

A New Approach to Polycyclic Azonia  
Cations by Ring-Closing Metathesis<sup>‡</sup>

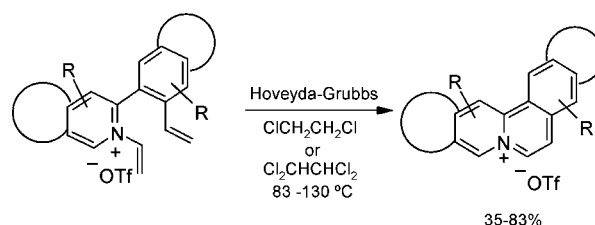
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## ABSTRACT

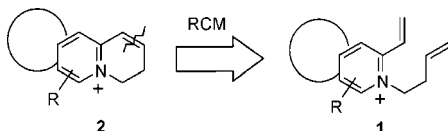


The ring-closing metathesis (RCM) reaction of *N*-vinyl- $\alpha$ -(2-styryl)azinium salts, using the Hoveyda–Grubbs catalyst, leads to different tricyclic and tetracyclic azonia cations with moderate to good yields. This is the first time that a highly electron-deficient alkene such as an *N*-vinylpyridinium has been involved in an RCM process.

Recently, we reported the first examples of a diene<sup>1</sup> and enyne<sup>2</sup> ring-closing metathesis on azinium cations **1**, a process that gave dihydroquinolizinium cations **2**. This strategy proved to be very efficient for the synthesis of quinolizinium derivatives and related systems<sup>3,4</sup> (Scheme 1). Indeed, it can

disconnection. For this class of cations, which includes the dibenzo[*a,g*]quinolizinium cation **6** (the heterocyclic core of cationic alkaloids such as coralyne,<sup>7</sup> berberine, and protoberberines<sup>8</sup>), we envisaged an alternative diene ring-closing metathesis (RCM) process through the disconnection of a  $\beta$  bond (Scheme 2).

**Scheme 1.** 3,4-Dihydroquinolizinium from  $\delta$  Bond Disconnection



be envisaged as a unified approach to a range of azonia cations,<sup>5</sup> including the 3 benzoquinolizinium and many of the 18 possible dibenzo- and naphthoquinolizinium cations.<sup>6</sup>

There are, however, a small number of dibenzo- and naphthoquinoliziniums (**4–6**) for which this strategy, based on the disconnection of the  $\delta$  bond with respect to the quaternary nitrogen, is not feasible because the presence of two benzo fused rings precludes the appropriate bond

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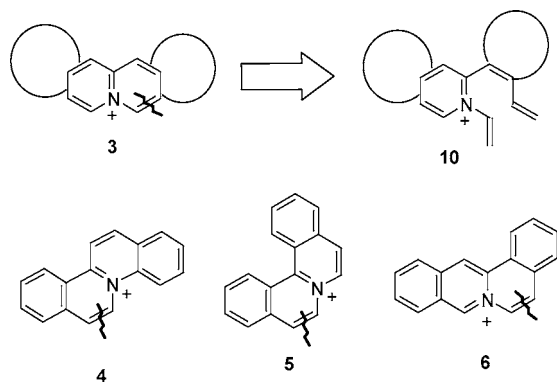
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<sup>‡</sup> Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday.

## Scheme 2. Azonia Cations from $\beta$ Bond Disconnection

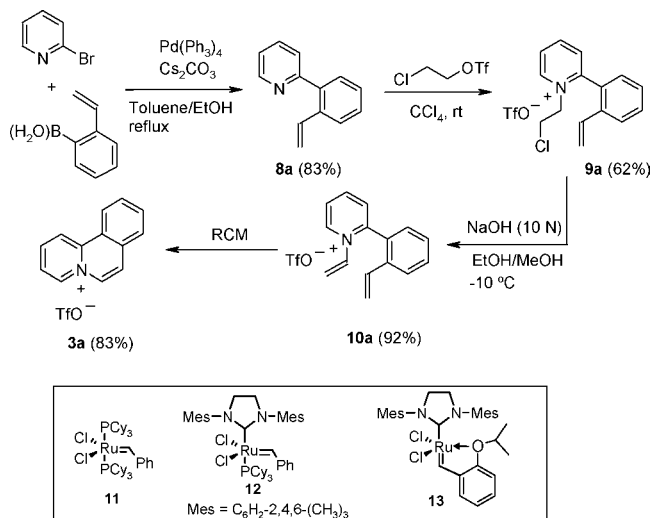


In this communication we report this new approach to polycyclic azonia cations by a diene ring-closing metathesis process involving, for the first time, a highly deficient *N*-vinylazinium system.<sup>9</sup>

