Libraries *via* Metathesis of Internal Olefins

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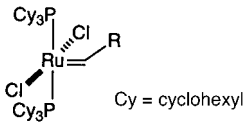
Dedicated to Prof. *Dieter Seebach* on the occasion of his 60th birthday

The cross-metathesis of internal olefins is applied for the combinatorial synthesis of small organic molecules; this reaction is conveniently carried out in neat olefin (oleic-acid derivatives) and requires only 0.001 equiv. of $[Ru(CHPh)Cl_2(PCy_3)_2]$ as catalyst (Cy = cyclohexyl).

1. Introduction. – The development of well-defined, single-component homogeneous olefin-metathesis catalysts has opened up new horizons in the fields of *r*ing-*o*pening *m*etathesis *p*olymerization (ROMP) and *r*ing-*c*losing *m*etathesis (RCM), affording polymers and cyclic compounds of various ring sizes, respectively [1]. The carbene-ruthenium complexes **1** developed by *Grubbs* and coworkers have found many applications in chemical synthesis as they are commercially available, only moderately air-sensitive, suited for reactions carried out in aqueous media [2], and tolerant towards many functional groups [1d] (for a study on functional-group tolerance with a slightly different catalyst precursor (but probably identical active species), see [3]).



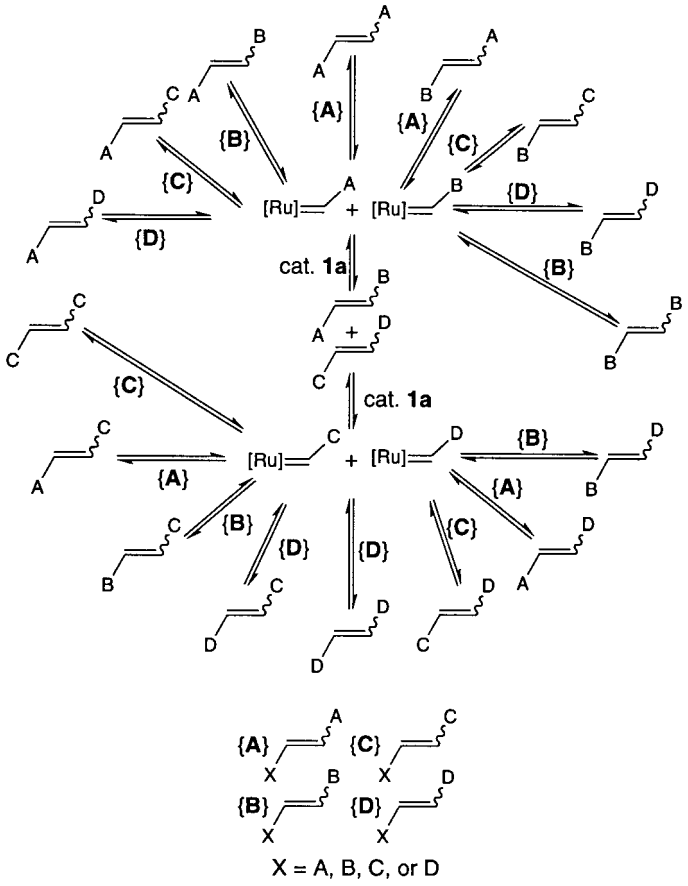
1a R = Ph
b R = Ph_2C=CH

Metathesis work with catalysts **1a,b** has focused mainly on cyclic olefins (ROMP chemistry) and *terminal* olefins (RCM chemistry). In the former case, the relief of ring strain contributes to drive the reaction to completion (although less-strained cyclic olefins can also be metathesized); in the latter case, the evolution of ethylene has been invoked as a driving force [4]. The literature on ruthenium-catalyzed metathesis of *internal* olefins is scarce[1]). Our interest in this area was greatly stimulated by the realization that cross-metathesis of two *internal* disubstituted olefins yields ten possible olefins (twenty compounds including (*E*)/(*Z*) isomers) as illustrated in *Scheme 1*.

It has been estimated that an optimal mixture complexity is about twenty substances per pool: if more complex mixtures are used, detection of active compounds is no longer reliable (for a review and discussion of optimal pool size, see [8]). Thus, the

[1]) Notable exceptions include *Schneider* and *Blechert*'s study of the cross-metathesis of substituted norbornene-like systems with hex-3-ene and 1,4-dimethoxybut-2-ene [5], and *Grubbs*' metathesis of pent-2-ene [1i]; for RCM of internal olefins, see [1h][6] [7].

