Stereoselectivity in Reactions of 1,2-Dioxy-Substituted Radicals: Electronic versus Chelation Control

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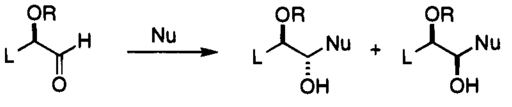
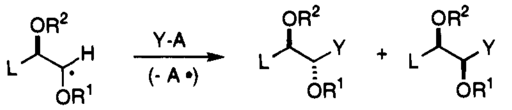
Recently, it has been shown that acyclic radicals can be used for highly stereoselective reactions.[1] Particular attention was devoted to the 1,2-asymmetric induction with stabilized radicals. Interestingly, the models which were proposed are strongly related to the ones previously developed for ionic or concerted reactions. For instance, ester-,[2] benzyl-,[3] and dialkylamino[4] -substituted radicals react according to a model based mainly on minimization of allylic 1,3-strain. On the other hand, the stereoselectivity observed with alkoxy-substituted radicals[5] is governed by a transition state similar to the Felkin–Anh model, which was originally developed for nucleophilic addition to carbonyl compounds.[6] In this report, we demonstrate that the stereoselectivity of 1,2-dioxy-substituted radicals (eq 2) is very similar to that for the nucleophilic addition to 2-alkoxy aldehydes and ketones (eq 1). Depending upon the reaction conditions, the stereochemistry is governed by the "electronic" Felkin–Anh[7] or the Cram[8] chelate transition state model.



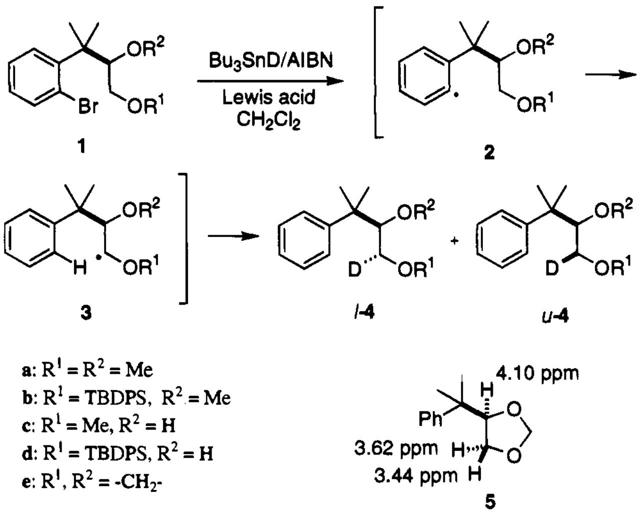
(1)



(2)

We designed a model system for the study of the effect of Lewis acidic additives on the stereoselectivity of 1,2-dioxy radical-mediated reactions (eq 2).[9,10] As it proved necessary to use a radical precursor which is stable under acidic conditions, we took advantage of the hydrogen atom abstraction reaction to generate the desired alkoxy-substituted radicals.[11] Compounds of type **1** (racemic) were prepared from 2-bromobenzyl bromide (see supplementary material), and upon treatment with Bu_3SnD/AIBN and sun lamp irradiation at 10 °C, they afforded the deuterated *l*-**4** and *u*-**4** via the radical intermediates **2** and **3** (Scheme 1). All the results of the deuteration experiments are summarized in Table 1.

Scheme 1



a: $R^1 = R^2 = Me$
b: R^1 = TBDPS, $R^2 = Me$
c: $R^1 = Me$, $R^2 = H$
d: R^1 = TBDPS, $R^2 = H$
e: $R^1, R^2 = -CH_2-$

In a first series of experiments, we examined the deuteration of radical **3a**. In the absence of Lewis acids, the major product is the *unlike* isomer *u*-**4** (Table 1, entry 1). The preferred formation of this diastereoisomer is best explained by an electronic Felkin–Anh transition state model (Figure 1, **A**).[12] Interestingly, the bulky (dimethylphenyl)methyl group accommodates well a gauche conformation with the 1-methoxy group. Different bidentate Lewis acids were tested for their ability to be chelated by the radical intermediate in order to revert the stereoselectivity (Figure 1, **B**).[13] Zinc chloride and titanium triisopropoxide monochloride were found to be inefficient (Table 1, entries 2 and 3) and diethylaluminum chloride inhibited completely the hydrogen transfer reaction (entry 5).[14] Freshly prepared magnesium iodide etherate[15] gave the *like* product *l*-**4a** with a high stereoselectivity (entry 4, 17:1). The reaction was

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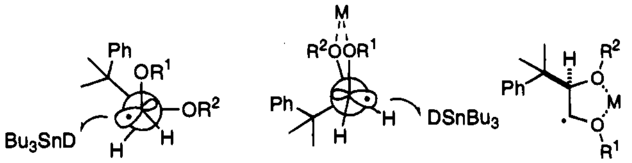
Table 1. Radical Deuteration of **1a**–**e** with Bu_3SnD (0.3 M) in the Presence of Lewis Acids at 10 °C[a]