Preliminary studies were carried out with the benzo[*a*]quinolizinium cation (**3a**), which is the simplest azonia cation that can be used as a model to study the feasibility of the strategy represented in Scheme 2. Our initial goal was the synthesis of the key intermediate 1-vinyl-2-(2-vinylphenyl)-pyridinium salt **10a**, which was envisaged to be achievable from the corresponding pyridinium salt **9a** by dehydrohalogenation. This salt seemed to be available from 2-(vinylphenyl)pyridine **8a**. The synthesis of **8a** was attempted using three different palladium-catalyzed reactions employing 2-bromo-pyridine and 2-vinylphenylboronic acid<sup>10</sup> or 2-vinylphenylzincate as reagents in Suzuki and Negishi couplings and tributyl(2-pyridyl) tin and 1-bromo-2-vinylbenzene as partners in the Stille reaction. Different conditions were tried but only the Suzuki reaction was successful in producing the coupled compound **8a**, which was obtained in 83% yield after optimization. The conditions used for the successful synthesis of the appropriate diene **10a** are shown in Scheme 3.

A study of the conditions for the metathesis reaction of **10a** showed that this deficient diene was able to afford the expected azonia cation **3a**<sup>11</sup> under different conditions using either Grubbs catalysts **11**<sup>12</sup> and **12**<sup>13</sup> or the Hoveyda–Grubbs catalyst **13**.<sup>14</sup> A summary of the different sets of conditions tested is shown in Table 1 along with the results obtained in this search for the optimum conditions.

## Scheme 3



Although first (**11**) and second (**12**) generation Grubbs catalysts did produce the metathesis reaction, the best yield (83%) was obtained with Hoveyda–Grubbs catalyst (**13**) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (entry 8)—probably because of its higher stability at the reaction temperature<sup>14</sup> (83 °C).

The scope of this metathesis reaction was studied with a variety of substituents either on the pyridinium or benzene rings of the divinyl compound as well as with the appropriate dienic systems, which should produce the tetracyclic azonia cations **4–7**. Most of the substrates employed in the RCM reaction were obtained by following the strategy shown in Scheme 3, but in some cases it was necessary to use alternative methods, for example, for **10e–g** and **10j** (details are given in the Supporting Information).

Initially all the dienic substrates **10b–j** were subjected to the RCM under the optimized conditions found for **10a**. Although these conditions afforded good yields for the 2-methylbenzo[*a*]quinolizinium (**3b**) (Table 2, entry 2), [1,3]-benzodioxolo[5,6-*a*]quinolizinium triflate (**3f**) (Table 2, entry 6) and the dibenzo[*af*]quinolizinium (**4**) (Table 2, entry 8), in the remaining cases the RCM reaction gave only moderate or low yields of the corresponding tricyclic or tetracyclic azonia cations. Consequently, we studied a new set of

**Table 1.** Results for the RCM of **10a**

entry	catalyst	conditions	( <b>3a</b> ) yield <sup>a</sup>
1	<b>11</b> (5%)	$\text{CH}_2\text{Cl}_2$ , rt, 24 h	39
1	<b>12</b> (5%)	$\text{CH}_2\text{Cl}_2$ , rt, 4 h	40
2	<b>12</b> (5%)	$\text{CH}_2\text{Cl}_2$ , rt, 24 h	39
3	<b>12</b> (5%)	$\text{CH}_2\text{Cl}_2$ , 40 °C, 48 h	25
4	<b>12</b> (10%)	$\text{CH}_2\text{Cl}_2$ , rt, 3 h	33
6	<b>13</b> (5%)	$\text{CH}_2\text{Cl}_2$ , 40 °C, 24 h	39
7	<b>12</b> (5%)	$\text{ClCH}_2\text{CH}_2\text{Cl}$ , 83 °C, 3 h	58
8	<b>13</b> (5%)	$\text{ClCH}_2\text{CH}_2\text{Cl}$ , 83 °C, 2.5 h	83

<sup>a</sup> Isolated yield.

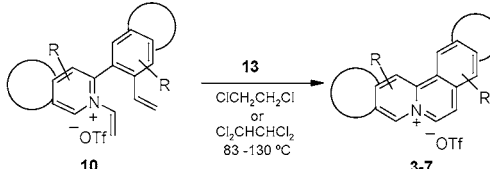
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**Table 2.** Azonia Cations **3–7** from RCM of Dienes **10**

