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PAPER

Diastereoselective radical mediated alkylation of a chiral glycolic acid derivative†‡

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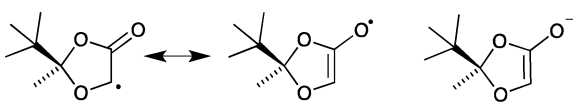
Radical alkylation of 2-(*tert*-butyl)-2-methyldioxolan-4-one, a chiral equivalent of glycolic acid, occurs with good to high diastereoselectivity that compares favorably with the corresponding enolate alkylation. The importance of the position of the transition state position, early or late, is highlighted.

Introduction

The stereochemical control of radical reactions has been a field of intense investigation in the past 20 years. Rules have been proposed to rationalize the results. Interestingly, these rules parallel the ones formerly developed for ionic and concerted reactions.[1] The enolate mediated alkylation of chiral equivalents of glycolic acid opens a direct access to optically active α-hydroxy acids and has attracted the interest of many synthetic chemists over the years.[2,3] The use of chiral 1,3-dioxolanone for the alkylation of α-hydroxyacids, has been pioneered by Seebach and Frater[4] and extended to glycolic acid derivatives.[5,6] In this last case, however, the diastereoselectivities were not as high as expected[7,8] except when *N*,*N*-diisopropyl-10-camphorsulfonamide was used as a chiral auxiliary for the ketal formation.[9] The corresponding radical process is less documented but interestingly, Beckwith has reported a highly stereoselective radical bromination of racemic 2-(*tert*-butyl)-1,3-dioxolan-4-one.[10] Surprisingly, closely related radical reactions with tin deuteride and allylstannane gave low stereoselectivities.[10,11] We report here a study of the stereochemical outcome of reactions involving 4-oxo-1,3-dioxolan-5-yl radical **A** derived from a chiral derivative of glycolic acid. The results are compared with the one obtained for the corresponding enolate **B** and a model is proposed to explain the important variation of stereoselectivities.



A **B**

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† This paper is dedicated to the memory of Professor Athel L. J. Beckwith, a genuine pioneer in organic free radical chemistry. His immense contribution to the development of radical reactions and the understanding of their stereochemical outcome is a constant source of inspiration.

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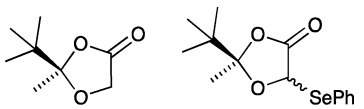
In order to compare radical and enolate mediated reactions, it was necessary to find a system that allows to perform both reaction types. As demonstrated by Beckwith,[10] the 2-(*tert*-butyl)-1,3-dioxolan-4-one system is suitable for radical processes but preliminary studies with 2-(*tert*-butyl)-1,3-dioxolan-4-one revealed that the corresponding enolate is difficult to alkylate due to competing decomposition. We have shown that the closely related 2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-one **1** leads to enolates that are sufficiently stable for efficient alkylation.[6,7a] Therefore, we decided to focus our attention on this substrate.

Results and Discussion

Radical reactions

Dioxolanone **1** was prepared by condensation of trimethylsilyl trimethylsilyloxyacetate with pinacolone in 92% yield by analogy to Pearson's procedure.[7a,12] The radical precursor **2** was prepared in 91% yield by selanylation of **1** with LDA/PhSeCl.[7a] The selenoacetal **2** is stable and can be stored at 4 °C for several weeks.



1 **2**

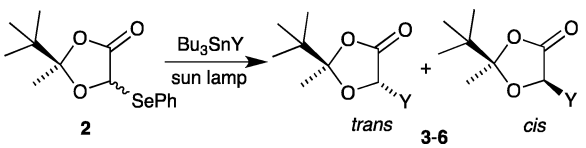
A first series of experiments was conducted with tin reagents at different temperatures (eqn (1)) and results are summarized in Table 1.[13] Deuteration experiments using tributyltindeuteride gave the mono deuterated compound **3** in good yields and moderate stereoselectivity (Table 1, entries 1–2). Increasing the temperature from 0 °C to 40 °C led, as anticipated, to a slight decrease of the stereoselectivity. Allylation using allyltributyltin was attempted next. The reaction at 40 °C (Table 1, entry 3) gave the desired product **4** with low diastereoselectivity and low yield due to dimerization of the intermediate captodative radical **A**. A higher yield of **4** was obtained at 80 °C together with an unexpected increase of diastereoselectivity (Table 1, entry 4). The temperature effect was further confirmed by running the reaction in toluene (or 1,2-dichlorobenzene) at temperatures ranging from –80 to 180 °C (Table 1, entries 5–11). Diastereoselectivties between 1 : 1

