Reagent-controlled Stereoselection in Radical Addition to α-Methylenebutyrolactones

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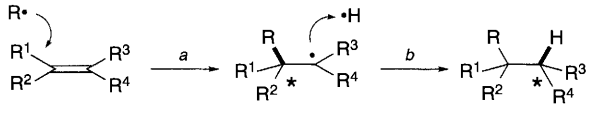
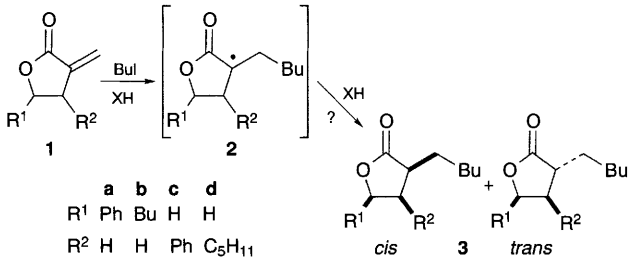
Some β- or γ-substituted α-methylenebutyrolactones are butylated with BuI and $(Me_3Si)_3SiH$ to give *cis*-α,β- or -α,γ-disubstituted lactones in high selectivities, while the same reaction with Bu_3SnH in the presence of bulky Lewis acid reverses the stereoselectivity to give a *trans*-disubstituted lactone as the major product.

Much interest in the diastereoselectivity of radical reactions, typically carried out with an alkyl halide, Bu_3SnH, and an alkenic substrate, has been focussed on the C–C bond formation step (*a* in Scheme 1), but not on the final C–H bond formation (step *b*).[1] even though the latter step also creates a new stereogenic centre. Cyclic α-methylene carbonyl compounds have been studied in detail in conjunction with step *b*, owing to their easy accessibility and applicability for the synthesis of naturally occurring products.[2] However, even for these substrates, the influence of an incoming alkyl radical and the ring substituent(s) was emphasized, and modification of reagents, such as the hydrogen radical donor or the additive, has not been investigated as a method of altering the stereoselectivity. We report here that the selectivity of radical transfer to some types of α-methylenebutyrolactones **1a–d**[3] (Scheme 2) can in fact, be significantly affected by the appropriate choice of such external reagents.

The reaction of **1a** with BuI in the presence of Bu_3SnH afforded **3a** with the *cis*:*trans* ratio ranging from 80:20 to 90:10 (Scheme 2, and entries 1–3 in Table 1).[1,4] The *cis* preference, determined at the step of the hydrogen radical transfer from Bu_3SnH to the intermediate α-carbonyl radical **2**, seems to increase as the reaction temperature decreases. Alternatively, treatment of **1a** with BuI and a Zn–Cu couple in aqueous ethanol (entry 4),[5] which should involve hydrogen radical delivery from the solvent, resulted in no improvement of the diastereoselectivity as compared to the former method. To test the feasibility of using another hydrogen radical donor, we chose $(Me_3Si)_3SiH$,[6] which is commercially available and is a recommended reagent as a less toxic alternative to Bu_3SnH. Gratifyingly, simple substitution of Bu_3SnH by $(Me_3Si)_3SiH$ as XH increased the diastereoselectivity from 80:20 (entry 1) to 98:2 (entry 5), even at the temperature of refluxing benzene! Control experiments verified that no *cis–trans* equilibrium of the product **3a** had occurred during the reaction so that this high *cis*:*trans* ratio was attributable to a kinetic delivery of hydrogen radical from $(Me_3Si)_3SiH$ to **2a**. The more sterically demanding



Scheme 1



Scheme 2

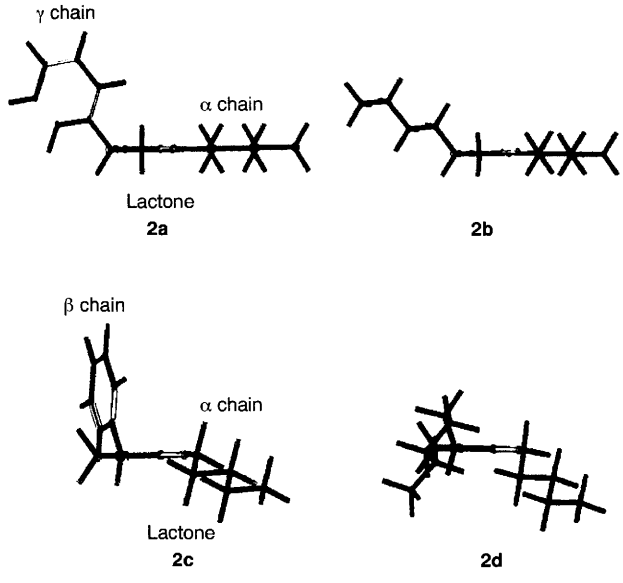


Fig. 1 Molecular structures of **2a–d**

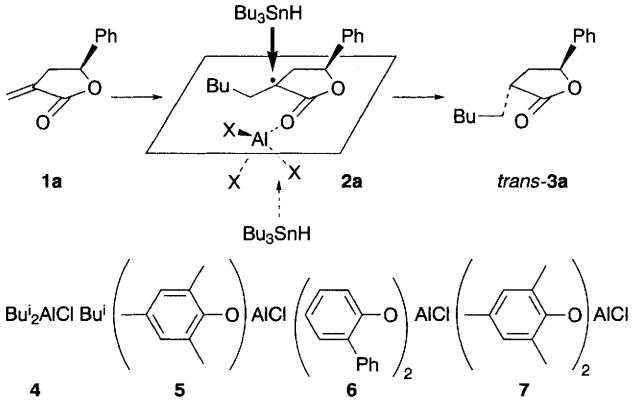
Table 1 Addition of Bu^t/H$^•$ to α-methylenebutyrolactone **1**[a]

