Enantioselective Oxidative (4+3) Cycloadditions between Allenamides and Furans through Bifunctional Hydrogen-Bonding/Ion-Pairing Interactions

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Enantioselective Oxidative (4+3) Cycloaddition between Allenamides and Furans through Bifunctional Hydrogen-Bonding/Ion Pairing Interactions

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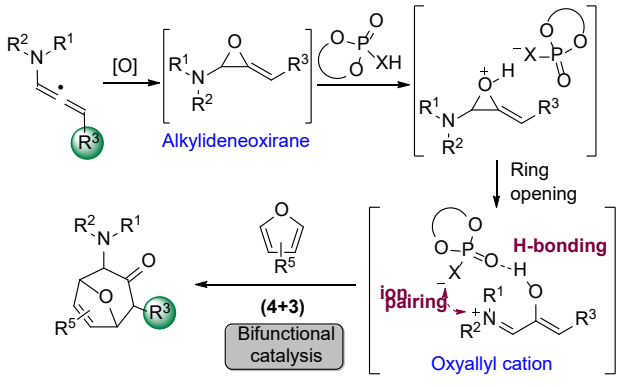
Abstract: BINOL-based *N*-trifluoromethanesulfonyl phosphoramides have been used to catalyze the enantioselective (4+3) cycloaddition between furans and oxyallyl cations, the latter being generated *in situ* by oxidation of allenamides. In this methodology, the chiral organic phosphoramide counteranion is proposed to engage in the activation of the oxyallyl cation intermediate through cooperative H-bonding and ion pairing interactions enabling an efficient chirality transfer that provide the final adducts with high diastereo- and enantioselectivities. Remarkably, the reaction shows a wide substrate scope, performing well with a variety of substituted allenamides and furans.

The construction of seven-membered rings[1] represents a more challenging task than the preparation of the smaller five- or six-membered analogues due to their higher ring strain and to entropy issues. In this sense, and in view of the widespread occurrence of this motif as key structural feature of many natural products and bioactive synthetic compounds, the development of efficient procedures for the synthesis of polysubstituted seven-membered carbocyclic scaffolds in a stereodefined way remains as a topic of interest. Among the different possibilities, (4+3) cycloadditions show up as key synthetic methodology for the stereoselective construction of the cycloheptane core,[2] in which the inherent stereochemical constrains associated to cycloaddition processes make this approach very convenient when developing a stereoselective variant. In particular, it is well known that allyl cations undergo smooth (4+3) cycloaddition with electron-rich dienes[3] and several successful examples have been developed in which this transformation has been rendered enantioselective by the incorporation of a chiral catalyst, although progress in this area dates from the last few years.[4] A particular case of this type of reactivity is the one that makes use of heteroatom-stabilized oxyallyl cations[5] and, in particular, a variety of examples have been reported, almost all focused on diastereoselective approaches that rely on the use of inherently chiral substrates[6] or on the chiral auxiliary methodology.[7] In fact, only two examples of catalytic and enantioselective (4+3) cycloadditions have been reported up to date. One of these reports made use of the iminium activation approach to activate the oxyallyl cation reagent[8] and the other relied on a Cu(II)/bis-oxazoline chiral Lewis acid as catalyst.[9] In addition, both methodologies require for a large excess (5-13-fold) of diene to provide synthetically useful yields and can only be employed with oxyallyl cations without any substituent at the terminal position. As a result, these remarkable pioneering efforts suffered from important limitations in terms of substrate scope, conditioning the range of architectures amenable to be reached and therefore existing a lack of alternative versions of this reaction that expand the potential of this approach to the enantioselective synthesis of more elaborated seven-membered ring systems. In particular, as mentioned, there is no precedent in which β-substituted oxyallyl cations are used as dipoles in this transformation, which therefore limits this methodology to cycloheptanone adducts without any substituent at the α'-position with respect to the ketone moiety.

In this sense, we wish to report herein that chiral BINOL-based Brønsted acids[10] can be used to catalyze the (4+3) cycloaddition[11] between differently substituted furans and oxyallyl cations generated *in situ* by oxidation of allenamides (Scheme 1). We relied on the hypothesis that such chiral Brønsted acids would favor the formation of the oxyallyl cation intermediate through ring-opening of the alkylideneoxirane intermediate that is generated upon regioselective epoxidation of the allenamide and would also remain attached to this oxyallyl cation through an unconventional bifunctional mode of activation that combines H-bonding and ion-pairing interactions,[12] therefore opening the way to transmit its stereochemical influence during the (4+3) cycloaddition process.