Scheme 1. *Generation of a Statistical Distribution of Ten Olefins from the Cross-metathesis of Two Disubstituted Olefins*

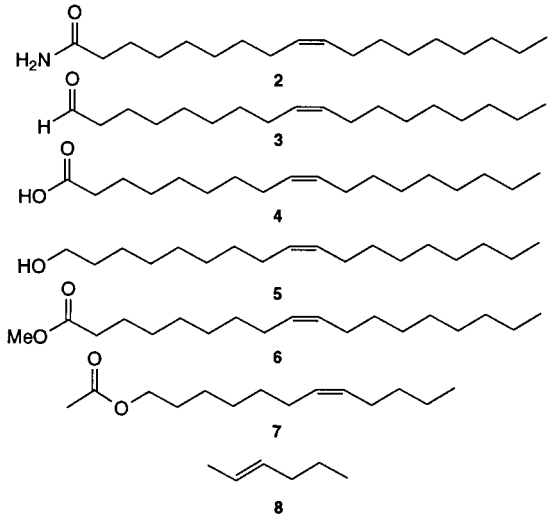


metathesis of two internal olefins offers interesting perspectives for the solution-phase combinatorial synthesis of small organic molecules [9][2]). Since the reaction is thermodynamically driven, a statistically controlled diversity mixture should be produced. If N is the number of *unequivalent* olefinic termini in a pool, the number of olefins generated by metathesis is given by $N \cdot (N + 1)/2$ (or $N \cdot (N + 1)$ compounds including $(E)/(Z)$ isomers). Since unsymmetrical olefins (heterodimers) can be produced *via* two ruthenium-carbene complexes, these olefins are twice as abundant as symmetrical olefins (homodimers) which are produced *via* a single ruthenium-carbene (see *Scheme 1*), thus reflecting a statistical distribution of olefins (equilibrium mixtures).

Oleic acid and its derivatives are ideal substrates to probe the metathesis of internal olefins. In the past, the self-metathesis of unsaturated fatty-acid esters has provided a convenient route to unsaturated diesters which are important intermediates for the

[2]) The metathesis of *terminal* olefins to combinatorially randomize the length of a linking tether has been applied for the generation of libraries [10].

production of polymers [11]. Recently, *Lerner*, *Boger* and coworkers have identified an oleic-acid-derived family of brain lipids that induces sleep [12]. The naturally occurring brain constituent oleamide (**2**) has been shown to accumulate and disappear under conditions of sleep deprivation and sleep recovery, respectively. While (*Z*)-octadec-9-enamide (= oleamide; **2**) proved most efficient, variation of the C=C configuration or position, and of alkyl chain length resulted in a decrease of the extent and duration of the observed effect [13].



2. Results and Discussion. – The self-metathesis of olefins **2**–**8** was carried out in CH_2Cl_2 in the presence of 0.01 equiv of **1a**[3]). GC/MS analysis of the crude reaction mixture revealed in all cases three olefins (six compounds including (*E*)/(*Z*) isomers) with molecular masses corresponding to the three products of self-metathesis[4]). The position of the C=C bond in the products of metathesis was determined unambiguously by ozonolysis and GC/MS analysis of the resulting aldehydes [14]. All substrates **2**–**8**, as well as the unfunctionalized alkenes resulting from metathesis, were used for calibration against octadecane. In all cases, a quantitative metathesis (affording a statistical distribution of products) was determined by GC (see *Scheme 2*).

For the self-metathesis of methyl oleate (**6**), ^{13}C-NMR and ^{13}C-resolved ^{1}H,^{1}H-TOCSY analysis of the reaction mixture allowed unequivocal peak assignment and characterization of all six compounds, (*E*)- and (*Z*)-**6**, (*E*)- and (*Z*)-**9**, and (*E*)- and (*Z*)-**10**; integration of the olefinic C-atom signals gave an (*E*)/(*Z*) ratio of 4.8 : 1 for all compounds (see *Scheme 2*).