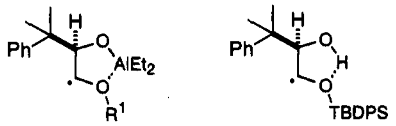
entry	pre-cursor	Lewis acid (equiv)	H-transfer (yield[b])	product	*l*-**4**/*u*-**4**
1	**1a**	*c*	72% (70%)	**4a**	1:2.5
2	**1a**	$ZnCl_2 \cdot OEt_2$ (1.3)[d]	47% (30%[e])	**4a**	1:1.4
3	**1a**	$Ti(OiPr)_3Cl$ (1.3)[c]	50% (20%[e])	**4a**	1:3.0
4	**1a**	$MgI_2 \cdot OEt_2$ (2.2)[d]	33% (50%[e])	**4a**	17:1
5	**1a**	Et_2AlCl (1.3)[d]	< 5% (74%)	**4a**	
6	**1b**	*c*	80% (83%)	**4a**[f]	1:3.0
7	**1b**	$MgI_2 \cdot OEt_2$ (2.2)[d]	65% (35%[e])	**4a**[f]	1:3.0
8	**1c**	*c*	36%[g] (75%)	**4a**[h]	1:1
9	**1c**	Et_2AlCl/Na_2CO_3 (1.1)[c]	13%[g] (83%)	**4a**[h]	20:1
10	**1c**	$MgI_2 \cdot OEt_2$ (1.3)[d]	26%[g] (35%[e])	**4a**[h]	6.1:1
11	**1d**	*c*	66% (70%)	**4a**[f]	2.7:1
12	**1d**	Et_2AlCl/Na_2CO_3 (1.1)[c]	12% (30%[e])	**4a**[f]	20:1
13	**1e**	*d*	34% (82%)	**4e**	20:1

[a] **1** (0.25 mmol), Bu_3SnD (0.3 mmol), and AIBN (4 mg) in 0.9 mL of solvent were treated with the Lewis acid and irradiated at 10 °C with a 300 W sun lamp for 15 h. [b] Not optimized. [c] In C_6H_6. [d] In CH_2Cl_2. [e] Unreacted starting material was recovered as single identified byproduct, corrected yield are in all cases > 70%. [f] After desilylation (TBAF/THF) and methylation (NaH/MeI). [g] Traces (<3%) of 1,4-H-transfer were detected. [h] After methylation (NaH/MeI).



A: Felkin-Anh electronic[5b] (*unlike* product)

B: chelation control (*like* product)



C **D**

Figure 1. Transition state models.

run with 2.2 equiv of $MgI_2 \cdot OEt_2$. Similar levels of stereoselectivity were obtained with 1.3 equiv, but the reproducibility under these conditions was more difficult to achieve on a small scale. We also examined the reaction of the 1-silyloxy-2-methoxy derivative **1b**. As already reported by Curran,[11] the percentage of H-transfer is higher with a silyl protective group. In the absence of Lewis acid, an *l*:*u* 1:3 mixture of diastereoisomers was formed (entry 6), presumably via an electronic Felkin–Anh transition state (Figure 1, **A**). As expected from literature precedents, the formation of a chelate is inhibited by the presence of the bulky protective TBDPS group,[16] and the stereochemistry is not altered by the addition of $MgI_2 \cdot OEt_2$ (entry 7). The presence of a nonprotected hydroxyl group in the 2-position was also investigated with **1c**. Without Lewis acid, the reaction is nonstereoselective (entry 8), but a high stereoselectivity (20:1) is obtained in favor of the *like* isomer with Et_2AlCl/Na_2CO_3 (entry 9). Formation of a chelated aluminum alkoxide (Figure 1, **C**) helps to rationalize the stereochemical outcome. The addition of Na_2CO_3 is necessary to trap the HCl which is formed upon mixing the Lewis acid with the free alcohol. $MgI_2 \cdot OEt_2$ (entry 10, 6.1:1) gives also preferentially the *like* isomer. The deuteration of the free alcohol **1d** was also investigated. In the absence of Lewis acid, the *like* isomer is already preferentially formed (entry 11); this result was attributed to intramolecular hydrogen bonding (Figure 1, **D**). Addition of a chelating agent enhances the stereoselectivity despite the large size of the silyl protective group (entry 12, 20:1). Finally, the cyclic methylene acetal **1e** was prepared and exposed to standard reaction conditions. A good stereoselectivity in favor of the *like* compound is observed (entry 13, 20:1). The relative configuration of this product was determined by preparation of the non-deuterated **5** by reduction of **1e** with Bu_3SnH/AIBN. NOE measurement allowed us to attribute unambiguously the ^{1}H-NMR signal as depicted in Scheme 1. The configuration of all the other products was attributed by chemical correlation. For instance, *l*-**4b**–**d** were converted to *l*-**4a**, and *l*-**4d** was converted also to *l*-**4e**.

In conclusion, we have demonstrated that the stereochemistry of reactions of 1,2-dioxy-substituted radicals is best explained by the electronic Felkin–Anh model in the absence of additive. In the presence of bidentate Lewis acids, the stereochemical outcome is reversed due to chelation of the transient radicals, and the Cram's chelation model applies. This represents the first example of chelation control for 1-alkoxy-substituted radicals.[17] The use of magnesium iodide etherate was found to be particularly convenient with the dimethoxy derivative. Aluminum-based Lewis acids are useful for controlling the stereoselectivity in 1-alkoxy-2-hydroxy-substituted radicals. Further investigations of the model and utilization of this strategy for the development of synthetically useful reactions are currently underway in our laboratory.

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Supplementary Material Available: Preparation of the radical precursors **1a**–**e**; general procedure for the radical deuteration; ^{1}H-NMR and ^{2}H-NMR spectra of **4a**,**e**; and NOE measurement of **5** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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