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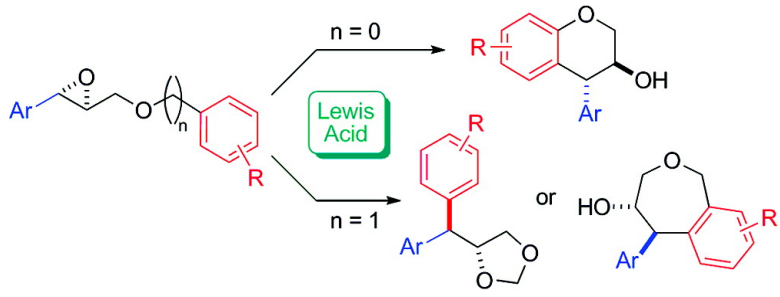

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Metal-Mediated Cyclization of Aryl and Benzyl Glycidyl Ethers: A Complete Scenario

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Glycidyl systems, readily available in enantiomerically pure form by Sharpless epoxidation,[1] are versatile scaffolds that can be submitted to many different selective transformations.[2] Intramolecular processes involving their epoxide ring are particularly interesting, since they can provide access to a variety of substituted heterocyclic systems both in racemic and in enantiomerically pure form.[3] In this context, it has been reported that aryl glycidyl ethers **1**, when treated with a catalytic amount of $AuCl_3$ in the presence of AgOTf in 1,2-dichloroethane at high temperatures for prolonged periods of time, lead to 3-chromanols **2** as the only reaction products.[4] On the other hand, we have shown that enantiomerically pure benzyl glycidyl ethers **3**, when treated with $BF_3 \cdot Et_2O$ in dichloromethane at low temperature for short periods of time lead to either 4,5-disubstituted tetrahydrobenzo[*c*]oxepin-4-ols **4** or to 4-diarylmethyl-1,3-dioxolanes **5** through stereospecific processes, depending on the substitution pattern of the benzyl residue.[5]

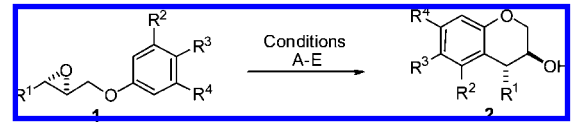
In spite of the close similarity of these reactions, it has been reported[4] that a Lewis acid such as $BF_3 \cdot Et_2O$ fails to induce the conversion of **1** into **2** and that the Au(III) catalyst was absolutely required for the reaction to take place. According to this, the intermediacy of an arylgold(III) species formed through an auration step[6] has been proposed as a mechanistic alternative for this transformation. We were intrigued by the possibility of this mechanistic duality, and given the interest of the considered reactions and of the products arising therefrom, we decided to reinvestigate this set of processes from the perspective of its mechanistic nature.

As the starting point of this research, we examined the Lewis acid reactivity of a family of aryl glycidyl ethers **1a**−**i**, most of them in enantiomerically pure form (**1h** and **1i** were racemic). The results of this study have been summarized in Table 1.

In contrast with the results discussed above,[4] but in full agreement with our previous findings,[5] $BF_3 \cdot Et_2O$ induces the high yield (79%), stereospecific cyclization of **1a** into 3-chromanol **2a** after a short treatment at −55 °C in dichloromethane (entry 1). Even more conveniently, the same reaction can be induced by $FeBr_3$ (10 mol%)[7] at 20 °C (Conditions B), **2a** being obtained in 92% yield after 30 min (entry 2). It is interesting to realize that for this particular substrate the use of $AuCl_3$/3AgOTf (2.5 mol%) in 1,2-dichloroethane, although involving harsher reaction conditions (50 °C) and a more prolonged reaction time (4 h), leads to lower yields than the more conventional Lewis acids.[4]

The use of $FeBr_3$ under the same very mild conditions employed for **1a** allowed the stereospecific, high yield cyclization of aryl phenylglycidyl ethers **1b**−**g** to 3-chromanols **2b**−**g**. For substrates bearing less nucleophilic aryloxy fragments, like **1b**, increased amounts of $FeBr_3$ (30 mol%) and extended reaction times (1 h) are required for complete conversion (entry 3).

