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Induction of asymmetry on the [4+3] cycloaddition reaction of C2-functionalized furans

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Abstract—A study of the induction of asymmetry on the [4+3] cycloaddition reaction of some 13 C2-substituted furan derivatives with 2-oxyallyl cation is presented. The asymmetry was induced by a chiral auxiliary on C2 of furan. A *cis* diastereospecificity and a high *endo* diastereoselectivity are observed in almost all studied cases. On decreasing the distance between the stereocenter of the chiral auxiliary and the reactive C2-carbon of the furan ring, the π-facial diastereoselectivity is increased, especially by using chiral furyl-sulfoxides. © 2002 Elsevier Science Ltd. All rights reserved.

The [4C(4π)+3C(2π)] cycloaddition reaction[1] between C2-functionalized furans and oxyallyl cations is an elegant and efficient method to synthesize polyfunctionalized cycloheptenes. These synthons facilitate the straightforward synthesis of molecules having a seven-membered ring.[1,2] Moreover, the oxidative cleavage of the carbocycle is also a good method to synthesize, on a stereoselective manner, linear polysubstituted synthons (Fig. 1) that could be transformed into subunits of biologically active natural products,[3,4] which are usually prepared by reiterated aldol reactions with difficult stereocontrol. Recently, *C*-glucosides and carbohydrates including those with unnatural configuration have been synthesized by this methodology.[5]

The [4+3] cycloaddition reaction is generally used as one of the initial steps of the synthetic pathways, and due to the resulting bicyclic cycloadduct has low conformational freedom, this reaction is a very adequate step to induce asymmetry in the overall synthetic process. On the other hand, in the [4+3] cycloaddition reaction four stereocenters are simultaneously formed, whose relative configuration is conditioned by mechanistic reasons, resulting in a high stereoselectivity.

Surprisingly, in the literature there are only a few references to the preparation of enantio-enriched cycloheptane synthons via [4+3] asymmetric cycloadditions.[6] On the basis of these precedents, we planned the study of the induction of asymmetry in the [4+3] cycloaddition reaction by using chiral furan derivatives. We introduced on C2 of the furan ring a chiral substituent (in most cases an easily removable chiral auxiliary). We thought of this alternative to be promising due to the excellent diastereoselectivity obtained by us in preceding works on [4+3] cycloaddition reactions of achiral C2-functionalized furans.[7]

This approach has, a priori, several advantages with respect to other possible methodologies to induce enantioselectivity in this reaction:

(a) The use of C2-functionalized furans results in the formation of cycloadducts having a doubly functionalized bridge-head, which facilitates the opening of the oxygen bridge to afford 3,6-difunctionalized cycloheptanes with controlled and defined relative stereochemistry (Fig. 1). This fact also facilitates the removal and recycling of the chiral auxiliary.

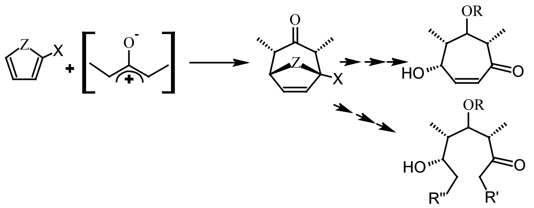

Figure 1. Preparation of useful C_7 synthons by [4+3] cycloaddition reactions.

Keywords: [4+3]-cycloaddition; oxyallyl cation; *syn–anti*; *endo–exo*; π-facial diastereoselectivity; chiral auxiliary; furan.

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(b) Our previous experience in the reactivity of achiral C2-substituted furans[7] allowed us to select the most adequate diene as substrate in order to get the highest *cis*/*trans* and *endo*/*exo* diastereoselectivities, in such a way that we could obtain almost stereo-specifically the *cis*–*endo* diastereoisomeric cycloadducts. This facilitates the study of the π-facial diastereoselectivity ('enantioselectivity' after removal of the chiral auxiliary) because it reduces the number of formed stereoisomers from eight to two (Fig. 2).

(c) Taking into account that C2 and C5 carbon atoms of furan are prochiral and that they decisively participate in the transition state of the [4+3] cycloaddition process, one expects a higher efficiency of the chiral auxiliaries if they are anchored on C2 or C5 rather than further away from these reactive centers.

(d) The π-facial diastereomeric cycloadducts should be separable at this stage by conventional achiral methods, and after removal of the chiral auxiliary, it should be possible to get the corresponding pure enantiomers.