Table 1 Radical reactions of **2** with Bu_3SnY according to eqn (2)[a]

Entry	Y	T	Product	Yield	*trans*/*cis*
1	D	0 °C	**3**	87%	6 : 1
2	D	40 °C	**3**	87%	4.5 : 1
3	CH_2=$CHCH_2$	40 °C	**4**	30%	1.8 : 1
4	CH_2=$CHCH_2$	80 °C	**4**	78%	3.5 : 1
5	CH_2=$CHCH_2$	–80 °C[b]	**4**	5%	1 : 1
6	CH_2=$CHCH_2$	–10 °C[b]	**4**	50%	1.4 : 1
7	CH_2=$CHCH_2$	30 °C[b]	**4**	55%	1.6 : 1
8	CH_2=$CHCH_2$	50 °C[b]	**4**	70%	2.5 : 1
9	CH_2=$CHCH_2$	80 °C[b]	**4**	65%	3.3 : 1
10	CH_2=$CHCH_2$	110 °C[b]	**4**	80%	4.5 : 1
11	CH_2=$CHCH_2$	180 °C[c]	**4**	30%	7 : 1
12	CH_2=$C(SiMe_3)CH_2$	40 °C	**5**	27%	6.8 : 1
13	CH_2=$C(SiMe_3)CH_2$	80 °C	**5**	85%	9.2 : 1
14	CH_2=$C(CO_2Me)CH_2$	40 °C	**6**	43%	16 : 1
15	CH_2=$C(CO_2Me)CH_2$	80 °C	**6**	87%	11.5 : 1

[a] A solution of **2** (1.0 mmol) and Bu_3SnY (4.0 mmol) in benzene (4 mL) was irradiated with a 300 W sun lamp at the indicated temperature. [b] Reaction performed in toluene. [c] Reaction performed in 1,2-dichlorobenzene.

(–80 °C) and 7 : 1 (180 °C) were recorded. The allylation with tributyl-(2-trimethylsilylallyl)tin gave **5** with higher diastereoselectivities and a similar temperature dependence (Table 1, entries 12 and 13). Finally, reaction with 2-(methoxycarbonyl)allyltributyltin at 40 °C afforded **6** (Table 1, entries 14) with a much higher *trans* selectivity compared to the less activated allylstannanes (Table 1, entries 3 and 12). In this case, however, increasing the temperature led to a decrease of diastereoselectivity (Table 1, entry 15). The *trans* relative configuration of the major isomer of **6** was established by difference n.O.e measurements (see ESI‡).



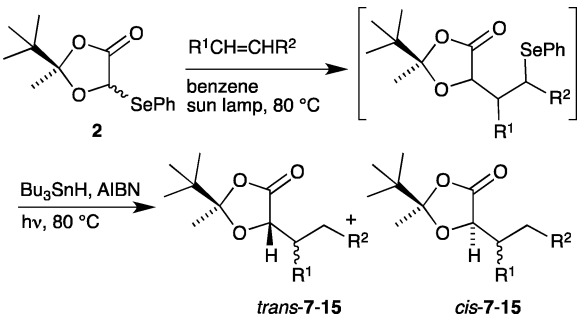
(1) (1)