The compounds **2**–**8** were then tested pairwise towards cross-metathesis. A *ca.* 2 mM solution of two olefins in CH_2Cl_2 was treated with 0.01 equiv. of **1a** under Ar. After 36 h stirring, the crude reaction mixture was submitted to GC analysis. A typical

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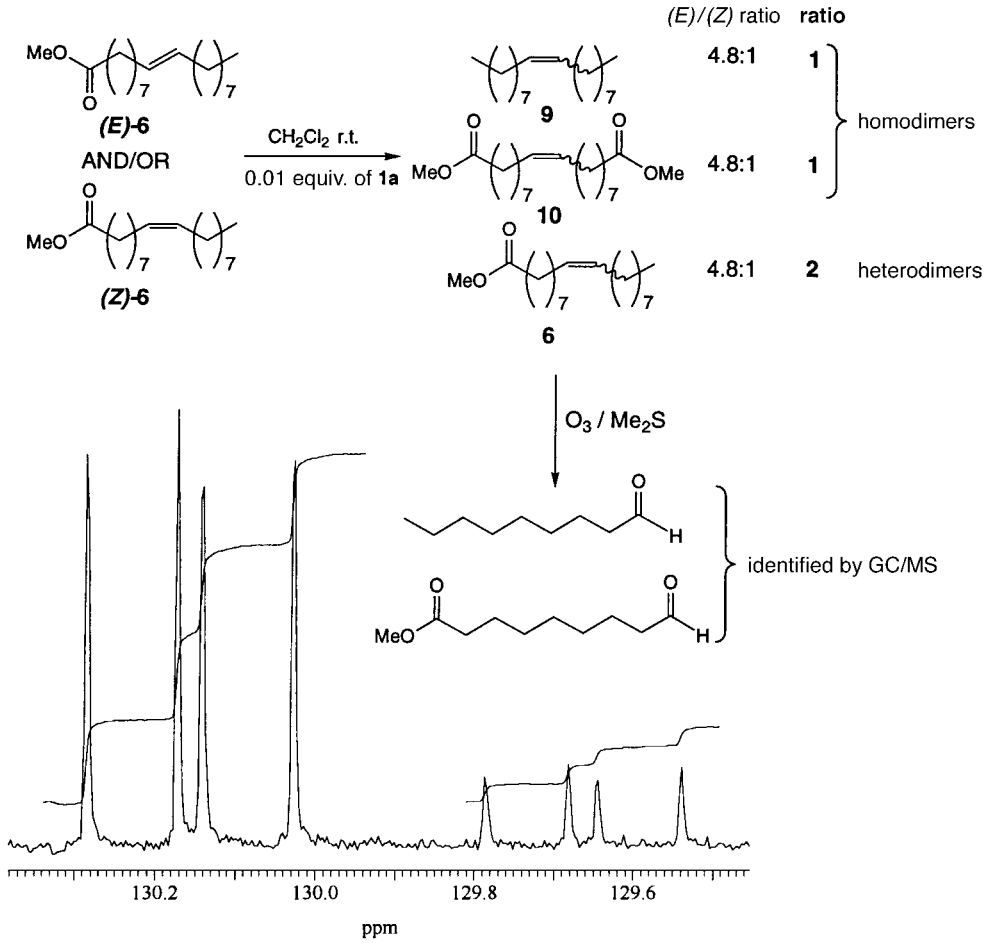
[3]) Despite repeated efforts, the metathesis of oleylamine (as well as of its protonated form) could not be achieved.

[4]) The low-molecular-mass compounds resulting from the cross-metathesis with **8** could not be detected in all cases by GC. The presence of all other metathesis products, however, suggests unequivocally that these alkenes are indeed formed.

Scheme 2. *Self-metathesis of Methyl Oleate* (**6**) *and Ozonolysis Allowing the Determination of the C=C Bond Position in the Products.* Bottom left: ^{13}C-NMR olefinic region of the reaction mixture.



chromatogram is presented in the *Figure*. All ten expected olefins (twenty compounds including $(E)/(Z)$ isomers) were identified and characterized by GC/MS analysis. Again here, the reactions were quantitative and yielded a statistical distribution of the ten olefins. For all metathesis products, the $(E)/(Z)$ ratio was 4.5 ± 0.5 (determined independently by GC and ^{13}C-NMR)[5]). Interestingly, this reaction could

[5]) After screening of the library for a given activity, let us assume that a pool containing ten olefins (twenty compounds including $(E)/(Z)$ isomers) has been identified. The following deconvolution strategy is proposed. Self-metathesis of a single olefin produces two homodimers and the substrate olefin (heterodimer) which are separated (*e.g.*, by prep. GC) and tested individually for activity. Cross-metathesis of two homodimers produces the individual heterodimers (as well as the homodimers whose activity has been tested). Once an active olefin has been identified by this procedure, both $(E)/(Z)$ isomers must be synthesized. As outlined in *Scheme 2*, ozonolysis of the homodimers yield the starting materials for the synthesis of these isomers *via* a *Wittig* reaction [15].

be carried out in *neat* olefin. In such a case, the catalyst loading could be reduced to 0.001 equiv. of **1a**.