(e) Both enantiomers of the chiral auxiliary can be used in order to get stereoselectively one or other of the π-facial diastereomeric cycloadducts.

In the present work we have synthesized and used as diene substrates in [4+3] cycloaddition reactions some 13 chiral C2 functionalized furans (Table 1). The design and selection of the C2-attached chiral groups was based on several criteria in order to analyze their influence on the stereo-differentiation of the furan faces: (a) the distance between the reactive center of the furan derivative and the closest stereocenter of the chiral auxiliary (proximity rule); (b) the volume and shape of the auxiliary; (c) the stereo-electronic nature of the organic function that acts as a linker between the furan ring and the chiral auxiliary, considering the geometry and the conformational freedom that this function gives to the linker. We have chosen several linking functions to attach the chiral auxiliary to C2 of furan: carbonate, ester, thioether, sulfoxide and cycloalkyl linkers.

When reacting chiral furans as dienes with a symmetrically substituted oxyallyl cation it is possible to obtain eight diastereomeric cycloadducts (Fig. 2), due to both faces of the chiral furan being diastereotopic. Depending on the stereo-differentiating efficiency of the chiral auxiliary, the energy of the different transition states could be very different, in such a way that the diastereomeric cycloadduct resulting from the attack of the allyl cation through the most accessible face of the furan should be selectively formed (Fig. 3). This type of stereoselectivity is known as π-facial diastereoselectivity.

If the [4+3] cycloaddition reactions follows a concerted mechanism[1] and the oxyallyl cation adopts a 'W' configuration,[1] four transition states are possible, because the two types of coupling are possible (compact and extended[1]) through both faces of the furan (Fig. 3). In this case due to the chiral auxiliary is still anchored in the products, the cycloadducts resulting from the same type of coupling are diastereoisomers to each other. If the chiral auxiliary is removed they become enantiomers. So, the π-facial diastereoselectivity observed in the cycloaddition process is an indirect measure of the 'enantioselectivity' once the chiral auxiliary is separated.

Initially we used the cycloaddition methodology based on the generation of the 2-oxyallyl cation by reduction of 2,4-dibromo-3-pentanone with copper, in the presence of sodium iodide under reflux of acetonitrile, which was described by Hoffmann[8] (Table 1, entries 1–7, 11, 12, 14, 17, 19 and 21). Since this methodology involves more energetic conditions we designed a new methodology that requires milder reaction conditions,[9] with the intention of raising both the yield (by decreasing the formation of byproducts) and the π and facial diastereoselectivity by decreasing the conformational freedom of the reactants. In this new methodology we generated the oxyallyl cation by reduction of 2,4-diiodo-3-pentanone with a zinc–copper couple at lower temperatures (0–20°C), under ultra-sonication or magnetic stirring (Table 1, entries: 8–10, 13, 15–16, 18, 20 and 22–24).

In all cases, we got high *cis*/*trans* and *endo*/*exo* diastereoselectivities. The high *cis* stereoselectivity could be interpreted on the basis of both the preferential adoption of the 'W' configuration by the oxyallyl cation and the concerted mechanism of the cycloaddition reaction. The almost exclusive formation of the *endo* isomers could be due to the fact that the extended approach leading to the formation of the *exo* product is

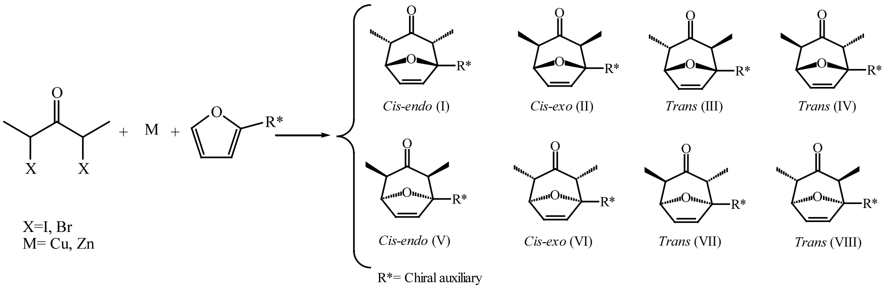


Figure 2. Eight possible diastereomers resulting from the [4+3] cycloaddition reaction of chiral furans and a symmetric oxyallyl cation.

