

Use of Competition Kinetics with Fast Reactions of Grignard Reagents

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Competition kinetics are useful for estimation of the reactivities of Grignard reagents if the reaction rates do not differ widely and if exact rates are not needed. If the rate of mixing is slower than the rate of reaction, the ratios between the rates of fast and slow reagents are found to be too small. This is concluded from experiments in which results obtained by competition kinetics are compared with results obtained directly by flow stream procedures. A clearer picture of the reactivity ratios is obtained when the highly reactive reagent is highly diluted with its competitor. A fast reagent may account for almost all the product even when present as only 1 part in 100 parts of the competing agent. In this way allylmagnesium bromide is estimated to react with acetone, benzophenone, benzaldehyde, and diethylacetaldehyde ca. 1.5×10^5 times faster than does butylmagnesium bromide. The rates found for the four substrates do not differ significantly, and it seems possible that there is a ceiling over the rate of reaction of this reagent, for example, caused by diffusion control. This may explain that competition kinetics using allylmagnesium bromide have failed to show kinetic isotope effects or effects of polar substituents with isotopically or otherwise substituted benzophenones. A recently reported α -deuterium secondary kinetic isotope effect for the reaction of benzaldehyde with allylmagnesium bromide was observed at -78°C , but was absent at room temperature. It is suggested that the reaction of benzophenone and benzaldehyde with allylmagnesium bromide has a radical-concerted mechanism since no radical-type products are produced and since no color from an intermediate ketyl is observed even at -78°C .

Introduction

Fast Grignard reactions usually have been measured by flow methods of various types.^{1,2} This is convenient if the half-life for the reaction is more than 5 ms. Reactions 10 or 20 times faster may still be measured, but flow methods are then time-consuming, require delicate apparatus, and are inaccurate. It would be convenient to find reaction rates for fast reagents by comparison with well-known rates of less reactive reagents. As shown by Felkin and Frajerman,³ this is, however, not a straightforward procedure. When they allowed allylic Grignard reagents to react with acetone in competition with propylmagnesium bromide, the results were not consistent. The reason was that reactions of the allylic reagents were much faster than the mixing process, so that the reactions were mixing controlled.

When competition kinetics were first introduced in 1926, Francis⁴ explained that the method is unreliable when very fast reagents are used. The ratio between the products from the two competing reactions tends to be statistically controlled, that is, they are determined by the concentrations of the competing reagents, rather than kinetically controlled by the reactivity of the competing reagents. The reason for this is that when the two solutions obtain contact in the initial phase of mixing, the highly reactive reagent is depleted locally. This gives

the less reactive reagent the chance to get more than its fair share of the substrate.⁵

Felkin improved his measurements by adding the acetone as vapor, highly diluted with nitrogen. While the relative reactivities for allyl- and propylmagnesium bromide were found by simple mixing (dropwise, magnetic stirring) to be 7:1, this ratio changed to 700:1 by using the slow addition. Felkin also compared the reactivities of allyl-, crotyl-, and 2-pentenylmagnesium bromide toward both acetone and methyloxirane and since he did not obtain results which were mutually consistent, he knew that the results were improved, but not correct.

Mixing control corrupts the results of competition kinetics when a very fast reaction is compared with a slow reaction. In this case the rate ratio found is much lower than the true ratio. Dilution of the substrate, as in Felkin's case, improves the results and indicates higher rate ratios, but the extreme reactivity of allylmagnesium bromide is seen only when it competes with other fast Grignard reagents. Diluted 1:140 with benzylmagnesium bromide, allylmagnesium bromide still consumes 97% of the test substrate benzophenone (see below).

The purpose of the present work has been to check the reliability of competition kinetics with Grignard reagents by comparing rate measurements made by competition methods with reaction rates already measured by flow stream procedures. The investigation was thought to be important since competition kinetics has been widely

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used for mechanistic purposes, for example, for obtaining kinetic isotope effects.⁶⁻⁸

Discussion

Nature of the Grignard Reagent. Grignard reagents are complex mixtures of the Schlenk components dialkylmagnesium, alkylmagnesium halide, and magnesium halide, which are solvated with ether and are in a fluxional state in which the magnesium ligands, alkyl groups, halide ions, and solvent molecules are exchanged in very fast equilibria.^{9,10} It is obvious that the simplest competition experiment would be to add a very low concentration of a substrate to a large excess of two competing Grignard reagents. This procedure may be called an SD (substrate deficiency) experiment. Using SD, the constitution of the Grignard reagents will be very little influenced by the presence of the substrate and the reaction products. It is unavoidable, however, that the two Grignard reagents exchange ligands and, for example, form the mixed dialkylmagnesium. For this reason, exact results should not be expected and reaction rates determined by competition are bound to differ from rates determined directly.

