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# Synthesis of Polycyclic Compounds by a Cascade Cycloisomerisation/Diels–Alder Reaction

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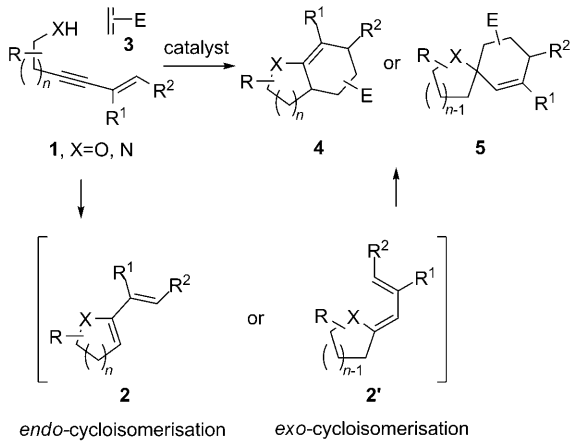
*Dedicated to Professor Saverio Florio on the occasion of his 70th birthday*

Cascade (domino) reactions provide an efficient way to construct complex molecular structures from readily available organic compounds.[1] Particularly interesting is the synthesis of heterocycles through cascade reactions, involving the intramolecular addition of a heteroatomic nucleophile to an alkyne that is activated by a π-acid[2] (as defined by Fürstner and Davies).[3] The increasing interest in this field of research is probably due to the ability of gold complexes to promote unusual processes. For example, some elegant new gold-catalysed reactions involving atypical intramolecular redox processes have recently been published.[4] In this context, we have developed several transition-metal-catalysed reactions of ω-alkynols based on the initial formation of enol ethers, through an intramolecular hydroalkoxylation process,[4] which react in situ with nucleophiles and/or electrophiles.[5] Following on with our interest in this field, we thought that the cycloisomerisation of functionalised enynes **1** would afford 1,3-butadiene derivatives **2** (or **2′**), which might then react in situ with appropriate dienophiles **3** to afford interesting fused bicyclic compounds **4** or spirocycles **5**, depending upon the initial mode of cyclisation (*endo* or *exo*) of enyne derivative, **1** (Scheme 1). The preliminary results of this reaction are given here.



Scheme 1. Concept of the cascade cycloisomerisation/Diels–Alder cycloaddition reaction.

First, we evaluated the reactivity of a series of functionalised enynes **1** ($n=1$), derived from 3-butyn-1-ol or 3-butyn-1-amine, in the presence of dienophiles, such as *N*-phenylmaleimide (**3a**) and tetracyanoethylene (**3b**). After screening catalysts we discovered that gold(III) chloride ($AuCl_3$) was the most suitable to perform the desired cascade 5-*endo* cycloisomerisation/Diels–Alder cycloaddition reaction.[6,7]

When the reaction was carried out in dichloromethane, at room temperature, we obtained compounds **4** in high yields (Scheme 2). Structural assignments of these new compounds were based on a series of $^1H$ NMR studies. Additionally, the structures of compounds **4d** and **k** were confirmed by single-crystal X-ray diffraction analyses.[8]

Compounds **4** are the result of an initial intramolecular hydroalkoxylation (products **4a–l**) or hydroamination (products **4m–o**) of the triple bond in **1**, followed by cycloaddition of the formed diene **2** with the corresponding dienophile **3**. In those cases in which *N*-phenylmaleimide **3a** was used, the corresponding products **4** were obtained as single diastereoisomers, because of an *endo*-cycloaddition of the corresponding intermediate **2** with *N*-phenylmaleimide (**3a**). It should be noted that in compounds **4a** and **o** isomerisation of the double bond into an endocyclic position occurs

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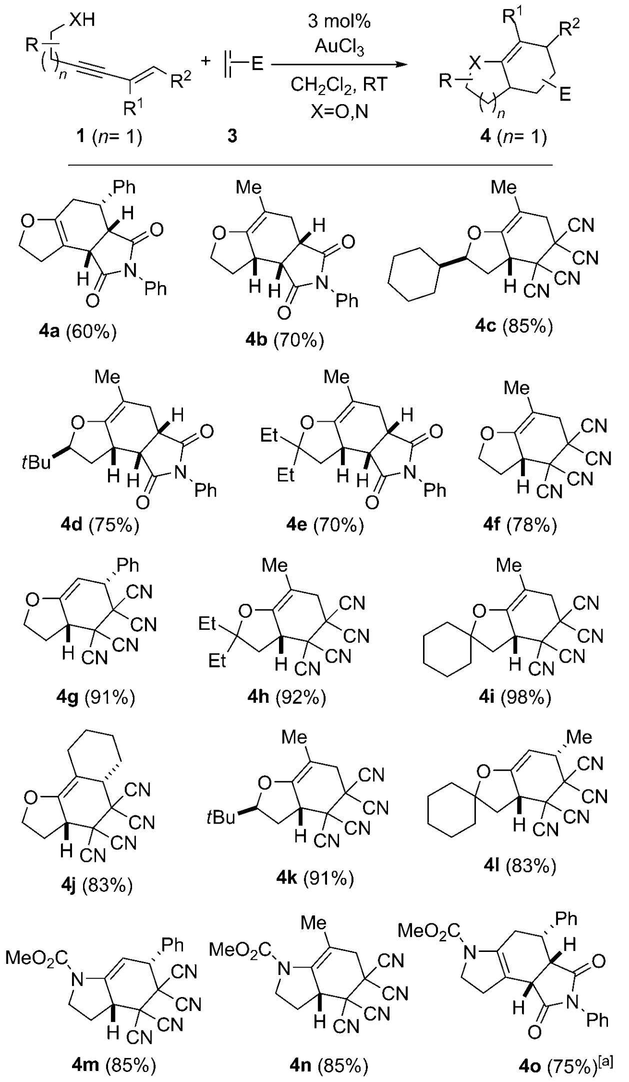
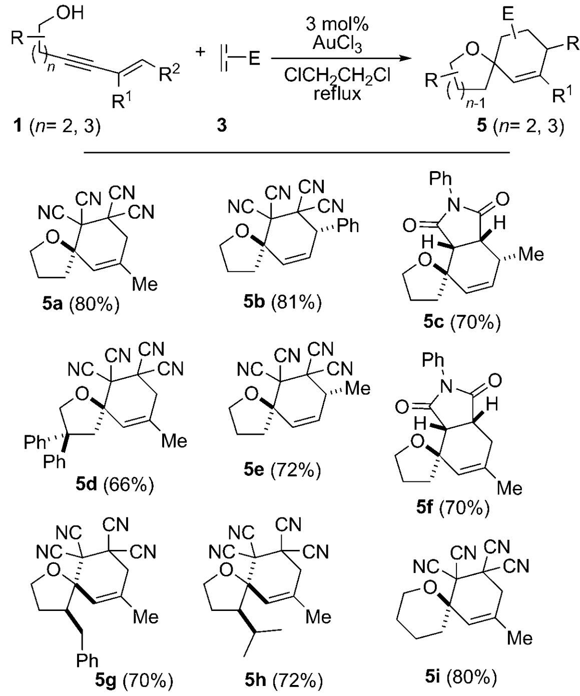


