Relative Reactivities of Acetals and Ethers under Friedel-Crafts Conditions

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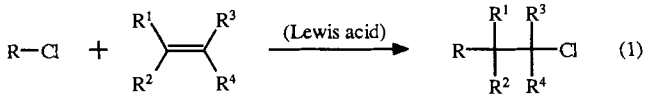
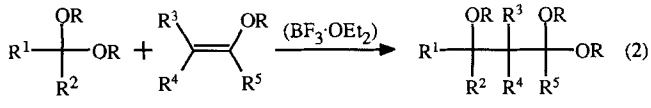
Competition experiments have been performed to determine the relative reactivities of acetals and ethers toward allyltrimethylsilane in the presence of catalytic amounts of $BF_3 \cdot OEt_2$. It is found that acetals $R-CH(OMe)_2$ and their phenylogous *p*-anisyl ethers $R-CH(p\text{-}MeOC_6H_4)(OMe)$ show very little differences in reactivity. The reactivity scales are employed to rationalize the results of Lewis acid-catalyzed additions of acetals and ethers to CC double bonds.

In the preceding article, we have shown that the electrophilicities of alkyl chlorides in the presence of catalytic amounts of Lewis acids are proportional to their solvolysis rates in ethanol[1]. This correlation represents a quantitative basis for our working hypothesis that alkylations according to eq. (1) can only give 1:1 adducts if the reactants RCl solvolyze faster than the products. Since solvolysis rate constants for most types of alkyl chlorides are known, the synthetic potential of reaction (1) can easily be predicted.



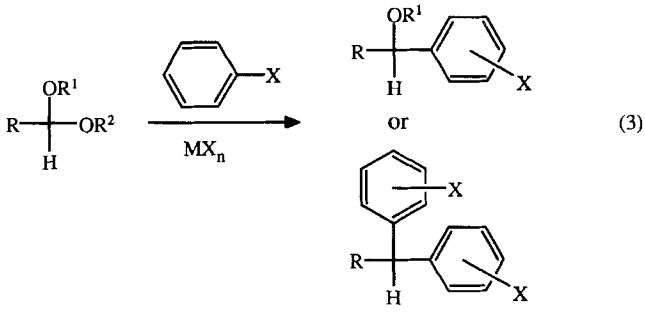
(1)

An analogous analysis of the outcome of acetal and ortho ester additions is not possible, as their solvolyses require acid catalysis, and the rate constants for the proton-catalyzed hydrolysis are not only a function of the Lewis acidity of the intermediate carboxonium ions. We had, therefore, investigated the relative reactivities of acetals and ortho esters towards methyl vinyl ether in the presence of $BF_3 \cdot OEt_2$ by competition experiments[2]. The reactivity scale, thus obtained, allowed the rationalization of the large manifold of alkoxyalkylations of vinyl ethers (eq. 2)[2].

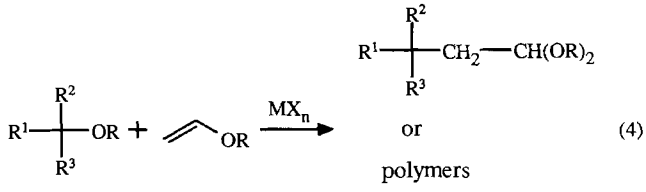


(2)

Since this reactivity series was restricted to acetals and ortho esters and did not include ethers, it did not allow predictions whether Lewis acid-catalyzed reactions of acetals with arenes yield benzyl ethers or 2:1 products arising from reactions with two arene molecules (eq. 3) and whether it was possible to produce acetals by reactions of ordinary ethers with enol ethers (eq. 4).



(3)



(4)

Results

The acetals and ethers listed in Table 1 react with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ to give 51–88% (isolated yield) of the expected S_E2' products, some of which have been described in ref.[1,3] Competition experiments, as described for alkyl chlorides in the preceding article[1], have been used to determine the relative reactivities of acetals and ethers in presence of $BF_3 \cdot OEt_2$ (Scheme 1).