Due to the high stability of the intermediate radical, it is possible to run addition of **2** to alkenes under phenylseleno group transfer conditions (eqn (2)).[14,15] A series of alkenes were investigated and results are summarized in Table 2. A good *trans* selectivity (*trans*/*cis* 10 : 1) was observed with 1-octene (Table 2, entry 1). In contrast to the allylation reactions, the stereoselectivity increases slightly when decreasing the temperature (compare entries 1–3 in Table 2). Methyl acrylate and phenyl vinyl sulfone gave higher stereoselectivities (Table 2, entries 4 and 5). The highest *trans* selectivity was obtained with alkenes activated by two electron withdrawing groups such as dimethyl fumarate (*trans*/*cis* 23 : 1) and *N*-phenylmaleimide (*trans*/*cis* 22 : 1) (Table 2, entries 6 and 7). As anticipated for these two last examples, low diastereoselectivities (1.5 : 1 and 1.9 : 1) were observed relative to the formation of the side chain stereogenic center. In order to test the influence of electronic factors, we examined the addition to different *para*-substituted styrenes (Table 2, entries 8–11). Electron withdrawing groups such as CF_3 and OAc have no effect on the stereoselectivity relative to unsubstituted styrene (*trans*/*cis* 10 : 1). The methoxy group induces only a slight decrease of selectivity (*trans*/*cis* 8.8 : 1).

Table 2 Phenylselanyl group transfer reactions of **2** with different alkenes according to eqn (3)

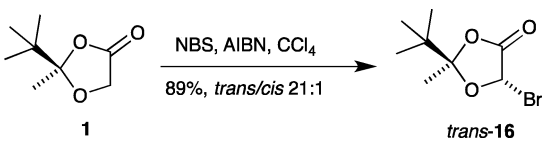
Entry	CHR^1=CHR^2	Product	Yield	*trans*/*cis*
1	CH_2=CHC_6H_{13}	**7**	65%[a]	10 : 1
2	CH_2=CHC_6H_{13}	**7**	70%[a,b]	7.5 : 1
3	CH_2=CHC_6H_{13}	**7**	25%[a,c]	12 : 1
4	CH_2=$CHCO_2Me$	**8**	67%	15 : 1
5	CH_2=$CHSO_2C_6H_5$	**9**	83%	16 : 1
6	(*E*)-MeO_2CCH=$CHCO_2Me$	**10**	79%	23 : 1[d]
7	*N*-Phenylmaleimide	**11**	79%	22 : 1[e]
8	CH_2=CHC_6H_5	**12**	37%	10 : 1
9	CH_2=$CH(p\text{-}CF_3\text{–}C_6H_4)$	**13**	40%	10 : 1
10	CH_2=$CH(p\text{-AcO–}C_6H_4)$	**14**	40%	10 : 1
11	CH_2=$CH(p\text{-MeO–}C_6H_4)$	**15**	50%	8.8 : 1

[a] Reaction performed in toluene. [b] Reaction performed at 110 °C. [c] Reaction performed at 25 °C. [d] Mixture of isomers (1.5 : 1) relative to the second stereogenic center. [e] Mixture of isomers (1.9 : 1) relative to the second stereogenic center.



(2)

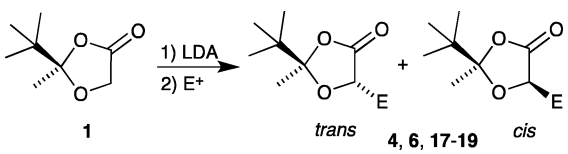
Finally, the radical bromination of **1** with *N*-bromosuccinimide (NBS) in refluxing CCl_4 was investigated (eqn (3)). In analogy to Beckwith's work,[10] a high stereoselectivity (*trans*/*cis* 21 : 1) and a good yield were obtained.



(3)

Enolate reactions

The alkylation of **1** *via* its enolate was investigated next (eqn (4)). Results are presented in Table 3. A standard procedure (LDA in THF) was used for the deprotonation, the electrophile was added at –78 °C and allowed to warm up to room temperature overnight (except for entry 5 where the reaction mixture was neutralized at –78 °C). Even in cases where the reaction was allowed to warm up to room temperature, it is believed that the reaction takes place at a temperature below –30 °C since rapid decomposition of the enolate is observed at higher temperature.