When the reactivities of two substrates toward the same Grignard reagent are to be compared, a small concentration of the Grignard reagent is added to an excess of the competing substrates, a GD (Grignard deficiency) experiment. The constitution of the Grignard reagent is, however, changed when it is added to an excess of a typical substrate (ketone, ester, etc.), because of the fast coordination equilibria. Alkoxides formed in the reaction likewise tie up active alkyl to give complexes of low reactivity. The results therefore do not pertain to the reactivity of the Grignard reagents as such, and there may even be a change of mechanism when going from SD to GD conditions.

An alternative way to obtain competition between two substrates is to react a highly diluted solution containing both the competing substrates with a normal concentration of the Grignard reagent for a short time, for example, by quenching the reaction mixture, a TD (time deficiency) experiment. The carbonyl carbon kinetic isotope effect in benzophenone reacting with *tert*-butylmagnesium chloride has been determined by both methods, and while no effect was observed⁶ when using GD, a significant effect was found⁷ using TD.

Competition kinetics with highly reactive reagents as mentioned above require the use of very low concentrations of the substrate. A limit to the degree of dilution is, however, set by the possibility of measuring the product distribution. The reaction mixture has to be concentrated and the various and inevitable impurities in the Grignard reagent tend to dominate in the GC analysis.

Mixing Process. Flow stream reactivity measurements have been performed for the reaction of many Grignard reagents in the reaction with a variety of

substrates. In a few cases rates have been measured for reactions with half-lives as short as 40 μs .¹¹ In such experiments the reacting solutions were forced into the mixing "T" under high pressure (5–7 bar), producing a liquid speed in the 0.22 mm reaction tube of 14 000 mm s^{-1} . Mixing took place in two phases, the first of which was the production of an emulsion and the second of which was the homogenization of the emulsion by diffusion. If the liquids had different refractive indexes, the emulsion phase could be observed in the glass mixing chamber as an opalescent cone which in the described experiment had a length of 0.5 mm corresponding to a mixing time of 35 μs . The very fast mixing is possible because of the low viscosity of ether; for aqueous solutions 1000 μs is considered very fast mixing.¹²

Mixing in the flow stream mixing chamber under these conditions is very much faster than, for example, mixing by pouring one solution into another. Since the separation of the mixing phase and the reaction phase is required if the true reaction rates are to be obtained, the high-speed experiments are a valuable "answer book" when the results from competition kinetics are to be evaluated. This is true even if the high-speed results are very crude, being based on a single reading of the temperature increase after a reaction time of 80 μs .

Results

SD Experiments. It has been found in the experiments reported here that if moderately reactive reactants and dilute substrate solutions are used, reaction rates found by competition kinetics correspond fairly well with rates obtained by flow stream methods, and the results are to some extent mutually consistent. With highly reactive Grignard reagents such as allylmagnesium bromide, or with highly reactive substrates such as α,β -unsaturated ketones, the rate ratios between the fast and the slow reagents found in this way are much smaller than the true values. High dilution of the test reagent improves the results, but the rate ratios measured are still much too low.

In Table 1 are shown rate data for benzophenone reacting with a series of Grignard reagents. The relative rate for each reagent was found in competition with benzylmagnesium bromide, but the table, for convenience, gives the rates relative to the rate for methylmagnesium bromide.

In Table 2 are shown the ratios between the reaction rates of methylmagnesium bromide and some alkylmagnesium bromides as calculated from the product ratios when the two Grignard reagents in equal concentrations are competing for benzalacetophenone. It is obvious that the reactivities of the fast reagents have had an "unfair" competition and show too low reactivity. All though the order of increasing reactivity is the same in the two columns, experiments with other combinations of the reagents gave results which were not consistent. The rate ratio in the direct competition of isopropylmagnesium bromide and ethylmagnesium bromide was found, for example, to be 3.90, while the values in Table 2 would indicate a ratio of $470/240 = 1.96$. Direct competition between phenyl- and ethylmagnesium bromide gave a ratio of ethyl to phenyl of 6.9 against 7.3 from the values in Table 2.