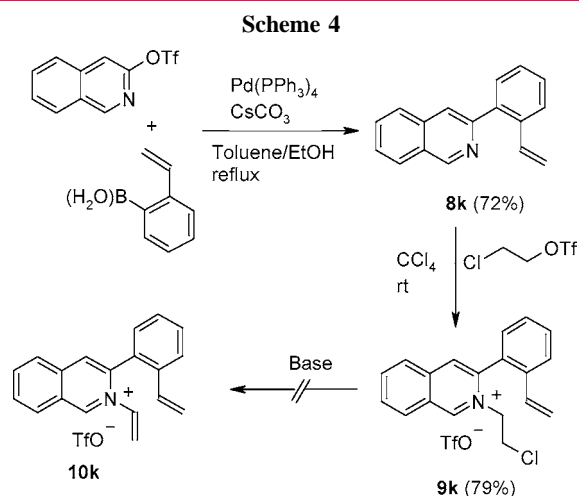
			
entry	<i>N</i> -vinyl- $\alpha$ -(2-styryl)azinium ( <b>10</b> )	azonia cation ( <b>3–7</b> )	yield <sup>a</sup> (%)
1			83
2			83
3			42
4			35
5			81 <sup>b</sup>
6			88
7			39
8			82
9			53 <sup>c</sup>
10			68 <sup>d</sup>

<sup>a</sup> Conditions: (5 mol %), ClCH<sub>2</sub>CH<sub>2</sub>Cl, 83 °C. <sup>b</sup> Conditions: (15 mol %), ClCH<sub>2</sub>CH<sub>2</sub>Cl, 100 °C, sealed tube. <sup>c</sup> Conditions: (5 mmol %), Cl<sub>2</sub>CHCHCl<sub>2</sub>, 130 °C. <sup>d</sup> Conditions: (10 mol %), ClCH<sub>2</sub>CH<sub>2</sub>Cl, 83 °C.

conditions to improve the yields of those reactions that gave poor results. We found that the temperature of the reaction and/or the amount of catalyst seemed to be significant factors to increase the yields of cations **3e**, **5**, and **7**. Thus, an increase in the amount of catalyst from 5% to 10% improved the yield of the naphtho[1,2-*a*]quinolizinium (**7**) from 45% to 68% (Table 2, entry 10). A change in the solvent from dichloroethane to tetrachloroethane allowed these reactions to be carried out at 130 °C, with a considerable improvement in the yield in the case of the dibenzo[*a,f*]quinolizinium (**5**) (from 12% to 53%) (Table 2, entry 9). In the case of 8-chlorobenzo[*a*]quinolizinium (**3e**) the best yield (from 23% to 81%) was obtained on heating the reaction mixture in a sealed tube at 100 °C in the presence of 15% of the catalyst (Table 2, entry 5). It is worth noting that none of these conditions led to an improvement in the yields of **3c**, **3d**, and **3g** (Table 2, entries 3, 4, and 7).

Some of these results can be rationalized by considering the difficulty that dienic substrates **10** have in adopting the appropriate planar conformation to produce the metathesis reaction. When the molecule is planar, a maximum level of steric repulsion is reached, whereas if the two rings adopt an orthogonal arrangement both the steric repulsion and resonance effect would be minimized. In the case of **3c** it is likely that the electronic effect would be determinant since the bromo-substituent reduces further the already high electron deficiency of the vinyl alkene attached to the pyridinium ring.

As stated earlier, the dibenzo[*a,g*]quinolizinium cation **6** was one of our target compounds since this cation is the core heterocyclic system of some relevant natural alkaloids. The precursor of this cation would be the dienic compound **10k**, the synthesis of which was attempted according to the method shown in Scheme 4. To date all our attempts to



generate the diene from **9k** in the presence of different bases (CsCO<sub>3</sub>, KOH, LiOH, Li<sub>2</sub>CO<sub>3</sub>, *t*-BuOK, Et(*i*-Pr)<sub>2</sub>N) have

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proved unsuccessful, with decomposition or complete dealkylation of **9k** observed.

In conclusion, the results described above show that RCM is a viable and general reaction on *N*-vinyl- $\alpha$ -(2-styryl)-azinium species to give polycyclic azonia cations using the Hoveyda–Grubbs catalyst under mild conditions.<sup>15,16</sup> The utility of this strategy, based on a metathesis process involving the formation of a  $\beta$  bond with respect to the bridgehead quaternary nitrogen, was demonstrated by the synthesis of benzo[*a*]-, dibenzo[*af*]-, dibenzo[*af*]-, and naphtho[1,2-*a*]quinolizinium salts in moderate and good yields. Ongoing work is focused on making available some cationic dienes, which are advanced precursors in the total synthesis of some biologically relevant cationic alkaloids such as coralyne, berberines, sempervirine, and flavocorylene, inter alia.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **3**, **10**, and precursors. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) General procedure for benzo- and naphthoquinoliziniums **3–7**. To a solution of **10** (0.15 mmol) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  or  $\text{Cl}_2\text{CHCHCl}_2$  under argon atmosphere, 5–15% of the catalyst **13** was added, and the reaction mixture was heated to 83–130 °C for 2.5–22 h. Then the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as eluent.

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