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Solid Phase Heterocyclic Synthesis *via* Ring Closing Metathesis: Traceless Linking and Cyclative Cleavage Through a Carbon-Carbon Double Bond¶

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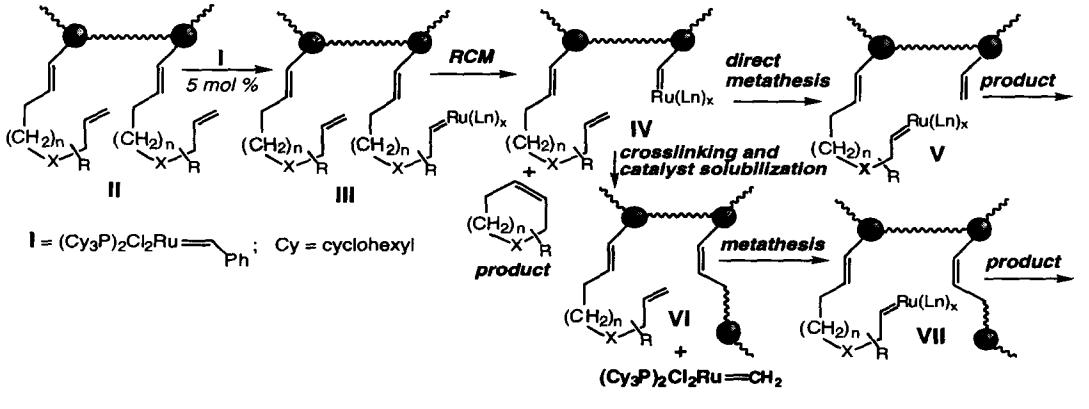
abstract: Ring closing metathesis was utilized to affect cyclative cleavage of resin-bound α,ω dienes in the solid phase synthesis of dihydropyarans, pipecolinic acid derivatives and Freidinger lactams. © 1997 Elsevier Science Ltd.

Over the past several years, small molecule solid phase synthesis has become an integral part of the drug discovery paradigm.[1,2] As a result, the need for new protocol has increased, particularly with regard to immobilization strategies since the final cleavage event is arguably the critical step in generating a quality library.

An overwhelming majority of small molecule libraries reported to date employ cleavage strategies wherein the linking elements (*i.e.* RCO_2H, RNH_2, $RCONH_2$, Ar-OH) are retained in their respective target molecules. Strategies which take advantage of traceless[3] and cyclative release mechanisms,[4] while fewer in number, are rapidly gaining popularity. The prospect of cyclative release is particularly attractive because only a successful ring forming reaction results in substrate cleavage. As a result, desired products are generally obtained in high purity. A typical scenario for the solid phase construction of heterocyclic molecules *via* cyclative substrate release involves the formation of a carbon-heteroatom bond. Indeed, lactones,[4c] lactams[4a,b,d] and tetrahydrofurans[4e] are available through variations of this manifold. We were intrigued, however, by the possibility of initiating cyclative substrate release through the formation of a carbon-carbon bond *via* ring closing metathesis.[1e,5-7] Recent reports detailing such a protocol[8] have prompted us to disclose our own efforts in this area.

As outlined in **Scheme 1**, we suspected a polymer supported, α,ω-diene could undergo ring closing metathesis upon exposure to Grubbs' ruthenium catalyst **I** to give the corresponding cycloalkene with concomitant cleavage. At the outset however, it was unclear whether the resin-bound ruthenium alkylidene

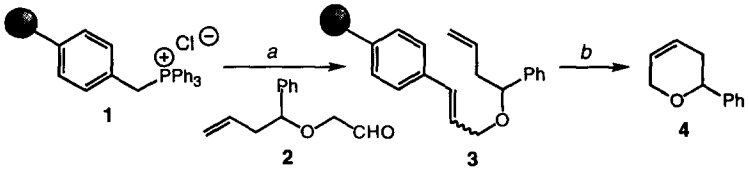
Scheme 1



complex **IV**, if formed, could efficiently re-enter the catalytic cycle. A test of the proposed sequence was therefore conducted using a simple diene substrate.

