# Cleavage of Styrene Derivatives from a Solid Support by Ring Closing Olefin Metathesis

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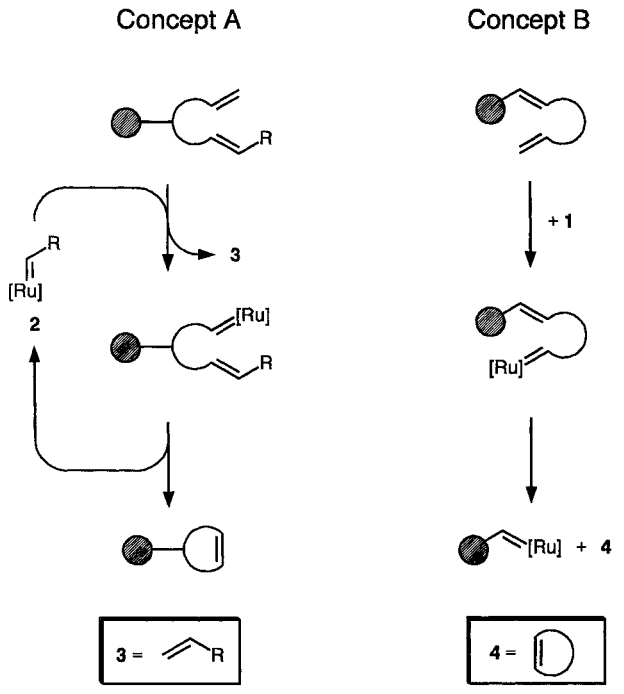
**Abstract**: Ring closing olefin metathesis of a diolefinic linker is demonstrated to be an effective method to release resin-bound substrates from their solid supports.

Solid phase mediated organic synthesis has been developing rapidly during the past few years and is beginning to have an impact on the development of pharmaceuticals.[1] In solid phase mediated organic synthesis, reactions are carried out on substrates which are covalently bound by a linker to a solid support. A final reaction step cleaves the linker and thus liberates the desired product from the solid support.

Our work is directed towards a generally applicable linking/cleaving strategy based on ring closing olefin metathesis[2] of a diolefinic linker. Cleavage of a diolefin is achieved by the recently introduced metathesis catalyst bis(tricyclohexylphosphine) benzylidene ruthenium dichloride (**1**),[3] which has been shown to effect metathesis on polystyrene-bound substrates.[4] The stability of the diolefin linking moiety, the mild conditions of its cleavage and the catalyst's tolerance of a variety of functionalities (carboxylic acids,[5a] carboxylic acid anhydrides,[5b] amides,[5c] aldehydes[5a] and ketones,[5d] alcohols,[5e] and sulfonamides[5f]) make this strategy worth being investigated.

There are two conceivable concepts A and B (Scheme 1) for this cleavage method.



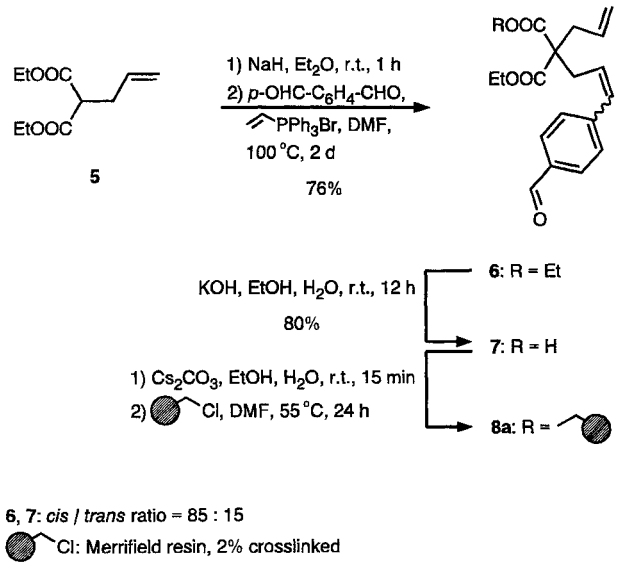

**Scheme 1**

According to concept A (Scheme 1), olefins can be released from a support by closing a ring which remains on the resin. Ruthenium carbene complex **2** (which is formed *in situ* from **1**) furnishes the desired olefin **3** by reacting with the less hindered double bond of the linking moiety. Complex **2** is reformed in an intramolecular ring-closing metathesis and thus **1** can be used in catalytic amounts.

Cyclic olefins **4** can be obtained according to concept B (Scheme 1). However, a fundamental disadvantage of this concept is the immobilization of the ruthenium carbene complex on the resin.