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Table 1. Reaction Rates for Reaction of RMgBr with Benzophenone Relative to the Rate of Reaction of Methylmagnesium Bromide^a

RMgBr	$k_{\text{RMgBr}}/k_{\text{MeMgBr}}$		RMgBr	$k_{\text{RMgBr}}/k_{\text{MeMgBr}}$	
	competition kinetics	flow stream kinetics		competition kinetics	flow stream kinetics
CH ₃ MgBr	1	1	<i>i</i> -C ₃ H ₇ MgBr	58	70
C ₆ H ₅ MgBr	2	1	<i>t</i> -C ₄ H ₉ MgBr	100	89
C ₃ H ₇ MgBr	6.1	11	C ₆ H ₅ CH ₂ MgBr	98	303
C ₂ H ₅ MgBr	8.5	24			

^a Based on either competition experiments between 0.5 M RMgBr and 0.5 M C₆H₅CH₂MgBr reacting with benzophenone (10⁻³ M) or reported flow stream rate measurements.¹¹ The pseudo-first-order rate constants for the reaction of benzophenone with 0.5 M methylmagnesium bromide and 0.5 M benzylmagnesium bromide in ether are 0.3 and 91 s⁻¹, respectively.

Table 2. Reaction Rates for Reaction of RMgBr (0.25 M) with Benzalacetophenone (2 × 10⁻⁴ M) Relative to the Rate of Reaction of Methylmagnesium Bromide (0.25 M)^a

RMgBr	$k_{\text{RMgBr}}/k_{\text{MeMgBr}}$		RMgBr	$k_{\text{RMgBr}}/k_{\text{MeMgBr}}$	
	competition kinetics	flow stream kinetics		competition kinetics	flow stream kinetics
CH ₃ MgBr	1	1	C ₃ H ₇ MgBr	175	550
C ₆ H ₅ MgBr	33	55	C ₂ H ₅ MgBr	240	1050
<i>t</i> -C ₄ H ₉ MgBr	34	89	<i>i</i> -C ₃ H ₇ MgBr	470	1400

^a Based on either (1) competition experiments between RMgBr and CH₃MgBr (1:1) or (2) reported¹¹ flow stream rate measurements. The pseudo-first-order reaction constant for benzalacetophenone reacting with methylmagnesium bromide is 20 s⁻¹.

Table 3. Ratios between Rates of Reaction of 0.02 M *tert*-butylmagnesium Chloride with a solution of benzophenones 0.2 M in each^a

run	ketone 1	ketone 2	competition	flow stream
1	Ph ₂ CO	3-fluoro-Ph ₂ CO	1:4	1:9
2	Ph ₂ CO	4,4'-dimethyl-Ph ₂ CO	2.7:1	8.0:1
3	Ph ₂ CO	3-methoxy-4'-chloro-Ph ₂ CO	1:4	1:3.8
4	4,4'-dimethyl-Ph ₂ CO	3-methoxy-4'-chloro-Ph ₂ CO	1:6	1:31

^a Method: GC measurements of the 1,2-addition products.

Table 4. Product Distribution in by the Reaction of an Alkylmagnesium Bromide 10⁻³ M with 2 Competing Substrates in Ethereal Solutions, 0.5 M Each

	CH ₃ MgBr	C ₂ H ₅ MgBr	C ₆ H ₅ MgBr	CH ₂ =CHCH ₂ Br
PhCHO/PhCOPh	> 3000:1			1.9:1
Et ₂ CHCHO/PhCOPh				1.95:1
CH ₃ CO CH ₃ /PhCOPh				2:1
PhCHO/PhCH=CHCOPh	1.5:1			

More consistent results seem to be obtainable by taking the Grignard reagents in uneven concentrations. Using a 1:100 mixture of ethyl/methylmagnesium bromide, the ethyl adduct still accounts for 10 times as much of the product as the methyl adduct. Assuming first-order kinetics with respect to the Grignard reagents, the relative reactivity is therefore 1000:1, which is close to the flow stream results.