(4)

Reactions with alkyl halides (Table 3, entries 1–4), acetone (Table 3, entry 5) and with 2-methoxycarbonylpropenyl phenyl sulfone (Table 3, entry 6) gave stereoselectivities between 1.7 : 1

Table 3 Enolate alkylation of **1** according to eqn (4)

Entry	Electrophile E^+	Product	Yield	*trans*/*cis*
1	MeI	**17**	87%	1.7 : 1[a]
2	$CH_2{=}CHCH_2Br$	**4**	81%	3.0 : 1[b]
3	$C_6H_5CH_2Br$	**18**	70%	3.6 : 1
4	$CH_3(CH_2)_7I$	**7**	20%	3.0 : 1
5	$(CH_3)_2C{=}O$	**19**	85%	3.0 : 1[c]
6	$CH_2{=}CH(CO_2Me)CH_2SO_2C_6H_5$	**6**	80%	5.0 : 1

[a] Taken from reference 6 [b] Taken from reference 7b. [c] Reaction entirely performed at −78 °C.

to 5 : 1. Efforts to increase the stereoselectivity by changing the base (NaHMDS, KHMDS) or adding cosolvents (HMPA, DMPU) were not successful. Exposing a sample of pure *trans*-**18** to the work-up conditions left it unchanged demonstrating that no epimerization of the acetal center occurred during the work-up procedure. The low diastereoselectivities are surprising relative to the excellent stereocontrol observed by Seebach and Frater during the alkylation of the dioxolane derived from lactic acid and pivalaldehyde.[4] The low diastereocontrol could not be attributed to the presence of the methyl substituent at position 2. Indeed, in a control experiment, we observed that the second alkylation proceeds with excellent stereoselectivities. For instance, the benzylation of **17** furnished **20** as a *trans*/*cis* 16 : 1 mixture of isomers (eqn (5)).

(5)

Discussion

Greiner has shown that *cis*-2,5-disubstituted dioxolan-4-ones are more stable than the corresponding *trans* isomers due to their existence in a half-chair or envelope conformations.[16] The two substituents of the *cis* isomer occupy pseudo-equatorial positions (Fig. 1). For example the 5-methylated dioxolanone **17** exists under equilibrium in refluxing cyclohexane as a *cis*/*trans* 95 : 5 mixture of diastereoisomers. This corresponds to a 8.8 kJ mol^{-1} difference in free energy.

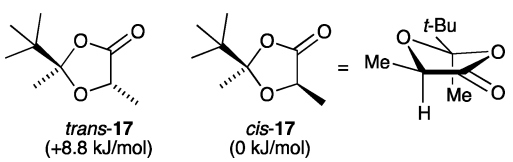


Fig. 1 Relative stability of *cis*- and *trans*-**17**.

The preferential formation of *trans* compounds in radical reactions (contrathermodynamic stereoselectivity) is best explained by the occurrence of early transition states for reactions with olefins and other radical traps.[17] This point was already pointed out by Beckwith and Zavitsas using AM1 calculations for the hydrogen atom transfer process with tributyltin hydride.[18] The major *trans* product is produced by the reaction of the radical from the less hindered face *anti* to the *tert*-butyl group. Factors which favor early (= reactant-like) transition states as well as steric effects are expected to favour the formation of the *trans* compounds. According to the Hammond postulate,[19] an increase of the exothermicity of the reaction by introducing a radical stabilizing substituent on the olefin should lead to a more early transition state and therefore to higher selectivity. This is the case for the reaction of **2** with the ester substituted allylstannane (Table 1, entries 14–15), which is more selective than the simple allyltributylstannane (Table 1, entries 3–4). The same trend is also present in the results collected in Table 2 (compare entries 1, 4, and 6 for instance). The high stereoselectivity of the bromination reaction (eqn (3)) can also be rationalized by this model since this process is expected to proceed *via* early transition state due to its high exothermicity.[20] Stereoelectronic effects may also influence the stereoselectivity as suggested by the lower selectivity observed for the addition to *p*-methoxy styrene (Table 2, entry 11) relative to less electron rich systems (Table 2, entries 8–10) and by the high selectivities observed with highly electrophilic radical traps such as NBS (eqn (3)), dimethyl fumarate and *N*-phenylmaleimide (Table 2, entries 6 and 7).

The stability of the intermediate captodative radical **A** contributes to this unexpected effect since it leads to less exothermic radical processes (less early transition states) than usual. Therefore, small changes of the relative stability of the products influence effectively the energy of the transition states. The highly stereoselective C–C bond formations involving 5-substituted 2-*tert*-butyl-4-oxo-1,3-oxazolidin-5-yl radicals reported by Beckwith[10] and Mattay[11d] can also be explained by this model. In their study, the products are disubstituted at C(5) and therefore the *cis* and the *trans* isomers possess similar energies and have no influence on the relative energies of the transition states.

