A new gold-catalysed azidation of allenes†

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A new gold-catalysed azidation reaction of allenes is presented as a new highly modular approach for the synthesis of substituted allyl derivatives containing nitrogen from simple precursors.

Organic azides are common building blocks for the synthesis of natural products and nitrogen-containing heterocycles of pharmacological relevance.1 As classic azides, allyl azides are useful precursors of many functional groups (e.g. amines, nitriles),2 and can be used in copper-catalysed 1,3-dipolar additions to alkynes for the synthesis of allyl triazoles.3 The classic synthesis of allyl azides involves the substitution of primary or secondary allyl derivatives with nucleophilic azides, like NaN₃ or TMSN₃ (Scheme 1a).4 However these methods have limitations, and mixtures of regioisomers are often obtained. Pd- and Mo-catalysed allylic azidations have been also described with better results in the selectivity and scope.5

Allenes are versatile starting materials for developing sequential reactions, affording new and efficient methods for the preparation of complex compounds of synthetic or biological importance. In this area, gold-catalysed intermolecular addition of nucleophiles to allenes is an important reaction that has been widely developed in the last few years, especially for oxygen nucleophiles,6 although the nitrogen7 and carbon-based nucleophile8 versions have also been described. We envisioned that nucleophilic azides could be used in a similar gold-catalysed reaction9 with allenes,10 as a new method for the synthesis of allyl azides. We report here the first examples of this concept and our efforts to develop this new methodology as a highly modular approach for the synthesis of allyl azides with extra functionalities that will enable a straightforward increase in molecular complexity from simple allenes (Scheme 1b).

The challenge of this reaction is that, in contrast with alcohols or amines, the available nucleophilic azides, NaN₃ or TMSN₃, do not have the necessary proton to furnish the protonolysis of the vinyl–gold complex intermediate and therefore, the catalytic cycle cannot be completed.11 In order to close the catalytic cycle, the volatile, toxic and explosive hydrazoic acid, HN₃,12 has to be cautiously generated in situ.13 Nevertheless, protonolysis of vinyl-gold(i) complexes is only one way to close the catalytic cycle and other electrophiles can be employed to break the C–Au bond without the need for hazardous reagents.14

Using commercially available cyclohexylallene (1a) and Ph₃PAuCl/AgOTf, we first investigated the optimal conditions for the hydroazidation reaction. We found that TMSN₃ was the best source of the nucleophilic azide, and trifluoroacetic acid (TFA) in DCM was the best proton source to provide clean complete conversion to the expected allyl azide 2a, with its regioisomer 2a₀, together with allyl trifluoroacetate, 3a, plus acetamide 4a as an unexpected product (Scheme 2).15

Scheme 1 Different approaches for the synthesis of allyl azides.

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Scheme 2 Gold-catalysed hydroazidation of cyclohexylallene.

AgOTf seemed to be the most effective chloride abstractor in this reaction, and was used for catalyst screening.16 NHC–Au complexes did not favour the azidation reaction, and 3a was obtained as the major component in low conversions. The best result was obtained with [(PhO)₂PdCl] as the catalyst. In a final approach to get the optimum conditions, we found that the best ratio of products and
Comparison of the reaction profile by analysis of the $^{31}$P NMR spectra in experiments A and B, where the addition of the allene and the azide were reversed, suggests that the azide coordinates to the gold in both cases, even when the allene is present in the reaction, and therefore an inner-sphere mechanism cannot be ruled out.  

Interestingly, after addition of TFA both reactions exhibited a broad signal in $^{31}$P NMR around 100 ppm together with a sharp singlet at 127 ppm from the free (PhO)$_3$P, which grew over the reaction time.  

This suggests the CF$_3$CO$_2$ is capable of displacing either the (PhO)$_3$P or the N$_3$ from the gold to reach a complex equilibrium where at least three allene–gold complexes might be involved with different ligands/counterions.  

The exchange of $\text{TiO}^-$ by CF$_3$CO$_2^-$ and the displacement of (PhO)$_3$P were also observed in experiment C, where TFA was added first. Further shift of the $^{31}$P NMR signal after addition of the TFA suggests the formation of the complex (PhO)$_3$PAut$^-$OCOF$_3$. The signal from free (PhO)$_3$P was also observed in this reaction when azide was added, suggesting an equilibrium with the complex [(N$_3$)Au(OCOF$_3$)]. When the allene was added to this mixture a similar reaction profile to the experiments A and B was observed. Analysing the signals of the $^1$H NMR spectra we could not observe the proposed vinyl–gold intermediate, but clean conversion to the products, suggesting fast protonolysis. A similar rate of formation of the different products was observed in all experiments after all the components had been added, implying similar catalytic species involved after addition of the acid and suggesting that coordination with the allene and/or the N$_3^-$ might be the rate limiting step for the reaction. When we followed the reaction using NMR under catalytic conditions, a broad signal around 100 ppm, and free (PhO)$_3$P (127 ppm) were observed in $^{31}$P NMR spectra, which suggests that the complicated equilibrium between the complexes shown in Scheme 3 might be existing under catalytic conditions.