Scheme 1. Chiral Brønsted acid-catalyzed formation of oxyallyl cations and subsequent (4+3) cycloaddition.

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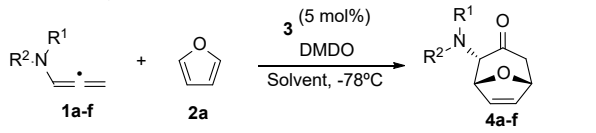
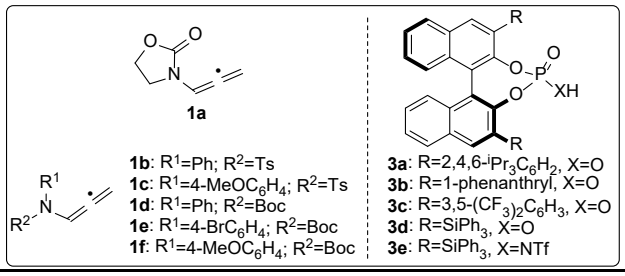
We started our work by surveying the ability of a variety of chiral phosphoric acids as potential catalysts for the transformation using the reaction between allenamide **1a** and furan **2a** as model system and using dimethyldioxirane (DMDO) as oxidant to generate the alkylideneoxirane (Table 1).[13] We initially realized that an important background reaction was going to compete with our reaction design when we performed it without any catalyst at -78ºC (entry 1).[14] Next, several BINOL-based phosphoric acids with a variety of substituents at the 3,3-position (**3a**-**3d**) were tested but in all cases the reaction proceeded with moderate yield and providing almost racemic material (entries 2-5). Only a slight improvement in enantioselection was observed when changing to the more acidic *N*-trifluoromethanesulfonyl phosphoramide catalyst **3e** (entry 6).[15]

Table 1. Screening for the best experimental conditions.[a]





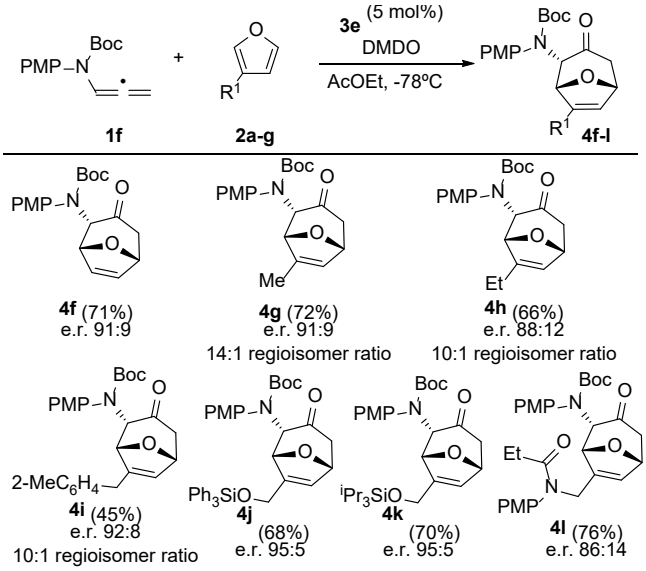
Entry	Substrate	Catalyst	Solvent	Yield [%][b]	e.r. [c]
1	**1a**	none	Toluene	27	-
2	**1a**	**3a**	Toluene	69	54:46
3	**1a**	**3b**	Toluene	45	50:50
4	**1a**	**3c**	Toluene	65	58:42
5	**1a**	**3d**	Toluene	53	54:46
6	**1a**	**3e**	Toluene	44	62:38
7	**1b**	**3e**	Toluene	17	80:20
8	**1c**	**3e**	Toluene	13	85:15
9	**1d**	**3e**	Toluene	37	82:18
10	**1e**	**3e**	Toluene	29	78:22
11	**1f**	**3e**	Toluene	63	85:15
12	**1f**	**3e**	CH_2Cl_2	60	82:18
13	**1f**	**3e**	THF	39	80:20
14	**1f**	**3e**	EtCN	68	81:19
15	**1f**	**3e**	AcOEt	78	91:9
16[d]	**1f**	**3e**	AcOEt	71	91:9

[a] Reaction carried out in a 0.1 mmol scale of **1a-f**, using 13.0 eq. of **2a**, 2.0 eq. of DMDO (as solution in the corresponding solvent) and 5 mol% of catalyst in the indicated solvent at -78ºC. [b] Yield of pure product after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out using 1.0 eq. of **2a**, 3.0 eq. of **1f**, 6.3 eq. of DMDO and 5 mol% of **3e**.