Table 1. Lewis Acid Mediated Cyclization of Aryl Glycidyl Ethers **1** to 3-Chromanols



entry	product	R^1	R^2	R^3	R^4	cond[a]	yield [%]
1	**2a**	Ph	OMe	H	OMe	A	79
2	**2a**					B	92
3	**2b**	Ph	H	H	H	B[b]	61
4	**2c**	Ph	H	OMe	H	B[c]	92
5	**2d**	Ph	Me	H	Me	B	88
6	**2d**					C	97
7	**2e**	*p*-BrPh	OMe	H	OMe	B	76
8	**2f**	Ph	H	I	H	C[b]	73
9	**2g**	Ph	H	*t*-Bu	H	B	95
10	**2g**					C	99
11	**2h**	H	H	*t*-Bu	H	D	94[d]
12	**2h**	H				E	91[e]
13	**2i**	H	H	H	H	D	18
14	**2i**	H				E	17

[a] Cond. A: $BF_3 \cdot Et_2O$ (30 mol%), CH_2Cl_2, −78 or −55 °C, 30 min. Cond. B: $FeBr_3$ (10 mol%), CH_2Cl_2, 20 °C, 30 min. Cond. C: $FeBr_3$/3AgOTf (10 mol%), CH_2Cl_2, 20 °C, 30 h. Cond. D: $FeBr_3$/3AgOTf (10 mol%), $ClCH_2CH_2Cl$, 80 °C, 48 h. Cond. E: $FeBr_3$/3AgOTf (10 mol%), $ClCH_2CH_2Cl$, 140 °C, microwaves, 40 min. [b] 30 mol% catalyst, 60 min. [c] Reaction time was 60 min. [d] 57% conversion. [e] 53% conversion.

The unsubstituted glycidyl ethers **1 h**−**i**, lacking the activation of the epoxide ring toward ring-opening provided by the aryl substituent, are sensitive probes for the efficiency of the different Lewis acid types in the cyclization process. Taking **1i** as a model substrate, different Lewis acids known to induce the ring opening of epoxides [$BF_3 \cdot Et_2O$, $FeBr_3$, $InCl_3$, $LiClO_4$, $Cu(OTf)_2$, $Cu(ClO_4)_2$, $Zn(OTf)_2$] were tested under different experimental conditions.[8] In no case the expected 3-chromanol **2i** was formed, the only identified minor reaction products being halohydrins **6i**.[9] In view of the results reported by He,[4] we decided to explore the use in the reaction of $FeBr_3$ in combination with AgOTf with the aim of increasing the electrophilicity of the iron salt. Gratifyingly enough, **2i** was obtained, albeit in a modest 18% yield, under these conditions (Conditions D, entry 13). It is worth mentioning that, in our hands, use of the $AuCl_3$/3AgOTf catalyst (5 mol%) under identical experimental conditions afforded **2i** in 11% yield.[10] Use of Conditions D allowed preparation of **2h** in 94% yield (57% conversion, entry 11). Interestingly, reaction times for the preparation of **2h**−**i** could be drastically reduced (from 48 h to 40 min) without yield decrease by performing the reactions at 140 °C with microwave irradiation (Conditions E, entries 12 and 14). The $FeBr_3$/3AgOTf reagent was subsequently tested under milder conditions (Conditions C) for substrates **1a**−**g**. Except for the results in entries 6 and 10, only marginal yield increases were recorded.

The results obtained with unactivated substrates (**1h**−**i**) provide a clear indication that the cationic Au(III) or Fe(III) species likely

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generated in the presence of AgOTf can efficiently mediate the formation of **2** when halide delivery is avoided (Figure 1).

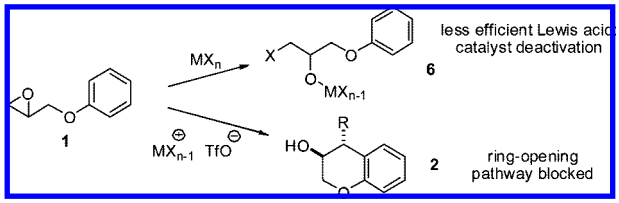
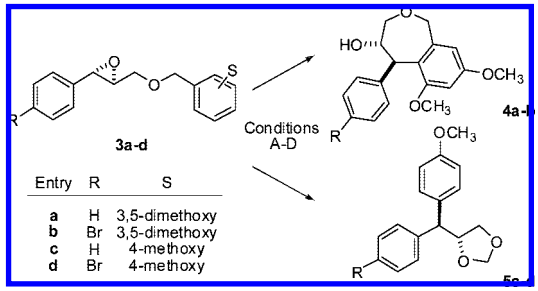


Figure 1. Reaction pathways of aryl glycidyl ethers with Lewis acids.