Table 1 Scope of the gold-catalysed hydroazidation of allenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allene</th>
<th>Yield (%)</th>
<th>C1/C0 (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Cy 1a</td>
<td>59</td>
<td>2a : 2a' (3.7 : 1)</td>
</tr>
<tr>
<td>2</td>
<td>R = n-hexyl 1b</td>
<td>48</td>
<td>2b : 2b' (1.9 : 1)</td>
</tr>
<tr>
<td>3</td>
<td>R = n-octyl 1c</td>
<td>47</td>
<td>2c : 2c' (1.8 : 1)</td>
</tr>
<tr>
<td>4</td>
<td>R = Ph, 1d</td>
<td>62</td>
<td>2d</td>
</tr>
<tr>
<td>5</td>
<td>R = (MeO)$_2$C(CH$_2$)$_2$, 1e</td>
<td>43</td>
<td>2e : 2e' (3.8 : 1)</td>
</tr>
<tr>
<td>6</td>
<td>R = CH$_2$N-phenanthalimide, 1f</td>
<td>48</td>
<td>2f : 2f'</td>
</tr>
<tr>
<td>7</td>
<td>R = (Boc)$_2$NCH$_2$, 1g</td>
<td>38</td>
<td>2g</td>
</tr>
<tr>
<td>8</td>
<td>R = R' = Me, 1h</td>
<td>2h : 2h' (3.7 : 1)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>R = Ph, R' = n-octyl, 1i</td>
<td>76</td>
<td>2i</td>
</tr>
<tr>
<td>10</td>
<td>R = Br, R' = n-Pr, 1j</td>
<td>67</td>
<td>2j : 2j' (1.3 : 1)</td>
</tr>
<tr>
<td>11</td>
<td>R = Br, R' = i-Pr, 1k</td>
<td>55</td>
<td>2k : 2k' (1.67 : 1)</td>
</tr>
<tr>
<td>12</td>
<td>R = Ph(CH$_2$)$_2$, R' = n-Pr, 1l</td>
<td>70</td>
<td>2l : 2l' (1.1 : 1.13)</td>
</tr>
<tr>
<td>13</td>
<td>R = Ph(CH$_2$)$_2$, R' = i-Pr, 1m</td>
<td>80</td>
<td>2m : 2m' (1 : 1)</td>
</tr>
<tr>
<td>14$^e$</td>
<td>R = p-CF$_3$Ph, 1n</td>
<td>74</td>
<td>2n</td>
</tr>
<tr>
<td>15$^e$</td>
<td>R = p-CF$_3$Ph, R' = n-Pr, 1o</td>
<td>67</td>
<td>2o</td>
</tr>
<tr>
<td>16</td>
<td>R = p-CF$_3$Ph, R' = n-octyl, 1p</td>
<td>72</td>
<td>2p</td>
</tr>
</tbody>
</table>

a 3 observed in traces (< 5%) in the reaction mixture.  
b 4a isolated as a by-product (15%).  
$^c$ Methyl ketones isolated as by-products: 4b (R = n-hexyl, 16%), 4c (R = (MeO)$_2$C(CH$_2$)$_2$, 17%), 4f (R = CH$_2$N-phenanthalimide, 32%).  
d Run without water (0.08 M).  
e Deprotection of one Boc was observed under reaction conditions.  
$^f$ 100% conversion; products not isolated due to volatility issues.  
g Reactions carried out at 30 °C for 60 h.

The reaction works for mono- and disubstituted allenes with different functionalities, but functional groups sensitive to acid are not well tolerated. Allyl azides 2 from the attack to the less substituted carbon of the allene were obtained as the major or only product in moderate to good yields. The regioselectivity of the reaction seems to be dominated by electronic effects: allenes where the substituent was directly substituted with a phenyl group gave only one regioisomer as the major or only product in moderate to good yields. The regioselectivity of the reaction seems to be dominated by electronic effects: allenes where the substituent was directly substituted with a phenyl group gave only one regioisomer as the major or only product in moderate to good yields.

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detailed mechanistic study is underway in our laboratories. Further investigation into this and a more comprehensive understanding of these reactions are necessary. Preliminary mechanistic studies point out to a complex mechanism involving multiple steps, including nucleophilic addition, elimination, and trapping. Allenes, but functional groups sensitive to acid are not well tolerated.

All the control experiments gave negative results (see ESI for details). For silver effect in gold catalysis, see: D. Wang, R. Cai, S. Sharma, J. Irak, S. K. Thummampanelli, N. G. Akhmedow, H. Zhang, X. Liu, J. L. Pettersen and X. Shi, J. Am. Chem. Soc., 2012, 134, 9012–9019. Gold-catalysed reaction of allenes in the presence of water gives allyl carbonates, the starting material was recover unreacted, implying that our reaction was carried out in the absence of gold or silver complexes, the starting material was recover unreacted, implying that our reaction was carried out in the absence of gold or silver.

Notes and references


2 For selected examples of in situ generation of HN3 using TMSN5, see: (a) W. Zhou, J. Xu, L. Zhang and N. Jiao, Tetrahedron, 2009, 65, 1794–1798. However, despite the high excess of water, we do not observe significant amounts of hydration of the alene in our reaction, and formation of 3 is minimised.

3 Different proton sources and additive to modulate the pH were tested, being TFA (3 eq.) plus water (5 eq.) the best combination for yield and selectivity. See Tables S2 and S3, in ESI.