It can be concluded that the reactivity-selectivity principle[21] does not apply for the dioxolanyl radicals **A** at the temperature used to run our radical reactions (below 100 °C). Such behaviour is well documented in the literature and is related to the isoselective relationship.[22,23] The increase of selectivity when increasing the temperature observed for the allylation of **2** with allyltributyltin and (2-trimethylsilylallyl)tributyltin (Table 1, entries 5–13) is unexpected but not exceptional.[23] The more product-like character of the transition state of this reaction reinforces the influence of entropy factors that favor the formation of *trans*-**4** at higher temperature. Similar effects have been reported by Metzger *et al.* for hydrogen atom transfer involving late transition states.[24]

The low stereoselectivity of enolate reactions can be rationalized by similar arguments. The hypothesis that the transition states of enolate reactions are not very early is reasonable. Therefore product stability influences the stereochemical outcome of the reactions and favors the formation of the more stable *cis* products. This explains also why the second alkylation is more stereoselective (eqn (5)). Indeed, the thermodynamic stability of the *cis* and *trans* isomers of 5,5-disubstituted dioxolanones are similar and their influence on the stereochemical outcome vanishes.

Conclusions

In conclusion, we have presented here radical processes where increasing the exothermicity results in a stereoselectivity

enhancement. Such effects are limited to particular cases but they are probably more frequent than expected as demonstrated by the work of Beckwith,[21] Giese[22] and Metzger.[22b,24] Moreover, in the perspective of using a chiral dioxolanone derived from glycolic acid for asymmetric synthesis of α-monoalkylated α-hydroxyacids, the radical mediated alkylation compares favourably to the enolate alkylation. This point is best illustrated by the preparation of the *n*-octylated derivative **7** that provides a *trans*/*cis* 10 : 1 ratio (65% yield) *via* radical pathway *versus* a 3 : 1 ratio (20%) *via* enolate alkylation.

Experimental

General procedure 1. Radical reaction of 2 with Bu_3SnY

A soln. of **2** (1.0 mmol) and Bu_3SnY (4.0 mmol) in benzene (4 ml) was irradiated with a 300 W sun lamp. The reaction was monitored by TLC. After solvent evaporation, the crude product was purified by flash column chromatography (FC).

General procedure 2. Radical addition of 2 to olefins

A soln. of **2** (1.5 mmol) and the olefin (1.0 mmol) in benzene (4.5 ml) was irradiated with a 300 W sun lamp at 80 °C. The reaction was monitored by TLC. After solvent evaporation, the crude product was purified by FC.

General procedure 3. Radical addition of 2 to 4-substituted styrenes

A soln. of **2** (1.5 mmol) and 4-substituted styrene (1.0 mmol) in benzene (4 ml) was irradiated with a 300 W sun lamp under reflux. The reaction was monitored by TLC. After complete disapearance of the styrene derivative, the reaction was cooled down to rt. Bu_3SnH (3 mmol) and AIBN (10 mg) were added and the irradiation was continued for 2 h at rt. After solvent evaporation, the crude product was purified by FC.

General procedure 4. Enolate alkylation of 1

Diisopropylamine (10 mmol) and 1.6 M BuLi (10 mmol) were added at −78 °C to THF (20 ml) containing HMPA (2 ml). After 5 min, a soln. of **1** (10 mmol) in THF (5 ml) was added dropwise. After 15 min at −78 °C, the electrophile (30 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm up to rt over 2 h. Sat. aq. $NaHCO_3$ (10 ml) and Et_2O (200 ml) were added and the organic layer was separated, washed with sat. $NaHCO_3$ (5 × 20 ml), dried (Na_2SO_4). After solvent evaporation, the crude product was purified by FC.

Product description

5-Allyl-2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-one 4

Radical procedure. According to General procedure 1, from **2** (313 mg, 1.0 mmol) and allyltributylstannane (1.32 g, 4.0 mmol). After evaporation, FC (Et_2O/hexane, 1 : 20) gave **4** (155 mg, 78%) as a 3.5 : 1 *trans*/*cis* mixture of diastereoisomers. Spectroscopic data are in accordance with literature.[7b]

Acknowledgements

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