Metal-Free Intramolecular Carbonyl–Olefin Metathesis of *ortho*-Prenylaryl Ketones

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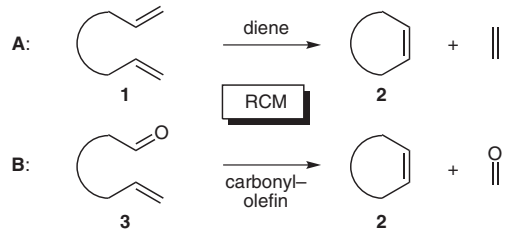
Dedicated to Prof. S. Blechert on the occasion of his 65th birthday

Abstract: On treatment with boron trifluoride etherate as a Lewis acid, acetophenone and benzophenone derivatives bearing a prenyl (or a related) side chain in *ortho*-position were shown to undergo intramolecular carbonyl–olefin metathesis, in the absence of any transition-metal catalyst. The cationic cyclization process is supposed to proceed via an oxetane intermediate, which fragments to give the cyclization product (indene or 1,2-dihydronaphthalene) and a ketone (acetone) as a stoichiometric by-product. Several substrates were shown to afford the metathesis products with up to 93% yield.

Key words: olefin metathesis, cyclization, Lewis acids, carbenium ions, oxetanes, natural products

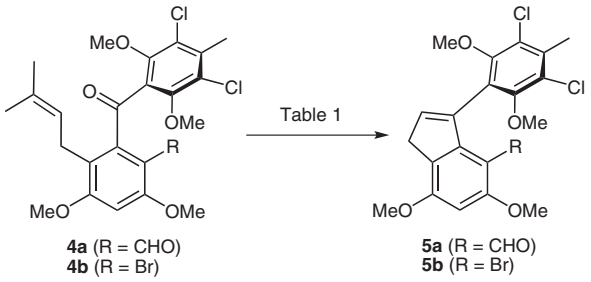
During the last decades, ring-closing olefin metathesis (RCM) has evolved into one of the most powerful methods of C–C bond formation in organic chemistry (Scheme 1).[1] Parallel to the development of various effective catalysts (transition-metal carbene complexes)[2] a large number of applications of RCM both in academic and in industrial synthesis have been reported.[1,3] The elegance of the methodology is also reflected by the prodigious mechanism involving metalacyclobutane intermediates formed by reversible [2+2] cycloaddition.[4]



Scheme 1 Ring-closing metathesis (RCM) starting either from a diolefin (diene metathesis; **A**) or from an unsaturated carbonyl compound (carbonyl–olefin metathesis; **B**)

While diene metathesis (Scheme 1; **A**) represents the common pattern to prepare cyclic olefins (**2**) through RCM, only a few examples for intramolecular carbonyl–olefin metathesis (Scheme 1, **B**) have been described. Following early work in the Grubbs laboratory,[5] the synthesis of cycloalkenes from olefinic ketones and esters, respectively, was only achieved in the presence of stoichiometric amounts of Mo-, W- or Ti-alkylidenes.[6]

Against this background we considered our recent discovery of an efficient 'metal-free' carbonyl–olefin ring-closing metathesis of sufficient importance to justify some further investigation. In the course of the total synthesis of the marine natural product pestalone[7] we had treated the *ortho*-prenylated benzophenone derivative **4a** with $BF_3{\cdot}SMe_2$ in the attempt to achieve selective deprotection (de-O-methylation).[8] To our surprise, a cyclized side-product was formed in 20% yield and identified by X-ray crystallography as the arylindene **5a** (Scheme 2).



Scheme 2 Lewis acid promoted cyclization of the pestalone derivatives **4a** and **4b**

By varying the reaction conditions (Lewis acid, solvent, and reaction time) we succeeded to optimize the formation of **5a** to 84% (Table 1, entry 3). With a related substrate, i.e. the brominated compound **4b**, we initially observed mainly decomposition under similar conditions. However, when we switched to $BF_3{\cdot}OEt_2$ (as an even more common reagent) we obtained the metathesis product **5b** in 93% yield after aqueous workup and purification (Table 1, entry 6). The structure of **5b** was also confirmed by X-ray crystal structure analysis (Figure 1).[9]

Interestingly, the unexpected and facile formation of the indene derivatives **5a** and **5b** represents a rare and by far the most efficient example of a metal-free carbonyl–olefin metathesis reaction.[10]

We were thus curious whether this type of transformation is unique for the highly substituted benzophenone substrates of type **4** or if it would also be observed for *ortho*-prenylaryl ketones and related substrates of type **6** in general. According to our mechanistic proposal[7] (Scheme 3) the BF_3-promoted process starts with a Prins-type (*exo*-

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Table 1 Variation of Reaction Conditions for the Cyclization of **4a** and **4b**, According to Scheme 2[a]