Concept B (Scheme 1) was used recently to synthesize a seven-membered lactam. Olefins, as ethylene or octene, were supplementarily added to liberate the ruthenium carbene complex from the solid support in a cross-metathesis reaction, but yields for the cleavage did not exceed 44% with substoichiometric amounts (30%) of catalyst **1**.[6]

To test concept A (Scheme 1), a suitably functionalized resin was obtained according to Scheme 2. Terephthalaldehyde was mono-olefinated[7] in a Michael-Wittig tandem process[8] with the anion of commercially available allylmalonate **5** and triphenyl vinylphosphonium bromide. Selective saponification of the resulting bisalkylated malonate **6** furnished monoacid **7** which was transformed into its cesium salt and bound to Merrifield resin.[9] A loading of 0.55mmol/g was determined from the weight gain of the resin.



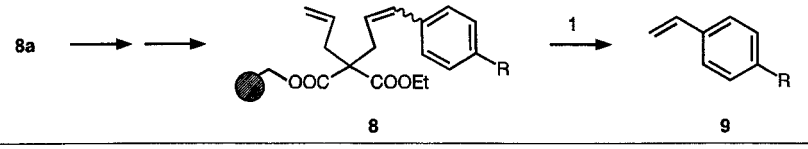

**Scheme 2**

To show the stability of the linker under different reaction conditions as well as the compatibility of catalyst **1** with different functionalities, a number of functional group conversions were carried out on aldehyde resin **8a** (Table 1).

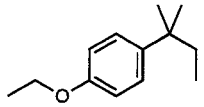
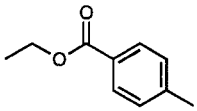
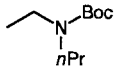
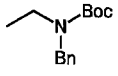
Reduction with sodium borohydride in dimethylformamide[10] led to polymer-bound alcohol **8b**. This alcohol was transformed into phenolic ether **8c** under Mitsunobu conditions[11] and to toluic acid ester **8d** by DCC condensation.

Condensation of resin **8a** with propylamine or benzylamine using orthoformate as dehydrating agent[12] yielded the corresponding imines **8e**, **8f**. These were reduced by sodium cyanoborohydride in acidified dimethylformamide[13] to **8g** and **8h** and subsequently transformed into carbamates **8i** and **8k**, respectively.

**Table 1.** Transformations of Polymer-Bound Aldehyde **8a** and Release of Products by Ring Closing Olefin Metathesis




**8** **9**

| Functional Group Transformations | Cleavage of Products from Solid Support | Overall Yield* |
|---|---|---|
| **8a**: R =  a → **8b**: R =  b → **8c** | 3% **1** → **9c**: R =  | 32% |
| **8b**: R =  c → **8d** | 6% **1** → **9d**: R =  | 55% |
| **8a**: R =  d → **8e**: R =  e → **8g**: R =  f → **8i** | 9% **1** → **9i**: R =  | 26% |
| **8a**: R =  g → **8f**: R =  e → **8h**: R =  f → **8k** | 9% **1** → **9k**: R =  | 33% |
| **8a**: R =  h → **8l** | 23% **1** → **9l**: R =  | 24%** |

(a) $NaBH_4$, DMF, r.t., 12 h. (b) *p*-*t*-Amyl-$C_6H_4$-OH, DEAD, $PPh_3$, $CH_2Cl_2$, THF, r.t., 12 h. (c) *p*-$CH_3$-$C_6H_4$-COOH, DCC, DMAP, $CH_2Cl_2$, r.t., 12 h. (d) *n*-$PrNH_2$, $HC(OCH_3)_3$, $CH_2Cl_2$, r.t., 12 h. (e) $NaBH_3CN$, DMF, AcOH, r.t., 12 h. (f) $Boc_2O$, $CH_2Cl_2$, $Et_3N$, r.t., 12 h. (g) $BnNH_2$, $HC(OCH_3)_3$, CH2Cl2, r.t., 12 h. (h) PhCH2PPh3Br, NaOCH3, DMF, then add **8a**, r.t., 12 h.

*yields and amounts of catalyst **1** are referred to the initial loading of aldehyde resin **8a**.

***cis* / *trans* ratio = 40 : 60

A polymer-bound stilbene (**8l**) was obtained by reacting resin **8a** with benzylphosphonium ylide in dimethylformamide.[14]

These reactions were monitored by IR spectroscopy of the resins.

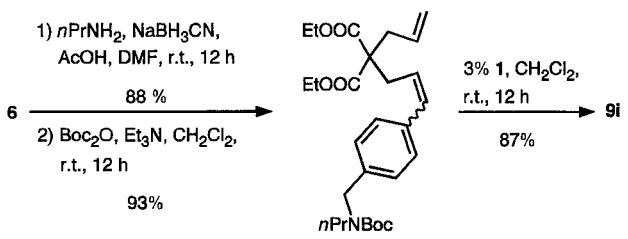
Styrene derivatives **9c**, **9d**, **9i**, **9k**, **9l** were released from resins **8c**, **8d**, **8i**, **8k**, **8l** by metathesis catalyst **1**.[15]

The results are summarized in Table 1.