As shown in **Scheme 2**, aldehyde **2**[9] was loaded onto polystyrene methylenetriphenylphosphonium resin[10] **1** *via* the intermediacy of the corresponding ylide. The resulting resin-bound diene **3** was resuspended in dichloromethane and treated with catalyst **I** (5 mole% based on loading).[11] After filtration and evaporation, the expected dihydropyran **4** was obtained in 71% yield (43% overall) and in >95% purity as determined by ^{1}H NMR at 400 MHz.[12]

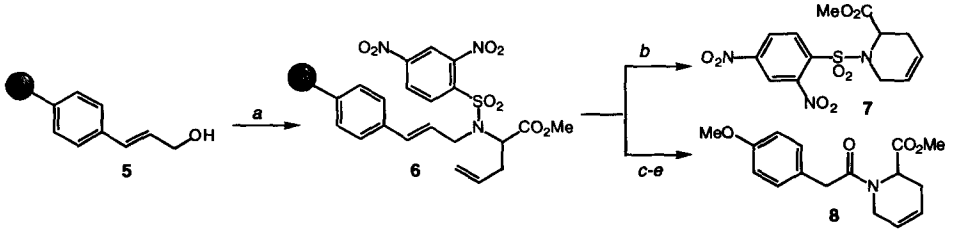
Scheme 2



(*a*) *n*-BuLi, THF, RT. (*b*) catalyst **I** (5 mol %), CH_2Cl_2, RT, 16h , 43% overall.

Having demonstrated the efficacy of catalyst **I** toward the cyclative release of a simple, resin-bound diene substrate, our attention turned to the synthesis of substituted nitrogen heterocycles (**Scheme 3**). Towards this end, treatment of the cinnamyl alcohol resin **5**[10] with with the 2,4-dinitrobenzenesulfonamide of allyl glycine methyl ester under Mitsunobu conditions[13,14] gave intermediate **6**. Direct cleavage using ring closing metathesis[5] gave the pipecolinic acid derivative **7** while sulfonamide removal[14a] followed by acylation[15] and cleavage[5] gave the corresponding unsaturated pipecolinate **8**.

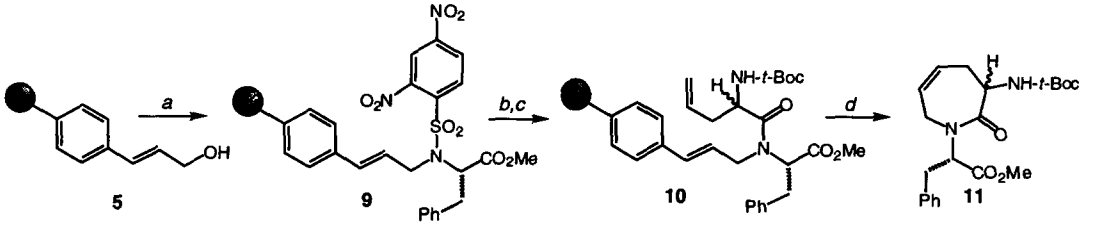
Scheme 3



(*a*) allyl glycine methyl ester-2,4-dinitrobenzenesulfonamide, DEAD, PPh_3, THF, RT, 16h, 70%.[16] (*b*) catalyst **I** (5 mol% based on loading), CH_2Cl_2, RT, 16h, 62%. (*c*) *n*-$BuNH_2$, CH_2Cl_2, RT, 2h. (*d*) *p*-methoxyphenylacetic acid, 1-methyl-2-chloropyridinium iodide, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, reflux, 16h. (*e*) catalyst **I** (5 mol% based on loading),[16] CH_2Cl_2, RT, 16h, 22% from **6**.

Finally, the method was applied to the synthesis of Freidinger lactams[17,18] as shown in **Scheme 4**. Mitsunobu reaction[13,14] between the 2,4-dinitrobenzenesulfonamide of phenylalanine methyl ester and cinnamyl alcohol resin **5** gave intermediate **9**. Sulfonamide cleavage[14a] followed by acylation with racemic *t*-Boc-allyl glycine[15] provided the penultimate resin-bound diene **10**. Cyclative cleavage *via* ring closing metathesis[5] then gave the desired lactam **11** as a 1:1 mixture of diastereomers.

Scheme 4



(*a*) phenylalanine methyl ester-2,4-dinitrobenzenesulfonamide, DEAD, PPh_3, THF, RT, 16h, 69%.[16] (*b*) *n*-$BuNH_2$, CH_2Cl_2, RT, 2h. (*c*) (±)-*N*-*t*-Boc-allyl glycine, 1-methyl-2-chloropyridinium iodide, EtN(*i*-Pr)$_2$, CH_2Cl_2, reflux, 16h. (*d*) catalyst I (5 mol % based on loading),[16] 1,2-dichloroethane, 80°C,16h,16% from **9**.

In summary, we have shown that ring closing metathesis is effective for promoting the cyclative release of functionalized, resin-bound diene substrates. The mild conditions under which cyclization is promoted, combined with the versatility offered by the solid phase 2,4-dinitrobenzenesulfonamide alkylations described herein, renders this a practical method for the construction of structurally diverse heterocycles.

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