Entry	1	XH/initiator	Conditions	3 *cis*:*trans*[b,c]	3 Yield (%)[b,d]
1	a	Bu_3SnH/AIBN	C_6H_6, reflux	80:20	63
2		Bu_3SnH/Et_3B	C_6H_5Me, 0 °C	81:19	51
3		Bu_3SnH/Et_3B	C_6H_5Me, −50 °C	90:10	44
4		Zn(Cu)[e]	EtOH–H_2O, room temp.	84:16	21
5		$(Me_3Si)_3SiH$/AIBN	C_6H_6, reflux	98:2	60 (60)
6	b	Bu_3SnH/AIBN	C_6H_6, reflux	51:49	41
7		$(Me_3Si)_3SiH$/AIBN	C_6H_6, reflux	78:22	62–65 (53)
8	c	Bu_3SnH/AIBN	C_6H_6, reflux	66:34	60
9		$(Me_3Si)_3SiH$/AIBN	C_6H_6, reflux	92:8–94:6	64 (60)
10	d	Bu_3SnH/AIBN	C_6H_6, reflux	24:76	65
11		$(Me_3Si)_3SiH$/AIBN	C_6H_6, reflux	37:63	52 (54)

[a] See Scheme 2. Reactant ratio of **1**: BuI : Bu_3SnH [or $(Me_3Si)_3SiH$] : Et_3B = 1 : 3 : 3 : 0.3. AIBN in a catalytic amount. Concentration of **1** *ca.* 0.1 mol dm^{-3}. [b] Determined by ^{1}H NMR analysis. [c] Structural assignments were made in comparison with authentic samples prepared independently. [d] Isolated yields in parentheses. [e] Under sonication.

character of $(Me_3Si)_3SiH$ than Bu_3SnH could account for the higher selectivity.[7] Other α-methylenebutyrolactones **1b** and **c** also afforded *cis*-**3b** and -**3c**, apparently in higher selectivities, with $(Me_3Si)_3SiH$ (entries 6–9). However, one exceptional case is β-alkyl-α-methylenebutyrolactone **1d**, which gave *trans*-**3d** as the major product (entries 10–11). This anomalous behaviour of **1d** may be explained in terms of the molecular shape of the intermediate **2d**, which has been calculated† and is shown in Fig. 1 together with those of **2a–c**. The β- or γ-substituent of **2a–c** definitely blocks only one face of the lactone ring against the hydrogen radical delivery from XH, while in radical **2d**, the α-pentyl and β-pentyl groups each cover both sides of the lactone ring, and the former seems to have the prevailing effect. This would account for the above *trans*-selectivity and the small change in the diastereoselectivity in switching the reagent from Bu_3SnH to $(Me_3Si)_3SiH$.

Having succeeded in achieving a highly selective synthesis of *cis*-disubstituted butyrolactones, we then turned our attention to the reversal of this selection. The formation of *trans*-butyrolactone requires a delivery of hydrogen radical from the same face as the lactone substituent. It occurred to us that the presence of a bulky Lewis acid[8,9] in the radical reaction of **1a** would alter the reaction course, as illustrated in Scheme 3. Thus, the Lewis acid coordinates to the carbonyl oxygen of **2a** from the less hindered face (*i.e.* opposite to the lactone substituent)[10] and forces the incoming hydrogen donor to attack at the face where the lactone substituent is located. Several aluminium compounds such as **4–7**‡ (1.1 equiv. **1a**) were examined as Lewis acids. The reactions were carried out under similar conditions to those used for entry 3, Table 1 and the product **3a** was obtained in the following yields and *cis*:*trans* ratios: no Lewis acid; 44%, 90:10; **4**: 58%, 57:43; **5**: 55%, 46:54; **6**: 95%, 43:57; **7**: 91%, 40:60. In accord with our expectation, increasing the bulkiness of the Lewis acid enhanced the *trans*-selectivity of the product **3a**, and, eventually, **7** reversed the forementioned *cis*-selectivity to give *trans*-**3a** as the major product.



Scheme 3

These methods for the external control of the stereochemistry at the α-position of a butyrolactone will be applicable to other related substrates and reactions. Study along this line is now in progress.

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Footnotes

† Calculation was done with MOPAC/PM3. The most stable conformers are shown in Fig. 1. Consideration of these conformers was judged to be sufficient for our discussion.

‡ Compounds **5–7** were prepared *in situ* from Bu^i_2AlCl and the appropriate phenol.

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