Resins **8c** and **8d** furnished olefins **9c** and **9d**, respectively, in good purity, as indicated by TLC of the reaction mixtures. Resin **8d** had to be exposed twice to fresh portions of 3mol% of catalyst **1** to complete the cleavage. A third exposure of the resin to **1** yielded only traces of additional product. The styrene derivatives were thus formed with an average yield of 68% (**9c**) and 82% (**9d**) per step.

Carbamates **9i** and **9k** were released from resins **8i** and **8k**. Both resins had to be exposed three times to a solution of 3mol% catalyst **1** before the cleavage was complete. This was monitored by the shrinking of strong IR absorptions of the resins at 1685cm$^{-1}$ (**8i**) and 1691cm$^{-1}$ (**8k**), which were assigned to the carbamate C=O stretch. Carbamates **9i** and **9k** were obtained with an average yield of 71% and 76% per step, respectively.

Catalyst **1** is known to be inactivated in the presence of unprotected amino groups.[5a] To test whether incomplete carbamate formation on resin **8g** is responsible for the higher amounts of catalyst **1** needed in the cleavage of **9i** from resin **8i**, carbamate **11** was obtained according to Scheme 3 by reductive amination of aldehyde **6** and subsequent carbamate formation. Compound **11** underwent smooth metathesis to styrene derivative **9i** with 3mol% of catalyst **1**, which suggests that parts of the catalyst added to resin **8i** are inactivated by impurities on the resin.




**11**

**Scheme 3**

Vinylstilbene (**9l**) was obtained only in a moderate yield, despite the high amounts of catalyst used. This might be due to the formation of a conjugation-stabilized ruthenium stilbenylmethylidene carbene complex as an intermediate in the metathesis catalytic cycle. This complex is supposedly a poor catalytic species because of its low ground state energy relative to the generally accepted metallacyclobutane intermediate.[16]

In all cases, the disappearance of an IR absorption of the resins at 1639-1642cm$^{-1}$ of medium strength, which was assigned to the stretch of the terminal C=C double bond of the linker, served as an indication of an achieved ring closure. Residual catalyst was removed by silica gel column chromatography.

In conlusion, it was shown that ring closing olefin metathesis is not only a tool for cyclic products but can also be used in solid phase mediated organic chemistry to release non-cyclic olefins from a solid support.

**References and Notes**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(15) *Representative cleavage procedure*: 400mg (0.208mmol) of resin **8d** (loading 0.52mmol/g calculated from the loading of aldehyde resin **8a**) were suspended in 3 ml of dry $CH_2Cl_2$ (Argon glovebox). 5 mg (6.08µmol, 3mol%) of $(PCy_3)_2Cl_2Ru$=CHPh **1** were added and the mixture was stirred for 12h at room temperature. The mixture was then passed through a glass filter and the collected resin was washed with $CH_2Cl_2$. The crude product was obtained by evaporation of the filtrate and purified by silica gel column chromatography. 23mg (44%) of **9d** were obtained as a colorless oil. The resin was exposed to the same conditions a second time to give another 6mg (11%) and a third time to yield only traces (< 1mg) of **9d**. — 1H NMR (200 MHz, $CDCl_3$): δ[ppm] = 2.40 (s, 3H), 5.26 (dd, 1H, *J* = 11/1Hz), 5.34 (s, 2H), 5.76 (dd, 1H, *J* = 18/1Hz), 6.73 (dd, 1H, *J* = 18/11Hz), 7.23 (d, 2H, *J* = 8Hz), 7.42 (s, 4H), 7.96 (d, 2H, *J* = 8Hz). — $^{13}$C NMR (50 MHz, $CDCl_3$): δ[ppm] = 21.6 ($CH_3$), 66.2 ($CH_2$), 114.2 ($CH_2$), 126.4 (CH), 127.4 ($C_q$), 128.4 (CH), 129.1 (CH), 129.7 (CH), 135.7 ($C_q$), 136.4 ( CH), 137.5 ($C_q$), 143.7 ($C_q$), 166.5 ($C_q$). — MS (EI) *m/z* = 252 (M, 80%), 119 (100%), 117 (90%), 91 (60%). — HR-MS ($C_{17}H_{16}O_2$): calcd 252.1150, found 252.1143. — IR ($CCl_4$): 1/λ [$cm^{-1}$] = 690 (m), 721 (w), 753 (vs), 827 (s), 835 (s), 910 (m), 990 (m), 1020 (s), 1102 (vs), 1119 (vs), 1177 (vs), 1209 (w), 1268 (vs), 1309 (m). 1374 (m), 1407 (m), 1448 (w), 1514 (m), 1576 (m), 1612 (s), 1629 (w), 1718 (vs), 2884 (w), 2925 (m), 2951 (m), 2980 (w), 3007 (m), 3038 (w), 3088 (w).

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