Table 1 shows that aromatic acetals and benzhydryl ethers possess comparable reactivities. Since not all competition constants given in Table 1 are linked with each other, they can not be combined to give a single reactivity scale. This goal can be achieved by relating these data to the rela-

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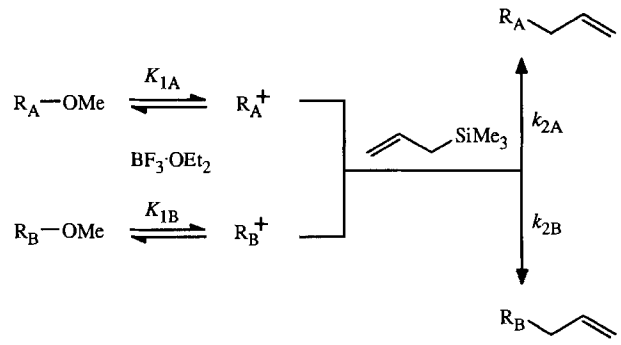
Scheme 1



tive reactivities of alkyl chlorides from ref.[1] as described below.

Table 1. Competition constants for the $BF_3 \cdot OEt_2$ – catalyzed reactions of acetals and ethers with allyltrimethylsilane in CH_2Cl_2 at −70°C

	Reactant A		Reactant B	$\kappa_{A/B}$
1	(p-$MeOC_6H_4$) $CH(OMe)_2$	2	(p-$MeOC_6H_4$)$_2$ CHOMe	1.5 ± 0.1
1	(p-$MeOC_6H_4$) $CH(OMe)_2$	3	(p-MeC_6H_4) $CH(OMe)_2$	3.4 ± 0.1
2	(p-$MeOC_6H_4$)$_2$ CHOMe	3	(p-MeC_6H_4) $CH(OMe)_2$	2.3 ± 0.1
3	(p-MeC_6H_4) $CH(OMe)_2$	4	C_6H_5 $CH(OMe)_2$	4.3 ± 0.3
3	(p-MeC_6H_4) $CH(OMe)_2$	4	C_6H_5 $CH(OMe)_2$	3.1 ± 0.2[a]
5	(p-ClC_6H_4) $CH(OMe)_2$	6	(p-MeC_6H_4)$_2$ CHOMe	9.5 ± 0.3
6	(p-MeC_6H_4)$_2$ CHOMe	9	(p-MeC_6H_4) (C_6H_5) CHOMe	12.0 ± 0.6[a]
7	n-C_3H_7-$CH(OMe)_2$	8	$(\overline{CH_2})_2$-CH=CH-$\dot{C}$HOMe	5.6 ± 0.1

[a] Lewis acid $ZnCl_2 \cdot OEt_2$ instead of $BF_3 \cdot OEt_2$.

Let us assume that the reactions described in Scheme 1 involve a rapid preequilibrium[5]. As discussed in ref.[1], the competition constant is then given by eq. (5), where equilibrium and rate constants have the meaning defined in Scheme 1.

$$\kappa_{AB} = \frac{K_{1A}k_{2A}}{K_{1B}k_{2B}} \qquad (5)$$

Since in several examples the rate constants for the reactions of carbenium ions with π nucleophiles (k_{2A}, k_{2B}) have been found to be independent of the counterion[4], K_{1A} and K_{1B} are the only quantities in eq. (5) that are leaving group-dependent. As the ratios of two ionization constants (K_{1A}/K_{1B}) have been shown to be leaving group-indepedent if variable steric or anomeric effects are absent[7], κ_{AB} will be approximately equal for corresponding pairs of alkyl chlorides and methyl ethers. This conclusion is corroborated by comparison of the entry before last in Table 1 (κ_{AB} = 12.0) with the relative reactivity of the corresponding benzhydryl chlorides (κ_{AB} = 14.2[1]). By assuming the relative reactivities of (p-$MeOC_6H_4$)$_2$CHOMe/(p-MeC_6H_4)$_2$CHOMe and (p-MeC_6H_4)$_2$CHOMe/3-methoxycyclopentene to be 126 and 22.1, respectively, as determined for the corresponding