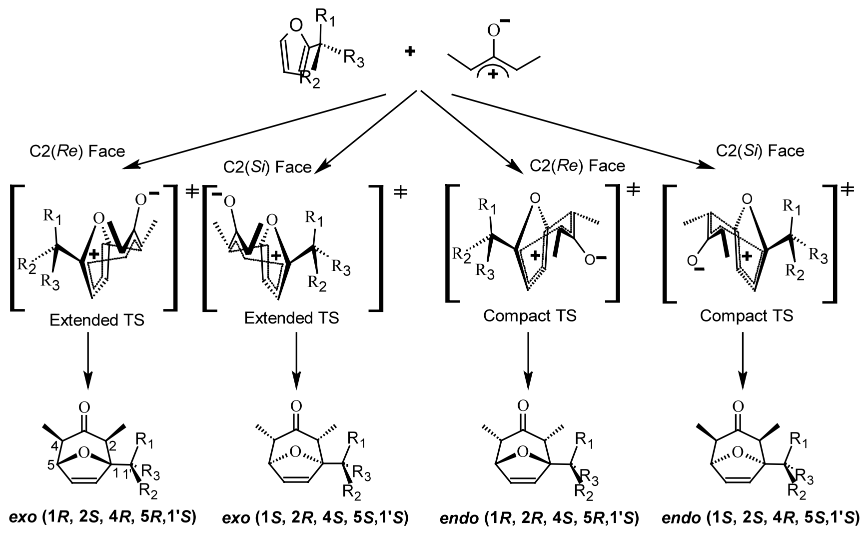


Figure 3. π-Facial diastereoselectivity. Formation of *endo*/*exo* diastereomers in a concerted process involving an oxyallyl cation with a 'W' configuration.

destabilized in front of the compact approach due to the presence of a bulky group on C2 of the diene.

In relation to the effect of the distance on the stereo-differentiation on the faces of the furan ring, we can observe from Table 1 that for long distances the π-facial diastereoselectivity is low or null (see entries 1–10, corresponding to 4 or 3 bonds distance). When the chiral auxiliary is approached to the furan by one or two bonds (see entries 12–24 and 11, respectively) the π-facial diastereoselectivity increases. The relation between the distance and the π-facial diastereoselectivity is not linear and it depends on other factors (compare, for example, entries 12–18 in Table 1).

One effect that should be analyzed is the influence of the volume and shape of the groups attached to the closest stereocenter (C*). This effect is more important when the C2–C* distance is shorter. Thus, when there is only one bond distance the increase of the size of substituents attached to the stereocenter, C*, considerably modifies the π-facial diastereoselectivity, even inverting it (compare entries 12–13 versus 14–16). For long distances this substitution effect could be observed but to a lesser extent: compare the different furyl esters from entries 2–6 in Table 1. It is worth noting the 2-(*p*-tolylsulfinyl)-furan model that, under both the Hoffmann and modified experimental conditions, affords the highest diastereoselectivity observed in this work (entries 21–24).

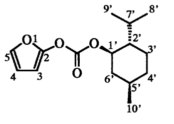
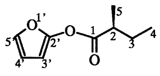
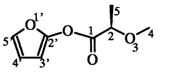
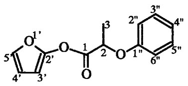
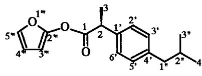
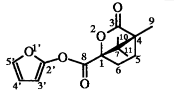
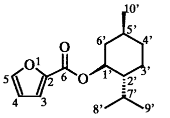
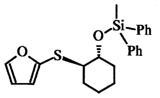
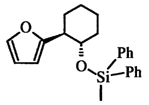
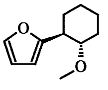
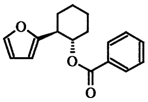
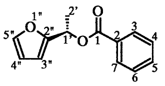
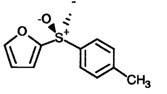
Looking at Table 1 it is possible to observe that when using the mild experimental conditions the yield is always higher than that obtained by using the Hoffmann conditions. The yield becomes quantitative when NaI is not used as the initiator. This improvement of yields could be due to the increase of chemical selectivity by avoiding polymerization reactions of the oxyallyl cation, electrophilic additions to the furan ring or partial reductions of the cycloadducts. However, the conversion of the furan substrates at a given reaction time is lower than in the case of the Hoffmann conditions. As in the case of the experiments carried out under the Hoffmann reaction conditions (Table 1), we also got complete *cis*/*trans* and better *endo*/*exo* diastereoselectivities with the new milder conditions, which confirms that the oxyallyl cations generated by both procedures adopts a preferential 'W' configuration and that the process goes through a compact concerted mode.