In view of these results, we proceeded to work on the substitution pattern of the allenamide reagent, by modifying the nature of the two substituents at the nitrogen atom (entries 7-10). These experiments indicated that a donor/acceptor pattern was highly beneficial for the yield and stereocontrol of the reaction, obtaining a very promising 63% of cycloadduct **4f** in a 85:15 e.r. when the *N* atom of the allenamide was simultaneously substituted with *tert*-butoxycarbonyl and *para*-methoxyphenyl groups (entry 11).[16] Remarkably, yield and enantiocontrol could be further improved by changing the solvent to EtOAc (entry 15), not observing better results with other different solvents (entries 12-15). Moreover, the reaction could be carried out using furan as the limiting reagent (entry 16), which represents a remarkable improvement compared with the 13 eq. of diene previously required, that are also used in the other two examples of catalytic and enantioselective (4+3) cycloadditions reported.[8,9] With these optimized conditions in hand, we also surveyed a wide family of other different chiral *N*-trifluoromethanesulfonyl phosphoramide catalysts but without observing any improvement on the performance of the test reaction (see supporting information for details). In all these experiments cycloadducts **4a-f** were isolated as single diastereoisomers.

Once a robust experimental protocol for the reaction had been optimized, we next proceeded to explore the ability of unsubstituted allenamide **1f** to react with other different furans in order to check the synthetic potential of this transformation (Table 2). As it can be seen in this table, furans with a variety of different substituents at the 3-position proceeded to react efficiently with allenamide **1f** leading to the formation of the corresponding (4+3) cycloadducts in high yield and enantiocontrol. Moreover, the reaction was highly regioselective, furnishing in all cases either one single regioisomer out of the two possible ones or with higher than 10:1 regioisomeric ratio.

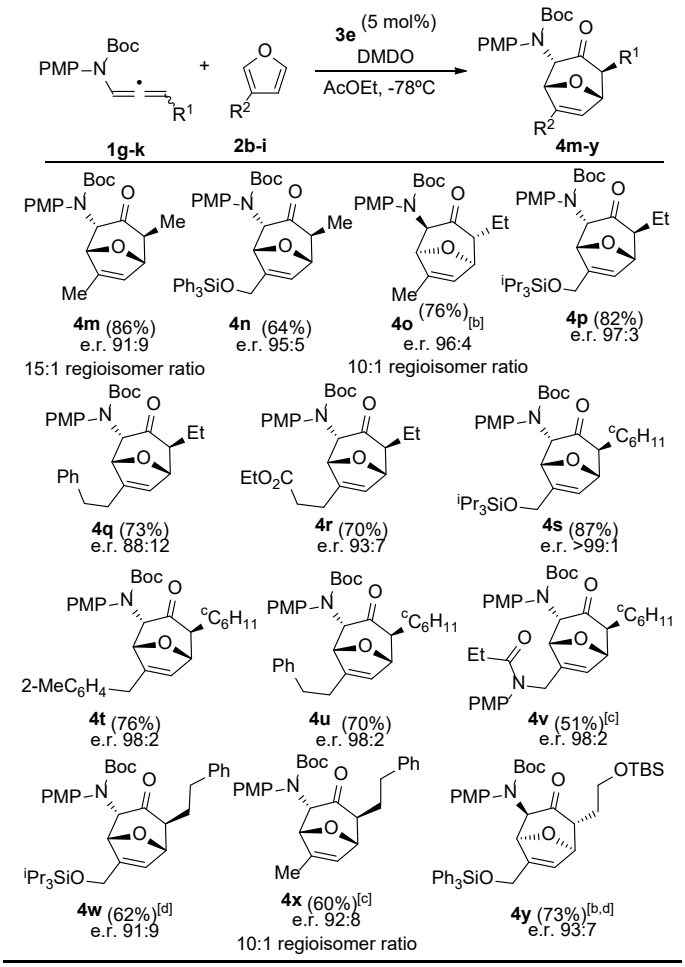
Table 2. Scope of the reaction using unsubstituted allenamide **1f**.[a]



[a] Reaction carried out in a 0.05 mmol scale of **2a-g**, using **3e** (5 mol%), **1f** (3.0 eq) and 6.3 eq. of DMDO (as solution in toluene) in AcOEt at -78ºC.