GD Experiments. GD may give misleading results even with rather slow reactions. When a millimolar solution of phenylmagnesium bromide reacted with a solution 1 M in acetone and 1 M in benzophenone, the product composition indicated a ratio between the rate of the two addition reaction of 4:1, while the rate constants for the two substrates reacting with phenylmagnesium bromide are 43 and 0.3 s⁻¹, a ratio of 143:1.

Rate ratios for the GD reactions of *tert*-butylmagnesium chloride with pairs of substituted benzophenones are given in Table 3 together with the ratios obtained from SD flow stream rate measurements. The Hammett ρ for the reaction was 3.0 using the flow stream values, but of the order of 1.5 using the competition experiments. The much lower Hammett ρ either may indicate a change in mechanism when going from SD to GD or may more likely be due to the leveling effect on the results caused by mixing control of these rather fast reactions. The

pseudo-first-order rate constant for 0.02 M *tert*-butylmagnesium chloride reacting with 0.25 M benzophenone in ether is 400 s⁻¹.

Reactions of Allylmagnesium Bromide. The reactivity of allylmagnesium bromide is extremely high, and the rates of its reactions with carbonylic substrates may not be measured by flow stream procedures. Felkin used competition kinetics and found the relative reactivity of allylmagnesium bromide and propylmagnesium bromide toward acetone to be 700:1. In the present work a series of competition experiments was performed using allylmagnesium bromide and benzylmagnesium bromide competing for very dilute solutions of benzophenone or acetone. The Grignard reagents were used in ratios of allyl:benzyl = 1:1.3, 1:11.6, and 1:128. In all experiments the allylic addition product dominated and only trace amounts of the benzylic adduct were found as shown in Table 5.

It is surprising that even in a dilution of 1:128 the allylic product accounts for 97% of the product in both reactions. The reactivity toward acetone of allylmagnesium bromide relative to benzylmagnesium bromide is in this experiment 0.90/0.07 × 26 = 3343. The ratio between allylmagnesium bromide and the 68 times less reactive propylmagnesium bromide would then be 227 000, which is 325 times the ratio found by Felkin.³ Toward

Table 5. Relative Reactivity of Allylmagnesium Bromide and Benzylmagnesium Bromide toward Benzophenone and Acetone at 20 °C at Various Concentrations

[C ₃ H ₅ MgBr]	[PhCH ₂ MgBr]	[Ph ₂ CO]	[(CH ₃) ₂ CO]	$k_{\text{allyl}}/k_{\text{benzyl}}$
0.35	0.45	2.5×10^{-4}		221:1
0.07	0.81	2.5×10^{-4}		190:1
0.007	0.90	2.5×10^{-4}		30:1
0.35	0.45		6.9×10^{-4}	103:1
0.07	0.81		6.9×10^{-4}	240:1
0.007	0.90		6.9×10^{-4}	26:1
0.0035	0.45		6.9×10^{-4}	35:1
0.088	0.113		6.9×10^{-4}	290:1

benzophenone the ratio $k_{\text{allyl}}/k_{\text{benzyl}}$ is $0.90/0.007 \times 26x = 3342$, and $k_{\text{allyl}}/k_{\text{propyl}} = 3342 \times 28 = 9.4 \times 10^4$.

The relative reactivity of allylmagnesium bromide increases when it is competing in a high dilution as shown in Table 5. Formally the reaction rates are then not first-order with respect to the reagent, especially at concentrations above 0.1 M, when the reaction rates reach a maximum and no longer increase with the concentration.

Attempts were made to use a GD approach for comparing a number of pairs of carbonylic compounds (Table 4). While benzaldehyde was found in competition experiments many thousand times more reactive than benzophenone toward the slowly reacting methylmagnesium bromide, it appears only slightly more competitive in the reaction with allylmagnesium bromide. Ethylmagnesium bromide is of moderate reactivity with ketones, but the reactions with aldehydes and with α,β -unsaturated ketones are exceedingly fast. The competition between benzaldehyde and benzalacetophenone for ethylmagnesium bromide indicated a reactivity ratio of 1.5:1.

Although allylmagnesium bromide appears to add somewhat faster to aldehydes and acetone than to benzophenone in the GD experiment (Table 4), it is surprising that benzaldehyde, diethylacetaldehyde, and acetone seem to vary so little in reactivity.