Scheme 2. Relative reactivities of acetals and ethers towards allyltrimethylsilane (CH_2Cl_2, −70°C)

		Compound	k_{rel}
126[a]	1	(p-$MeOC_6H_4$)$CH(OMe)_2$	4.19 x 10^3
	2	(p-$MeOC_6H_4$)$_2$CHOMe	2.79 x 10^3
	3	(p-MeC_6H_4)$CH(OMe)_2$	1.27 x 10^3
	4	$C_6H_5CH(OMe)_2$	3.02 x 10^2
	5	(p-ClC_6H_4)$CH(OMe)_2$	2.08 x 10^2
	6	(p-MeC_6H_4)$_2$CHOMe	2.21 x 10^1
22.1[a]	7	n-C_3H_7-$CH(OMe)_2$	5.60
	8	$(\overline{CH_2})_2$-CH=CH-$\dot{C}$HOMe	1

[a] Relative reactivities of the corresponding chloro compounds; see text.

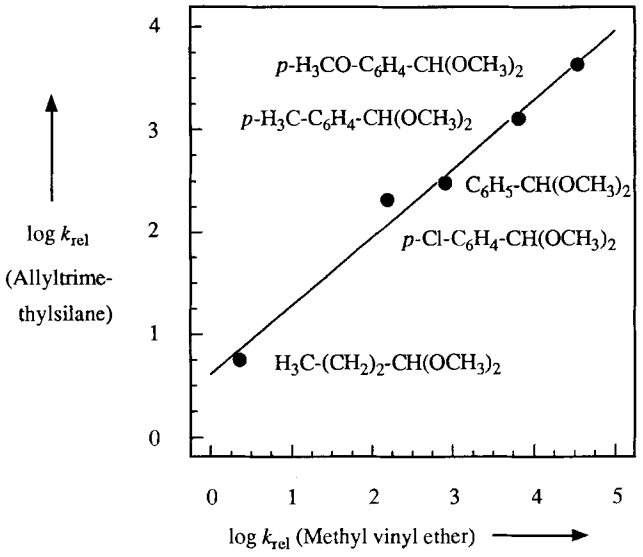


Figure 1. Correlation of the relative reactivities of acetals towards allyltrimethylsilane and methyl vinyl ether ($BF_3 \cdot OEt_2$, CH_2Cl_2, −70°C)

chloro compounds[1], the data of Table 1 can be connected to give the reactivity scale of Scheme 2.

The relative reactivities of the acetals listed in Scheme 2 can be compared with the relative reactivities of these compounds toward methyl vinyl ether as reference nucleophile[2]. Figure 1 shows a fairly good correlation between the two sets of data, and the correlation equation (6) indicates that variation of the acetal has a greater effect on the reactivity toward methyl vinyl ether than on the reactivity toward allyltrimethylsilane.

$$\log k_{rel}\,(\text{allyltrimethylsilane}) = 0.687 \log k_{rel}\,(\text{methyl vinyl ether}) + 0.49 \qquad (6)$$

Equation (6) now allows to adjust von der Brüggen's reactivity scale for acetals toward methyl vinyl ether[2] to the

scale of Scheme 2. Combination with some additional k_{rel} values for alkyl chlorides[1] as discussed above yields the electrophilicity scale of Figure 2. Because of the approximations necessary for its construction, this scale is less precise than that presented for alkyl chlorides in the preceding paper[1]. It may be more valuable for the synthetic chemist, however, because this reactivity order cannot be derived from readily available data (as solvolysis rates in the case of alkyl chlorides).