The 'living character' of the metathesis of internal olefins was assessed by adding a third olefin to a reaction mixture of two olefins in CH_2Cl_2 having reached equilibrium (0.05 equiv. of **1a**). After 48 h additional stirring, GC/MS analysis revealed a statistical

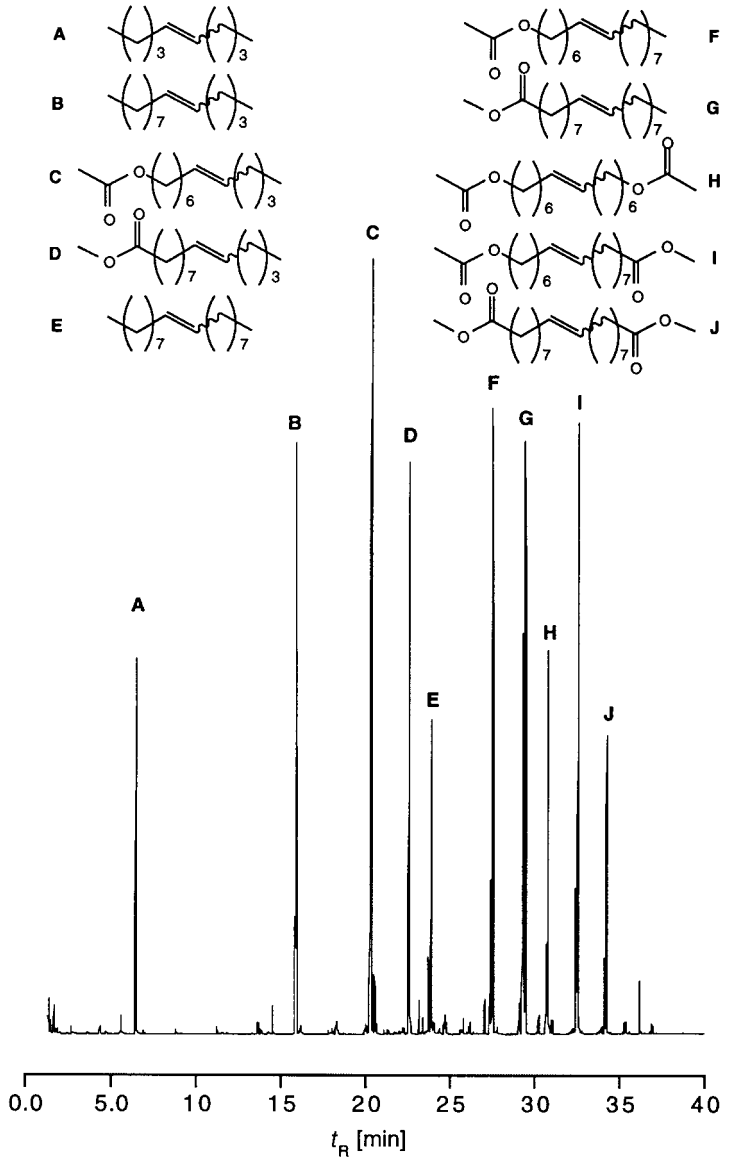


Figure. *GC Analysis* (crude reaction mixture) *for the cross-metathesis of ester* **6** *with acetate* **7** *in the presence of 0.01 equiv. of* **1a** *in* CH_2Cl_2

distribution of the expected $N\cdot(N+1)/2$ olefins (or $N\cdot(N+1)$ compounds including $(E)/(Z)$ isomers).

Despite the absence of any driving force, *i.e.*, relief of ring strain or ethylene evolution, the metathesis of internal olefins is characterized by a quantitative catalytic reaction generating no by-products, *i.e.*, atom economy [16][17]. The results outlined above thus demonstrate the applicability of this reaction for the generation of libraries of organic compounds. Our current efforts are aimed at further broadening the scope of this methodology by adding a hard *Lewis* acid to protect unfavorably positioned polar groups [18].

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