The only Grignard reagent which reacts with benzaldehyde with a rate which is slow enough to be measured by the flow stream procedure is methylmagnesium bromide. The pseudo-first-order rate constant for 0.02 M benzaldehyde reacting with 0.5 M methylmagnesium bromide was found to be about 1000 s^{-1} . Competition between a mixture of 0.97 M methylmagnesium bromide and 0.007 M allylmagnesium bromide for a 5×10^{-4} M benzaldehyde solution produced the addition products in the ratio 1:3.9, which indicates a rate for the addition of allylmagnesium bromide of $1000 \times 0.97/0.007 \times 3.9 = \text{ca. } 5.4 \times 10^5 \text{ s}^{-1}$. In competition with benzylmagnesium bromide the rate of addition of benzophenone to allylmagnesium bromide was, depending on the relative concentrations, found to be up to $4.1 \times 10^5 \text{ s}^{-1}$, Table 5. The numbers indicate that benzophenone and benzaldehyde are of similar reactivity toward allylmagnesium bromide. Competition experiments between allyl- and benzylmagnesium bromide for highly diluted acetone indicated a pseudo-first-order reaction constant $k_1 = 5 \times 10^5$ for the reaction of acetone with 0.25 M allylmagnesium bromide.

The extreme reactivity of allylmagnesium bromide and the apparent similarity of the reaction rates in the reactions with widely different substrates and the apparent absence of kinetic isotope effects and effects of polar substituents give the impression that the reagent, at room temperature and having a sufficient concentra-

Table 6. Relative Rates for the Reactions of Allylmagnesium Bromide (0.05 M) with Benzaldehydes Determined by GC on the Reaction Products^a

$k_{\text{PhCHO}}/k_{d_5\text{-PhCHO}}$	-78 °C	0.992 ± 0.005
$k_{\text{PhCDO}}/k_{d_5\text{-PhCHO}}$	-78 °C	0.948 ± 0.005
$k_{\text{PhCHO}}/k_{\text{PhCDO}}$	-78 °C	1.045 ± 0.007
$k_{\text{PhCHO}}/k_{d_5\text{-PhCHO}}$	25 °C	1.004 ± 0.005
$k_{\text{PhCDO}}/k_{d_5\text{-PhCHO}}$	25 °C	1.004 ± 0.005
$k_{\text{PhCHO}}/k_{\text{PhCDO}}$	25 °C	1.000 ± 0.007

^a The results are the average of two experiments.

tion, reaches a limit for the rate of its reaction. The limitation could be the rate of diffusion.

Benzaldehyde and Allylmagnesium Bromide. A recent report describes the determination of the secondary deuterium kinetic isotope effect (SDKIE) of allylmagnesium bromide reacting with α -deuteriobenzaldehyde using substrate deficiency competition kinetics.¹⁴ The reactions were carried out at -78 °C, and a normal KIE ($k_{\text{H}}/k_{\text{D}} = 1.04$) was taken as proof of a single electron transfer (SET) as the rate-determining step. The authors suggest that the same mechanism is operating at room temperature and also that this SET mechanism is operating with benzophenone.

The measurements at -78 °C were reproduced in this laboratory ($k_{\text{H}}/k_{\text{D}} = 1.045$), but no KIE was observed when the reaction was performed at 25 °C ($k_{\text{H}}/k_{\text{D}} = 1.00$, Table 6). The last fact may be due either to the apparent ceiling over the rate of reaction of allylmagnesium bromide (diffusion control?) or to a change of mechanism at room temperature. If a polar concerted mechanism, has a higher energy of activation than an SET mechanism an intersection of the Arrhenius plots is possible so that SET prevails at -78 °C and the polar mechanism at room temperature.

On the other hand, the similarity of the rates of reaction of allylmagnesium bromide and several rather unrelated substrates is obvious, Table 4. Measurement of the relative reactivity of benzaldehyde and 3-fluorobenzaldehyde indicated a near-zero Hammett ρ for the reaction. Yamataka likewise found a Hammett ρ near zero for the reaction with benzophenone with allylmagnesium bromide.¹⁵ It seems strange that no effect of polar substituents should be found in an electron-transfer reaction.