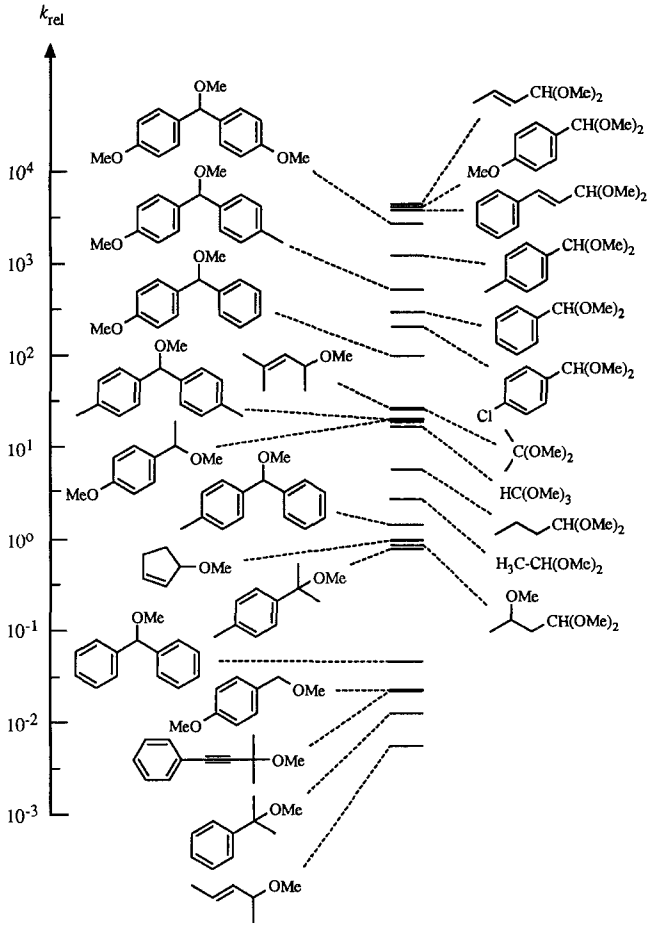


Figure 2. Relative reactivities of ethers and acetals towards allyltrimethylsilane (CH_2Cl_2, $-70°C$)

Consequences for Organic Synthesis

The relative reactivities of acetals in Figure 2 have already been used to explain, why the reactions of benzaldehyde acetals and of α,β-unsaturated acetals with alkyl vinyl ethers give better yields of 1:1 products than the corresponding reactions of saturated acetals[2]. Similarly, we have rationalized why only methoxy-substituted benzaldehyde acetals and α,β-unsaturated acetals had been reported to give 1:1 products with 1-alkoxy-1,3-butadienes[2].

The reactions of benzaldehyde dimethyl acetal with isobutene or styrene give products which incorporate a tert. alkyl ether and/or an α-phenyl alkyl ether substructure (Scheme 3). The isolation of such products is possible[8] since tert. alkyl ethers and α-phenyl alkyl ethers are even less reactive than the least reactive compounds depicted in Figure 2[1]. For the same reason, homoallylic ethers are produced in high yields from acetals and allylsilanes by the Hosomi-Sakurai reaction[9].

Scheme 3

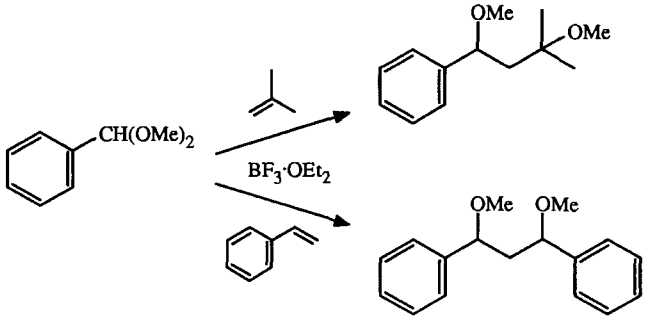
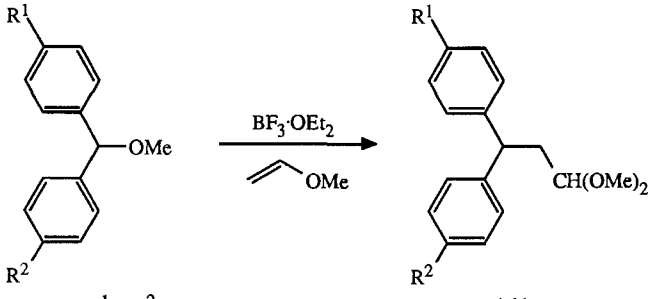


Figure 2 suggests dianisylmethyl- and ditolylmethyl methyl ether to be more reactive than saturated acetals. Consequently, we have now succeeded to combine these ethers with methyl vinyl ether to produce the acetals as shown in Scheme 4.