Importantly, one of the most remarkable features associated to this reaction is the high tolerance towards substitution at the terminal carbon atom of the allenamide substrate (Table 3), in deep contrast to the other existing two catalytic and enantioselective versions of (4+3) cycloaddictions using oxyallyl cations, in which only terminal allenamides were found to be reactive. In our case, a variety of racemic chiral allenamides containing simple linear alkyl chains (allenamides **1g** (R^1=Me) and **1h** (R^1=Et)) proceeded to react efficiently with a set of different 3-substituted furans (compounds **4m-r**) with good yields and enantioselection, also showing the possibility of performing the reaction in the presence of functionalized furans (adducts **4n**, **4p** and **4r**). In most cases, one single regioisomer was obtained in the reaction and in those few cases in which two regioisomers were observed, the major one was formed with a very high ratio. In addition, in all cases the final cycloadducts were formed as single diastereoisomers, showing a *trans* relative arrangement between the two substituents of the allenamide reagent.

Table 3. Scope of the reaction using γ-substituted allenamides.[a]



[a] Reaction carried out in a 0.05 mmol scale of **2b-i**, using **3e** (5 mol%), **1g-k** (3.0 eq) and 6.3 eq. of DMDO (as solution in toluene) in AcOEt at -78ºC. [b] The enantiomer of catalyst **3e** was used. [c] Reaction carried out with 1.0 eq. of allenamide, 2.5 eq. of DMDO and 2.0 eq. of furan. [d] Reaction carried out using 5.0 eq. of allenamide, 12.5 eq. of DMDO and 1.0 eq. of furan.

Even more interesting is the excellent performance provided by allenamide **1i** that incorporates a bulkier cyclohexyl group (compounds **4s-4v)** in which the (4+3) cycloaddition proceeded smoothly and with remarkably high enantioselectivity. Finally, other functionalized allenamides such as **1j (**R^1=CH_2CH_2Ph) and **1k** (R^1=CH_2CH_2OTBS) also demonstrated the excellent performance of the reaction (adducts **4w-y**), once again showing the possibility of incorporating functionalizations at this position (adduct **4y**). The only limitations observed for this reaction were found when allenamides with two substituents at the terminal position of the allene moiety were used, which were unable to provide any cycloaddition product even after prolonged reaction time or by carrying out the reaction at higher temperatures. The same applied to all attempts to carry out the reaction with furans incorporating substituents at the 2-position such as 2-methylfuran and 2,5-dimethylfuran. It has to be pointed out that the absolute stereostructure of the cycloadducts obtained by this protocol was established by single-crystal X-ray analysis of

enantiopure samples of compounds **4c** and **4x**,[17] for which a monocrystal could be obtained. Accordingly to the stereostructure obtained for this compound, the configuration of all other adducts **4a-y**, was established by assuming the same stereochemical outcome for all reactions between allenamides **1a-k** and furans **2a-i** based on mechanistic analogy.

In conclusion, we have shown that oxyallyl cations generated by oxidation of allenamides can be activated by chiral Brønsted acids towards a subsequent (4+3) cycloaddition process with furans, providing a direct and simple access to wide range of potentially valuable seven-membered rings in a highly regio- diastereo- and enantioselective way. The reaction relies on the potential of the conjugate base of the *N*-sulfonylphosphoramide catalyst to engage in a bifunctional mode of activation that combines H-bonding together with electrostatic interactions through ion pairing with the oxyallylcation dienophile and this combination enables an efficient chirality transfer to the newly formed bonds. Moreover, this catalytic system shows a remarkably wide substrate scope with respect to both furan and allenamide reagents that are amenable to be employed in this type of cycloaddition reaction, especially highlighting the excellent performance shown by racemic γ-substituted allenamides as the oxyallyl cation precursor.

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Keywords: Asymmetric catalysis · Cycloaddition · Ion Pairing Catalysis · Organocatalysis · Oxygen Heterocycles

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[16] We also checked at this point the occurrence of the competitive background reaction using allenamide **1f**. In this case, the reaction between **1f**, **2a** and DMDO in toluene at -78ºC provided **4f** in 39% yield after 72h.

[17] CCDC 1540881 (**4x**) and 1540882 (**4c**) contain 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