Allylmagnesium bromide is known¹⁶ to react with inversion of the triad, and a six-center cyclic concerted mechanism seems a possibility. If the carbon-magnesium bond is homolyzed by magnesium transfer, a tightly coupled radical pair may form. If the radical pair should be looked upon as a transition state, the reaction has a radical concerted mechanism, Figure 1.

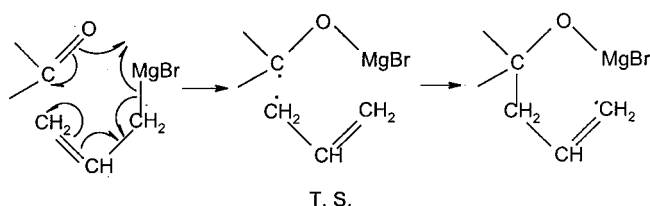
The radical concerted mechanism, which is virtually one step, agrees with the fact that no ketyl coloring is observed in the reaction of benzophenone and benzaldehyde with allylmagnesium chloride. Likewise there are no radical byproducts. Stepwise ET reactions of *tert*-butylmagnesium chloride and other Grignard reagents with benzophenone or benzaldehyde produce a strong ketyl color and many byproducts resulting from radical reactions.

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**Figure 1.**

Conclusion

Competition kinetics may be useful as a semiquantitative method for comparing the relative reactivity of two Grignard reagents toward a substrate. The rate ratios found between a fast and a slow reagent tend to appear to be too low. The reactivities of highly reactive reagents and substrates may only be demonstrated when the competition is performed with the reagents in uneven concentrations. Allylmagnesium bromide at room temperature seems to reach a maximum reaction rate, which cannot be exceeded and which is almost the same with many different carbonyl compounds.

Experimental Section

Materials. Benzyl- and allylmagnesium bromide were prepared under argon in ether (distilled from benzophenone ketyl) and sublimed magnesium by the slow (6 h) addition of distilled benzyl and allyl bromide using agitation. d_5 -Benzaldehyde was obtained from Cambridge Isotope Laboratories. $[\alpha\text{-D}]$ benzaldehyde was prepared according to ref 14.

Competition Kinetics. Substrate Deficiency. A mixture of 2 mL of solutions 0.5 M in each of the two competing Grignard reagents was prepared in a 10 mL disposable syringe. A 5 mL sample of a 2×10^{-4} M solution of the test

substrate in dry ether was prepared in a 5 mL disposable syringe. The syringes were connected by a polyethylene tube, and the substrate solution was pressed into the Grignard reagents. The reaction mixture was poured into an ammonium chloride solution, and the ether layer was separated, washed with water, and dried over magnesium sulfate. A $10 \mu\text{L}$ sample was injected into the gas chromatograph. The exact composition of the Grignard reagent mixture was found by reacting a small amount of the mixture with an excess of the substrate and analyzing by GC after workup.

Grignard Deficiency. A mixture of 2 mL of solutions 0.5 M in each of the competing substrates was prepared in a 10 mL disposable syringe. A 5 mL sample of a 10^{-3} M Grignard reagent was prepared in a 5 mL disposable syringe. The syringes were connected, and the Grignard reagent was pressed into the substrate solution. Workup was done as in the SD experiment. The exact composition of the substrate mixture was found by reacting a small amount with an excess of Grignard reagent and analyzing by GC.

KIE for $[\alpha\text{-D}]$ Benzaldehyde. Competition was measured between solutions of d_5 -benzaldehyde and (1) normal and (2) $[\alpha\text{-D}]$ benzaldehyde, 0.5 M in each, reacting with 0.05 M solutions of allylmagnesium bromide at (1) -78°C and (2) 25°C . Since the normal and the pentadeuterio reaction products were completely separated in GC, the KIEs could be directly calculated from the peak areas.

Gas Chromatography. A HP 5890 Series II instrument was used equipped with a standard injector, an FI detector, and a $100 \text{ m} \times 0.2 \text{ mm} \times 0.33 \mu\text{m}$ HP-5 capillary column. The retention times for the various reaction products were observed using an optimized temperature program, which allowed the best possible separation of the product peaks from the numerous peaks of byproducts. A HP 3354 integrator yielded the peak areas, which were normalized according to the effective carbon numbers (ECN) in the various products.

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