Scheme 2. Products **4** obtained by the cascade, 5-*endo* cycloisomerisation/Diels–Alder cycloaddition reaction. [a] The reaction was performed in 1,2-dichloroethane at reflux.

under the reaction conditions. We have no clear explanation for this isomerisation reaction. This unusual behaviour was observed only when *N*-phenylmaleimide **3a** reacted with dienes derived from styryl-substituted alkynes **1**. The reactions that form compounds **4c**, **d** and **k** are remarkable. As shown, these compounds are derived from chiral alkynol derivatives **1**. In these cases, we only observed the formation of a single diastereoisomer corresponding to those structures shown in Scheme 2. These results are significant as they indicate that the substrate-controlled synthesis of enantiomerically pure derivatives **4** from enantiomerically pure enynes **1** is possible.

The role of the gold catalyst in the Diels–Alder reaction was investigated by the independent synthesis of diene 5-[(*E*)-styryl]-2,3-dihydrofuran (**2g**). We observed that this diene did not react with tetracyanoethylene in the absence of the gold catalyst, under the reaction conditions previously described (room temperature). However, by heating the mixture at reflux in dichloromethane overnight we observed the formation of compound **4g**. These experiments indicate that the gold catalyst promotes the Diels–Alder reaction.

It should be noted that the formation of fused compounds **4** is due exclusively to the reaction of enyne derivatives **1** ($n=1$) through a 5-*endo*-type cycloisomerisation to give intermediates **2**. In accordance with Baldwin's rules, the alternative 4-*exo* cycloisomerisation reactions, to give the hypothetical exocyclic dienes analogous to **2′**, are disfavoured processes. In this context, we were intrigued about the behaviour of enynol derivatives with a longer chain between the hydroxyl group and the triple bond [see enyne derivatives **1** ($n=2$, 3) in Scheme 3]. In these cases competitive 5-*exo*/6-*endo* or 6-*exo*/7-*endo* processes may occur and so fused compounds analogous to **4** or spirocyclic products **5** could, in theory, be obtained (see Scheme 1). However, when we performed the reactions of these enynol derivatives (**1**; $n=2$ or 3) with dienophiles **3a** or **b**, in the presence of $AuCl_3$ (3 mol%) in dichloroethane at reflux, we were able to isolate only the spirocyclic products **5** (Scheme 3).



Scheme 3. Products **5** obtained by the cascade 5-*exo* or 6-*exo* cycloisomerisation/Diels–Alder cycloaddition reaction.

Compounds **5** are the result of an initial 5-*exo*- (for furan derivatives **5a–h**) or 6-*exo*-cyclcloisomerisation reaction (for pyran derivative **5i**) of the corresponding enynol derivatives **1** ($n=2$ or 3) to give dienes **2′**. We did not observe, in any case, the formation of products derived from the competitive, initial *endo*-cycloisomerisation reactions that would furnish dienes **2**. Structural assignments of compounds **5** were based on a series of $^1$H NMR studies. Additionally, the structures of compounds **5b** and **h** were confirmed by single-crystal X-ray diffraction analyses.[9]

In conclusion, a new $AuCl_3$-catalysed cascade reaction based upon an initial cycloisomerisation reaction of enynol or enynamine derivatives to form 1,3-butadiene derivatives that then undergo an in situ Diels–Alder cycloaddition reaction with appropriate dienophiles has been described. This new process affords interesting fused or spirocyclic compounds in an efficient and simple manner. The scope of these reactions and the possibility of applying this strategy to the synthesis of natural products are currently being investigated in our laboratory.

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**Keywords:** coupling reactions · Diels–Alder reactions · domino reactions · gold · homogeneous catalysis

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[8] CCDC-737926 (**4d**) and 737927 (**4k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] CCDC-766618 (**5b**) and 766619 (**5h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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