In relation with the π-facial diastereoselectivity we observe a slight increment of the stereo-differentiation of the furan faces in the case of dienes **10**, **11** and **13**, meanwhile in the case of furans **7**, **9** and **12** the π-facial diastereoselectivity is the same as that observed in the experiments carried out under Hoffmann conditions.

This small improvement of 2–3% in the π-facial diastereoselectivity could be interpreted on the basis of the lower reaction temperature (from 60 to 0–20°C) that reduces the conformational freedom at the level of the chiral auxiliary.

The results obtained from the experiments carried out in this work allowed us to draw interesting conclusions that represent a first step in the induction of asymmetry in the [4+3] cycloaddition reactions mediated by chiral C2 functionalized furans. We have obtained in this work excellent *cis*/*trans* and *endo*/*exo* diastereoselectivities and from zero to moderate (d.e. = 30% for furans **9**–**11**) or promising (d.e. = 54% in the case of furan **13**) π-facial diastereoselectivities. We have also opened the possibility, by designing the adequate chiral auxiliary, to stereo-specifically obtain an oxabicycle with *endo* (5*R*) or *endo* (5*S*) stereochemistry. We are now actively working in our laboratory in order to improve the conversion of substrates and the π-facial diastereoselectivity in the [4+3] cycloaddition reactions of chiral C2-functionalized furans.

Table 1. Results from the [4+3] cycloaddition reaction of 13 chiral furans and 2-oxyallyl cation

Entry	Chiral Auxiliary (R*)	C*-C2 Distance (Nº bonds)	X[a]	M[b]	T[c]	Energy source[d]	Cycloadduct	Conv. (%)	Yield (%)	DS[e] *cis:trans* (%)	DS[e] *endo:exo* (%)	DS[e] π-facial (%)
1[f]	 **1**	4	Br	Cu	60	H-MS	**14**	66	54	100:0	89:11	51:49
2[f]	 **2**	3	"	"	"	"	**15**	97	74	"	95:5	50:50
3[f]	 **3**	"	"	"	"	"	**16**	100	66	"	94:6	49:51
4[f]	 **4**	"	"	"	"	"	**17**	96	87	"	97:3	48:52
5[f]	 **5**	"	"	"	"	"	**18**	92	76	"	95:5	47:53
6[f]	 **6**	"	"	"	"	"	**19**	97	12	"	100:0	49:51
7[f]	 **7**	"	"	"	"	"	**20**	83	42	"	"	45:55
8		"	I	Zn	0	"	"	41	100	"	"	"
9		"	"	"	20	"	"	60	"	"	"	"
10		"	Br	Cu	"	"	"	50	"	"	"	"
11[f]	 **8**	2	"	"	60	"	**21**	80	80	"	"	54:46
12[f]	 **9**	1	"	"	"	"	**22**	66	53	"	"	37:63
13		"	I	"	0	US	**22**	55	100	"	"	"
14[f]	 **10**	"	Br	"	60	H-MS	**23**	69	66	"	"	63:37
15		"	I	"	0	US	"	37	85	"	"	65:35
16		"	"	Zn	"	"	"	56	100	"	"	"
17[f]	 **11**	"	Br	Cu	60	H-MS	**24**	60	70	"	"	63:37
18		"	I	"	0	US	"	32	100	"	"	65:35
19[f]	 **12**	"	Br	Cu	60	H-MS	**25**	57	38	"	"	46:54
20		"	"	Zn	20	"	"	40	100	"	"	"
21[f]	 **13**	"	"	Cu	60	"	**26**	55	51[g]	"	"	73:27
22		"	"	Zn	20	"	"	45	100	"	"	75:25
23		"	I	"	0	US	"	36	"	"	"	77:23
24		"	"	"	20	"	"	47	"	"	"	76:24

(a) Dihaloketone. (b) Reducing metal. (c) Inner temperature. (d) Energy source: H-MS= heating and/or magnetic stirring. US = ultrasound.
(e) DS: Diastereoselectivity. (f) Hoffmann conditions. (g) Partially reduced to sulfide.

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