Once the ability of Lewis acids to induce the cyclization of aryl glycidyl ethers **1** into 3-chromanols **2** had been established, we turned our attention toward benzyl glycidyl ethers **3**, with the goal of determining whether the $FeBr_3$, $FeBr_3$/3AgOTf, and $AuCl_3$/3AgOTf catalysts could also induce the reactions[5] shown in Table 2. Substrates **3a**−**b** were selected as precursors of tetrahydroben-

Table 2. Lewis Acid Mediated Cyclization/Rearrangement of Benzyl Glycidyl Ethers **3** to Tetrahydrobenzo[*c*]oxepin-4-ols **4** or to 4-Diarylmethyl-1,3-dioxolanes **5**



entry	substrate	product	conditions[a]	yield [%]
1	**3a**	**4a**	A	80
2	**3a**	**4a**	B	82
3	**3a**	**4a**	C	70
4	**3a**	**4a**	D	88
5	**3b**	**4b**	B	75
6	**3b**	**4b**	C	74
7	**3b**	**4b**	D	81
8	**3c**	**5c**	A[b]	59
9	**3c**	**5c**	B	25[c]
10	**3c**	**5c**	C	72
11	**3c**	**5c**	D	82
12	**3d**	**5d**	C	89
13	**3d**	**5d**	D	96

[a] Cond. A: $BF_3 \cdot Et_2O$ (30 mol%), CH_2Cl_2, −78 °C, 15 min. Cond. B: $FeBr_3$ (10 mol%), CH_2Cl_2, 20 °C, 60 min. Cond. C: $AuCl_3$/3AgOTf (2.5 mol%), $ClCH_2CH_2Cl$, 50 °C, 4 h. Cond. D: $FeBr_3$/3AgOTf (20 mol%), CH_2Cl_2, 20 °C, 30 min. [b] Reaction at −35 °C for 5 min. [c] 29% of the corresponding bromohydrin was also obtained. Reaction time was 90 min.

zo[*c*]oxepin-4-ols **4a**−**b** via *ortho* activation of the benzyl substituent, while **3c**−**d** were chosen as precursors to 4-diarylmethyl-1,3-dioxolanes **5** via *ipso* activation of the benzyl fragment. The results of the study have been summarized in Table 2 along with those obtained with $BF_3 \cdot Et_2O$, when available.[5]

When the stereospecific cyclization of **3a** is considered (entries 1−4), it becomes clear that Au(III) is also able to induce conversion into **4a**, although $FeBr_3$/3AgOTf and the other tested Lewis acids are more efficient mediators than $AuCl_3$/3AgOTf for this process. The less reactive **3b** displayed similar behavior.

While the cyclization of substrates **3** bearing an *ortho*-activated benzyl substituent to oxepinols **4** is normally very clean,[5] the corresponding Lewis acid induced rearrangement of *ipso*-activated substrates to diarylmethanes is a more critical process, normally accompanied by variable degrees of halohydrin formation. According to this, the rearrangement of **3c**−**d** leading to **5c**−**d** is a more stringent test for possible mediators. With substrate **3c** (entries 8−11), it becomes clear that the ability of the four Lewis acids to induce the rearrangement varies in the order $BF_3 \cdot Et_2O$ > $FeBr_3$/3AgOTf > $AuCl_3$/3AgOTf > $FeBr_3$. When the yield of the diarylmethane **5** is considered, the $FeBr_3$/3AgOTf reagent represents an optimal compromise (entry 11). The same trends are observed for the conversion of **3d** into **5d**.

In summary, the results reported here clearly show that the cyclization and rearrangement reactions of aryl and benzyl glycidyl ethers are Lewis acid mediated processes. While the $FeBr_3$/3AgOTf combination appears as the catalyst of choice for this set of processes, the cationic species presumably formed through the interaction of $AuCl_3$ with AgOTf is also able to mediate, albeit in a less efficient manner, the same reactions. From a mechanistic point of view, the observed reactivity trends clearly indicate that these cyclizations are of the Friedel−Crafts type.

From the perspective of practical use, cost and availability considerations[11] make iron bromide a most attractive alternative for these reactions and, in general, for processes where gold and other expensive metals merely act as Lewis acids.

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Supporting Information Available: Experimental details and product characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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