Scheme 4



2: $R^1 = R^2 = OMe$ yield: 51 %
6: $R^1 = R^2 = Me$ 62 %

In contrast, the corresponding reaction of methyl phenyl-*p*-tolylmethyl ether with methyl vinyl ether gave polymeric vinyl ether predominantly (^1H NMR). In accord with Figure 2, the resulting saturated acetals are more reactive than methyl phenyl-*p*-tolylmethyl ether, and the 1:1 products are, therefore, not isolable.

The reaction of *p*-anisaldehyde acetal with anisole gives a benzhydryl ether which is predicted by Figure 2 to possess a similar reactivity as the reactant acetal. The corresponding reaction gave only tris(*p*-anisyl)methane, and we have not been able to isolate the intermediate bis(*p*-anisyl)methyl methyl ether. On the other hand, Figure 2 predicts that a benzhydryl ether should be isolable from the reaction of benzaldehyde acetal with toluene. Our attempts to realize this reaction failed, however; disproportionation of the acetal turned out to be faster than the electrophilic aromatic substitution, probably because of the low nucleophilicity of toluene.

Conclusion

The reactivity scale shown in Figure 2 may serve as a guide for rationalizing and designing acetal and ether additions to CC double-bonded compounds. It should be noted, however, that it is not applicable to reactions with silylated enol ethers since in these cases rapid desilylation of the 1:1 adducts prevents sequential reactions and the formation of higher adducts.

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Experimental

General: See ref.[1]. – *Reaction products:* The products obtained by reaction of diarylmethoxymethanes and allyltrimethylsilane are identical to those formed by the analogous reactions with diarylchloromethanes and have been described in ref.[1]

For the reactions of aromatic acetals with allyltrimethylsilane, the procedure described in ref.[3] has been used: A solution of the acetal (2.00 g) in CH_2Cl_2 (4.5 ml) was added dropwise (15 min) to a cooled (−78°C, N_2 protection) mixture of allyltrimethylsilane (1.5 equivalents), CH_2Cl_2 (1 ml), and trimethylsilyl triflate (0.15 equivalents). After completion of the reaction the mixture was washed with an equal volume of concd. aqueous ammonia. The phases were separated, the organic layer was dried with $CaCl_2$ and evaporated.

Reaction with *benzaldehyde dimethyl acetal* (**4**): See ref.[3,10].

p-Anisaldehyde Dimethyl Acetal (**1**) (2.00 g, 11.0 mmol) and allyltrimethylsilane (1.88 g, 16.5 mmol) reacted within 2 h under the conditions described above to give 1.38 g (65%) of 4-methoxy-4-(4-methoxyphenyl)-1-butene with b.p. 58°C (bath)/0.15−0.2 mbar. – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.47 (mc, 2H, 3-H), 3.20 (s, 3H, 4-OCH_3), 3.82 (s, 3H, Ar-OCH_3), 4.12 (t, *J* = 8 Hz, 1H, 4-H), 4.88−5.18 (m, 2H, $=CH_2$), 5.51−6.03 (m, 1H, =CH−), 6.86, 7.22 (AA'BB' system, J_{AB} = 8 Hz, 4H, aromatic H). – The ^{1}H-NMR spectrum is in accord with the data in ref.[10].

p-Tolylaldehyde Dimethyl Acetal (**3**) (2.00 g, 12.0 mmol) and allyltrimethylsilane (2.05 g, 18.0 mmol) reacted within 2 h under the conditions described above to give 1.70 g (80%) of 4-methoxy-4-(4-methylphenyl)-1-butene with b.p. 60−63°C (bath)/1 mbar. – ^{1}H NMR (90 MHz, CCl_4): δ = 2.30 (s, 3H, CH_3), 2.37 (mc, 2H, 3-H, superimposed by the singlet at 2.30), 3.12 (s, 3H, 4-OCH_3), 4.00 (t, *J* = 8 Hz, 1H, 4-H), 4.78−5.12 (m, 2H, $=CH_2$), 5.43−5.96 (m, 1H, =CH−), 7.05 (s, 4H, aromatic H).

