	92
10	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3d**	>20:1	70 (**4g**)	74
11	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3e**	>20:1	92 (**4g**)	80
12	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3f**	>20:1	99 (**4g**)	96
13	Ts (**1b**)	$C(O)NPh_2$ (**2f**)	**3g**	>20:1	98 (**4g**)	99

[a]Reactions carried out on 0.05 mmol scale of **1** and **2** with 10 mol% of **3** in toluene (0.05 M) at 25 °C. [b]Determined by ^{1}H-NMR analysis of crude reaction mixture. [c]Yields refer to isolated pure products **4**. [d]Enantiomeric excess of **4** determined by HPLC on a chiral stationary phase. [e]Combined yield for both isomers **4** and **5**. [f]The structure and the absolute configuration of **5a** (89% e.e.) was determined by X-ray diffraction analysis. [g]**5b**: 87% ee. [h]**5c**: 10% ee.

In order to further improve the reaction, azaheptafulvene **1b** was evaluated, providing similar levels of selectivity, although we could observe that this substrate was significantly more reactive than **1a**, leading to the formation of cycloadduct **4g** in 96% yield and with 95% ee, in a significantly shorter time (entry 7). The structure of cycloadducts **4** and **5** were confirmed by X-ray diffraction analysis of **4g** and **5a** being its absolute configuration unambiguously determined. A series of experiments were then carried out in order to fine-tune the chiral scaffold of the catalyst (entries 7-13). Slightly inferior results were produced by *tert*-leucine and valine analogues (**3b-c**), and a significant drop of performance and enantiocontrol was observed with phenylglycine derivative **3d** (entry 10), while phenylalanine-derived catalyst **3e** showed to provide good yield and a moderate enantiocontrol (entry 11). Interestingly, optimal results were achieved with threonine-based catalysts (entries 12 and 13), and in particular, using the silyl-protected analogue **3g**, which afforded cycloadduct **4g** almost quantitatively with 98% ee (entry 13).

With optimal reaction conditions in hand, we decided to study the scope of the reaction with respect to structural modifications on both components, azaheptafulvenes **1** and allenic amides **2** (Table 2). In a first analysis, we could observe that the performance of the reaction was not affected at all by the nature of the sulfonamide group attached to the azaheptafulvene, isolating the corresponding cycloadducts in all cases in excellent yields and with very high enantioselectivity after 2-5 h (compounds **4f-i**).

Table 2. Scope of the reaction[a]



[a]Reactions carried out on 0.1 mmol scale of **1** and **2** with 10 mol% of **3g** in toluene (0.05 M) at 25 °C. Yields refer to pure isolated products **4f-u**, and ee was determined by HPLC on a chiral stationary phase. [b]Reaction carried out at 50 °C. [c]Reaction carried out on 1.0 mmol scale of **1b** and **2f**. [d]n.d.: not determined.

We next focused on the performance of substituted racemic allenic amides incorporating aryl groups of different electronic nature at the γ-position (Substrates **2g-o**). A slight increase of the reaction temperature was required

to overcome the reduced reactivity observed with this type of allenic amides, and reaction times could be shortened from 72-96 h at 25 °C to 18-36 h at 50 °C, while maintaining the excellent levels of enantiocontrol. In all cases, the corresponding [8+2]-cycloadducts **4j-r** were isolated as a single regio- and diastereoisomer with an exquisite enantiocontrol (99% ee or superior). The electronic nature of the aromatic ring did not affect the reaction performance significantly. Thus, the presence of one electron-withdrawing substituent on the different positions of the aryl group of the allenic amide was virtually irrelevant and the corresponding cycloadducts **4k-l** and **4o-p** were isolated essentially as a single enantiomer in high yields (71-86%). Alkoxy substituents were also well tolerated and the enantioselectivity was excellent in all cases (adducts **4m**, **4n** and **4q**). Similarly, the naphthyl derivative **4r** was isolated in good yield and with excellent enantiocontrol. The robustness of the reaction was evaluated with cycloadduct **4j** at a higher 1.0 mmol scale with satisfactory results (See example in Table 2). Additionally, several racemic γ-alkyl substituted allenic amides **2p-r** were evaluated using the optimal reaction conditions, observing that both γ-methyl and γ-ethyl-susbtituted substrates **2p** and **2q** reacted efficiently, providing adducts **4s** and **4t**. Remarkably, no side-product involving reactivity through the enolizable position of the γ-alkyl substituent was observed. An exception to the generally good reaction performance arose from the use of the bulkier γ-isopropyl substituted allenic amide (**2r**), which did not afford the corresponding cycloadduct after 96 h at 50 °C or 80 °C. The absolute and relative configurations of disubstituted azaazulenes **4k** and **4s** were also unambiguously determined by X-ray diffraction analysis and the absolute stereostructure of all other cycloadducts **4** obtained was assigned assuming an identical stereochemical outcome for all reactions.

The selectivity of the reaction can be rationalized on the basis of the following stereochemical model. Based on previous calculations carried out for amino acid-derived phosphines and benzyl allenoate,[13] a similar nucleophilic attack is assumed to occur between catalyst **3g** and allenic amides **2**. In these reported computational studies, the allenic component serves as a three-carbon component in (3+2)-cycloaddition reactions with imines[13a] and enones,[13b] in contrast to our allenic amides, which behave as two-carbon synthons (2π components). Despite these differences, our reaction must involve the same type of allyl phosphonium ylide intermediate that suggests a very plausible similar three-dimensional arrangement during the cycloaddition process. Taking into account this difference and in analogy with these reports we propose a tentative stereochemical model for the reaction in which an H-bond is established between the amide group of the catalyst and the sulfonyl group of the azaheptafulvene (Figure 1).

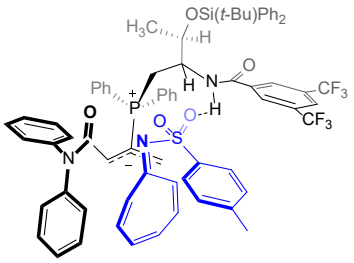


Figure 1. Stereochemical model.

In conclusion, we have demonstrated that racemic γ-substituted allenic amides are excellent 2π components for the enantioselective [8+2]-cycloaddition with azaheptafulvenes catalyzed by amino acid-derived amidophosphines. This reaction represents a direct strategy for the easy preparation of azaazulenoids scaffolds which have demonstrated to present important pharmacological and physical properties. Under optimal conditions a variety of mono- and disubstituted cycloadducts have been obtained in high yields with exquisite levels of peri-, regio-, diastereo- and enantioselectivity.

ASSOCIATED CONTENT

Complete experimental procedures, characterization data for the prepared compounds and crystallographic characterization data for compounds **4g**, **4k**, **4s** and **5a**. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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SYNOPSIS TOC.

The higher order cycloaddition between racemic γ-substituted allenic amides and azaheptafulvenes proceeds efficiently under chiral phosphine catalysis with complete periselectivity, leading to the exclusive formation of the [8+2] cycloaddition product. The reaction provides a direct access to aza-azulenoid adducts with a variety of substituents and with perfect levels of regio- and diastereoselectivity and with very high enantioselectivities