Entry	Starting material	Reagent (equiv)	Time (min)	Solvent[b]	Product (%)[c]
1	**4a**	$BF_3{\cdot}SMe_2$ (1.7)	120	A	**5a** (20)
2	**4a**	$BF_3{\cdot}SMe_2$ (6.0)	75[d]	A	**5a** (50)
3	**4a**	$BF_3{\cdot}SMe_2$ (1.7)	45	B	**5a** (84)
4	**4a**	$AlCl_3$ (1.7)	45	B	**5a** (36)
5	**4b**	$BF_3{\cdot}SMe_2$ (1.7)	45	B	**5b** (<5)
6	**4b**	$BF_3{\cdot}OEt_2$ (2.5)	45	B	**5b** (93)

[a] Reaction conditions: starting material (1 equiv), 0.05 M in solvent, 0 °C.
[b] Solvent A: CH_2Cl_2–SMe_2 (1:2); solvent B: CH_2Cl_2.
[c] Isolated yield.
[d] Reaction was performed at –30 °C.

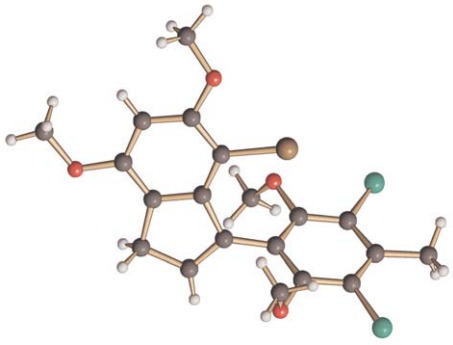
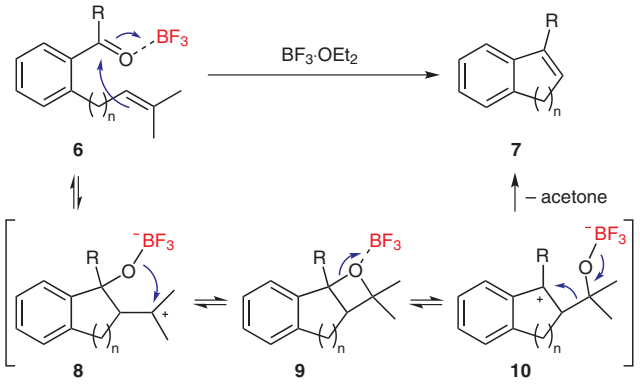


Figure 1 Structure of **5b** in the crystalline state[9]

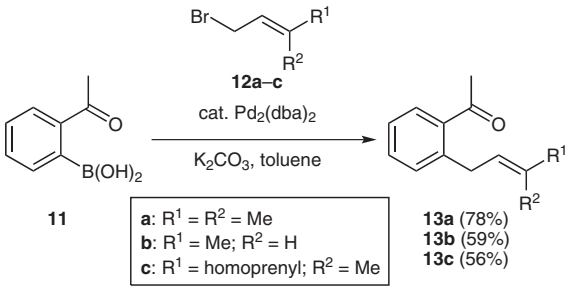
trig) cyclization of **6** to form a tertiary carbenium ion **8**, which isomerizes to the benzylic cation **10** via an oxetane intermediate **9**. At the end, the product **7** is liberated together with acetone in an entropically favored fragmentation step.[11]



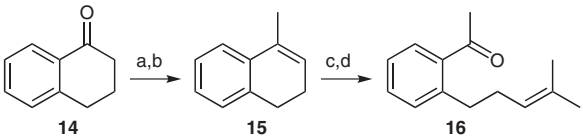
Scheme 3 Proposed mechanism for the BF_3-promoted metathesis cyclization of substrates of type **6**

To probe the generality of the reaction we decided to employ *ortho*-prenyl acetophenone (**13a**) and its analogues with a crotyl (**13b**) or a geranyl side chain (**13c**) as substrates. These compounds were prepared by Suzuki coupling[12] of 2-acetylphenyl boronic acid (**11**) with the allylic bromides **12a–c** (Scheme 4).

As another substrate of type **6**, which carries a homoprenyl side chain and would thus give rise to a six-membered metathesis product, we prepared the acetophenone derivative **16** as shown in Scheme 5. Starting from 1-tetralone (**14**), addition of methylmagnesium iodide and subsequent acidic dehydration[13] gave the dihydronaphthalene **15** in high yield. Ozonolysis of the double bond then afforded the keto aldehyde (after workup with dimethyl sulfide)[14] which was finally transformed into the homoprenyl acetophenone **16** by Wittig reaction.