4-Chlorobenzaldehyde Dimethyl Acetal (**5**) (2.00 g, 10.7 mmol) and allyltrimethylsilane (1.83 g, 16.0 mmol) reacted within 3 h under the conditions described above to give 1.84 g (88%) of 4-(4-chlorophenyl)-4-methoxy-1-butene with b.p. 76°C (bath)/1.5 mbar. – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.48 (mc, 2H, 3-H), 3.25 (s, 3H, 4-OCH_3), 4.18 (t, *J* = 8 Hz, 1H, 4-H), 4.90−5.20 (m, 2H, $=CH_2$), 5.51−6.03 (m, 1H, =CH−), 7.28 (mc, 4H, aromatic H).

4-Methoxy-1-heptene was synthesized from butyraldehyde dimethyl acetal (**7**) and allyltripropylsilane (instead of allyltrimethylsilane) to facilitate distillative workup of the reaction mixture (see ref.[1]): After dropwise addition (15 min) of **7** (1.14 g, 9.65 mmol) to a cooled (−78°C, N_2 protection) solution of $TiCl_4$ (1.07 ml, 9.76 mmol) in CH_2Cl_2 (30.0 ml), a mixture of allyltripropylsilane (2.12 g, 10.7 mmol) and CH_2Cl_2 (15 ml) was added dropwise within 1 h. The mixture was allowed to react for 3 h and was then washed with 5 N HCl (60 ml). The phases were separated, and the organic layer was dried with $CaCl_2/K_2CO_3$ and evaporated. Twofold distillation yielded 680 mg (55%) of 4-methoxy-1-heptene with b.p. 65°C (bath)/91 mbar. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.86−0.99 (m, 3H, 7-H), 1.26−1.57 (m, 4H, 5-H, 6-H), 2.22−2.34 (m, 2H, 3-H), 3.14−3.31 (m, 1H, 4-H), 3.35 (s, 3H, OCH_3), 5.02−5.13 (m, 2H, $=CH_2$), 5.72−5.94 (m, 1H, =CH−). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.21 (q, C-7), 18.52 (t, C-6), 35.63, 37.78 (2 t, C-3, C-5), 56.55 (q, OCH_3), 80.27 (d, C-4), 116.73 (t, $=CH_2$), 135.00 (d, =CH−). – MS (70 eV), *m/z* (%) = 87 (56), 85 (19), 55 (30), 45 (100), 41 (29). The M^+ peak could not be detected.

Methoxybis(4-methoxyphenyl)methane (**2**) *and Methyl Vinyl Ether:* Compound **2** (260 mg, 1.01 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml) and the solution cooled at −78°C (N_2 protection). After addition of $BF_3 \cdot OEt_2$ (50 µl, 0.4 mmol), a solution of methyl vinyl ether (92.8 mg, 1.65 mmol) in CH_2Cl_2 (25 ml) was added dropwise within 30 min. After 24 h the mixture was washed with an equal volume of dil. aqueous ammonia. The phases were separated, the organic layer was dried with $CaCl_2$ and the solvent evaporated in vacuo. Filtration over Al_2O_3 (neutral) with hexane/ether (80:20) and removal of solvents (0.1 mbar) yielded 160 mg (51%) of 3,3-bis(4-methoxyphenyl)propionaldehyde dimethyl acetal as a viscous oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (dd, J_{12} = 5.9, J_{23} = 8.0 Hz, 2H, 2-H), 3.27 (s, 6H, 1-OCH_3), 3.72 (s, 6H, aryl-OCH_3), 3.99 (t, J_{23} = 8.0 Hz, 1H, 3-H), 4.15 (t, J_{12} = 5.9 Hz, 1H, 1-H), 6.80, 7.14 (AA'BB' system, J_{AB} = 8.7 Hz, 8H, aromatic H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.61 (t, C-2), 44.02 (d, C-3), 51.67 (q, OCH_3), 54.13 (q, aryl-OCH_3), 101.84 (d, C-1), 112.88 (d, C_m), 127.59 (d, C_o), 135.93 (s, C_i), 156.96 (s, C_p). – $C_{19}H_{24}O_4$ (316.4): calcd. C 72.13, H 7.65; found C 71.75, H 7.58.

Methoxybis(4-methylphenyl)methane (**6**) (230 mg, 1.02 mmol) and methyl vinyl ether (92.8 mg, 1.60 mmol) were combined analogously to yield 180 mg (62%) of 3,3-bis(4-methylphenyl)propionaldehyde dimethyl acetal as a viscous oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 6H, CH_3), 2.30 (dd, partially masked, J_{12} = 5.9, J_{23} = 8.0 Hz, 2H, 2-H), 3.27 (s, 6H, OCH_3), 4.02 (t, J_{23} = 8.0 Hz, 1H, 3-H), 4.17 (t, J_{12} = 5.9 Hz, 1H, 1-H), 7.06, 7.13 (AA'BB'

Table 2. Determination of the competition constants in CH_2Cl_2 (10 ml) at −70°C

R_AOMe / mg		R_BOMe / mg	AS[a] / mg	[LA]/[R_AOMe]$_0$[b] (molar ratio)	[P_A]/[P_B] (molar ratio)	Time	Standard[c]	$k_{A/B}$
1 35.9	2	24.0	57	0.60	3.00	61 min	PPR	1.4
23.9		51.6	57	0.60	1.02	61 min	PPR	1.6
1 21.3	3	19.2	57	0.84	3.75	61 min	PPR	3.45
20.7		39.6	57	0.84	1.34	61 min	PPR	3.35
2 22.2	3	74.5	57	1.46	0.40	61 min	PPR	2.3
23.5		168.6	57	1.46	0.18	61 min	PPR	2.2
3 23.6	4	104.1	57	1.12	0.65	61 min	PPT	4.0
24.3		161.3	57	1.12	0.51	61 min	PPT	4.5
3 21.6	4	118.6	5.7	1.60[d,e]	0.46	63 h	PPT	2.9
22.2		204.1	5.7	1.60[d,e]	0.32	63 h	PPT	3.3
5 21.2	6	22.0	57	1.22	8.30	61 min	PPT	9.2
20.4		84.1	57	1.22	2.35	61 min	PPT	10.0
25.7		167.8	57	1.22	1.42	61 min	PPT	9.2
6 23.6	9	106.8	5.7	1.60[d,e]	--	90 h	PO	11.4
24.0		195.1	5.7	1.60[d,e]	--	90 h	PO	12.6
7 17.1	8	15.9	358	5.50	5.02	60 min	C	5.8
18.6		35.0	358	5.50	2.50	60 min	C	5.5
16.0		61.6	358	5.50	1.16	60 min	C	5.5

[a] AS = allyltrimethylsilane. – [b] Lewis acid (LA) is $BF_3 \cdot OEt_2$. – [c] HPLC analysis apart from the **7**/**8** couple which was analyzed by GC. Standards: C = cumene, PO = 1-phenyloctane, PPR = 1-phenylpropane, PPT = 1-phenylpentane. – [d] 5 ml of CH_2Cl_2. – [e] Lewis acid is $ZnCl_2 \cdot (OEt_2)_{1.03}$.

system, J_{AB} = 8.1 Hz, 8H, aromatic H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.11 (q, CH_3), 38.45 (t, C-2), 46.05 (d, C-3), 52.81 (q, OCH_3), 102.92 (d, C-1), 127.85 (d, C_o), 129.35 (d, C_m), 135.78 (s, C_p), 141.81 (s, C_i). – $C_{19}H_{24}O_2$ (284.4): calcd. C 80.24, H 8.51; found C 80.12, H 8.63.

Competition Experiments have been performed as described in ref.[1] by using $BF_3 \cdot OEt_2$ instead of $ZnCl_2$.

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