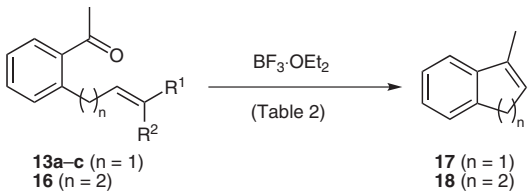


Scheme 4 Preparation of compounds **13a–c** through Suzuki coupling



Scheme 5 Synthesis of substrate **16**. *Reagents and conditions*: (a) MeMgI, EtO_2, r.t., 1 h; (b) HCl (3 N), r.t., 1 h, 98% over 2 steps; (c) O_3, MeOH, –78 °C, 4 h, then Me_2S, r.t., 24 h, 35%; (d) *n*-BuLi, *i*-$PrPPh_3I$, THF, –78 °C, 2 h, then r.t., 16 h, 30%.

With the substrates **13a–c** and **16** in our hands, the stage was set to study their tendency to undergo Lewis acid promoted ring-closing metathesis (Scheme 6).



Scheme 6 BF_3-induced RCM of substrates of type **13** and **16**

We were pleased to find that the envisioned transformations indeed took place, most smoothly with the prenyl- and homoprenyl-substituted substrates. Under optimized conditions (1.5 equiv of $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C, 60 min) the prenyl acetophenone **13a** afforded the methylindene **17** in a rather clean and high-yielding reaction (Table 2, entry 1).[15] Similarly, the homoprenyl-substitut-

Table 2 BF_3-Induced Metathesis Cyclization of Substrates **13a–c** and **16** According to Scheme 6[a]

Entry	Substrate	Product	Yield (%)[b]
1	**13a**	**17**	87
2	**13b**	**17**	traces[c]
3	**13c**	**17**	38
4	**16**	**18**	75

[a] Reaction conditions: **8a–8c** and **12** (1 equiv), 0.05 M solution in CH_2Cl_2, $BF_3{\times}OEt_2$ (1.5 equiv), –40 °C, 1 h.
[b] Isolated yield.
[c] Detected by GC–MS.

ed substrate **16** smoothly gave rise to the dihydronaphthalene **18** (entry 4).

While the *ortho*-geranyl acetophenone **13c** could also be successfully cyclized to give **17** (entry 3), the metal-free RCM reaction did not occur with *ortho*-crotyl acetophenone (**13b**) as a substrate. Only traces of the RCM product **17** could be detected by GC–MS in this case besides unreacted starting material. This result can be understood in terms of the proposed mechanism (compare Scheme 3). A second alkyl substituent at the distal position of the olefin **6** seems to be required to sufficiently stabilize the initially formed carbocation of type **8** (formation of a tertiary carbenium ion).

To further support the proposed mechanism, we performed an experiment (cyclization of **13a** to **17**) where we trapped the expected by-product (acetone) by the addition of *ortho*-nitrobenzaldehyde under basic conditions (NaOH).[16] The formation of indigo (as indicated by the occurrence of a deep blue insoluble solid) clearly proved the generation of acetone in accordance to the suggested mechanism.

In conclusion, we have shown that the Lewis acid mediated 'metal-free' carbonyl–olefin ring-closing metathesis[17] reflects a rather general reactivity option of *ortho*-prenylaryl ketones, i.e. a frequently occurring substructure in natural product chemistry. The surprisingly facile transformation is supposed to proceed (like the transition-metal-catalyzed olefin metathesis) via a four-membered-ring intermediate.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(17) **General Procedure for BF_3·Et_2O-Induced Ring-Closing Metathesis**: In an argon-flushed Schlenk tube *ortho*-prenyl acetophenone (**13a**; 250 mg, 1.32 mmol) dissolved in anhyd CH_2Cl_2 (26 mL) was cooled to –40 °C. Dropwise addition of BF_3·OEt_2 (0.25 mL, 1.98 mmol) afforded a yellow solution, which was stirred for 1 h at –40 °C. After addition of sat. aq $NaHCO_3$ (20 mL) at 0 °C the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica(cyclohexane) to provide 3-methyl-1*H*-indene (**17**; 150 mg, 1.15 mmol, 87%) as a colorless oil; R_f 0.65 (pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (dd, 3 H), 3.33 (m, 2 H), 6.21 (d, 1 H) 7.20 (dt, 1 H), 7.33 (q, 2 H), 7.46 (d, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): = 13.0, 37.6, 118.8, 123.6, 124.4, 126.0, 128.7, 139.9, 144.3, 146.1. IR-ATR:(film) = 3013 (w), 2931 (w), 1681 (m), 1460 (m), 1433 (m), 1379 (m), 1015 (m), 1001 (m), 943 (m), 760 (s), 717 (s) cm^{-1}. HRMS (EI, 70 eV): *m*/*z* calcd for $C_{10}H_{10}$: 130.0782; found: 130.079.