



Synthesis of polycyclic heterocycles via sequential Au-catalyzed cycloisomerization and Ru-catalyzed metathesis reactions

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ABSTRACT

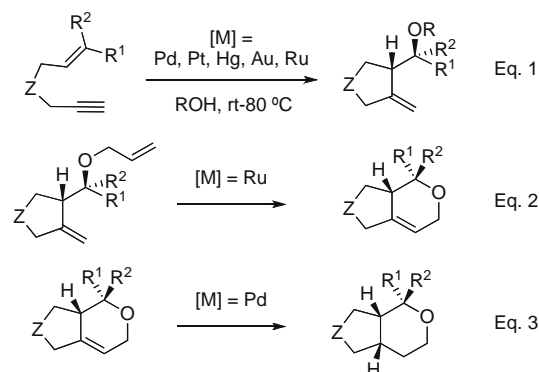
A sequential and efficient catalytic preparation of polycyclic heterocycles, including tetrahydro furo- or cyclopenta- pyran, hexahydropyrano pyrrolidine, and tetrahydroisochromene derivatives is described based on a gold-catalyzed cycloisomerization reaction followed by a Ru-catalyzed ring-closing metathesis. An isomerization of the alkene moiety leading diastereoselectively to cis tetrahydrocyclopenta[c]pyran and tetrahydro-1H-furo[3,4-c]pyran is observed in some cases. The catalytic hydrogenation reactions of these tetrahydropyrans led to the formation of polycyclic-functionalized saturated compounds.

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The transition metal-catalyzed reactions and specifically homogeneous catalysis have given a considerable impetus to the progress of the area of organometallic, organic, and industrial chemistries.¹ Among them, carbon–carbon and carbon–oxygen bond formations using gold² and ruthenium³ organometallic catalysts are fundamentally important because they provide successful solutions to environmental, economic concerns. Whereas gold catalysis was only recognized recently for the promotion of a myriad of transformations, ruthenium catalysis and more specifically ruthenium-catalyzed metathesis⁴ has been well established as an important tool for the organic chemist. As part of our ongoing program toward the development of catalytic cycloisomerization reactions,⁵ we have been interested in the synthesis of polycyclic derivatives and we have envisaged to test a sequential gold-catalyzed alkoxy cyclization with a ruthenium-catalyzed ring-closing metathesis reaction. We and others have indeed described metal-catalyzed alkoxy cyclization of enynes leading to cyclic ethers (Scheme 1, Eq 1).^{5,6} We anticipated that allylic derivatives might be engaged in Ru-catalyzed metathesis leading to bicyclic derivatives (Scheme 1, Eq 2). The resulting heterocycles would be valuable skeleton for the synthesis of natural and/or pharmaceutical product derivatives.⁷ Further hydrogenation reaction would then potentially allow the preparation of polycyclic heterocycles (Scheme 1, Eq. 3), controlling therefore three stereogenic centers by catalytic reactions. The sequential gold-catalyzed cycloisomerization/ring-closing metathesis has been scarcely described in the literature⁸ and only concerned the ring-closing metathesis reactions of a diene resulting from the addition of an allylsilane to 1,6-enynes^{8a} or a methoxycyclized bearing a geranyl and allyl side

chains.^{8b} These strategies respond to environmental concerns and contribute to the concept of green chemistry.¹

As gold catalysts have been described for the alkoxy cyclization step,^{5,6} we tested the allyloxy cyclization reaction on various enynes. The catalyst combining Au(III)/PPh₃ and various silver salts was chosen for this study and the reaction was conducted in allylic alcohol which is used as a solvent at room temperature (Table 1). The addition of allylic alcohol was successfully realized on carbon and heteroatom-linked 1,6-enynes (Table 1, entries 1–5). The allylic ethers **2a–e** were isolated in good to excellent yield. In the same manner as previously reported, one diastereomer was isolated for **2a**, **2b**, and **2e**. The lower reactivity of nitrogen-tethered enynes^{9,5c} prompted us to test the silver bis(trifluoromethanesulfonyl)imide as a halide-abstracting agent (Table 1, entries 4 and 5). The corresponding ethers were thus prepared under mild



Scheme 1.

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Table 1
Gold-catalyzed allyloxycyclization reaction of enynes **1c–j**



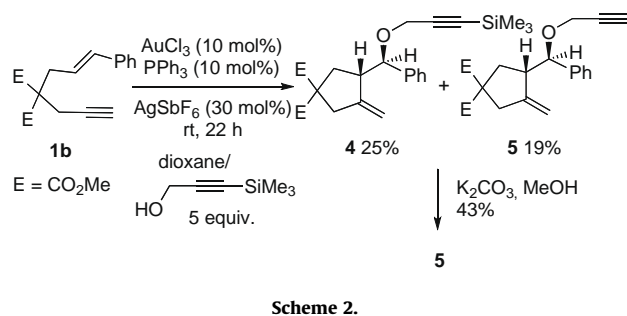
Entry	Enyne 1	Conditions	t (h)	Product 2	Yield ^a (%)
1		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgSbF ₆ 10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgOTf	2		79
			2.5		66
2		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgSbF ₆ 10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgOTf	1.5		90
			2.5		89
3 ^b		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgNTf ₂	4.5		56
4		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgNTf ₂	16		70
5		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgNTf ₂	2.5		53
6		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgSbF ₆ 10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgNTf ₂	72	SM	/
			72		
7		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgOTf	53		26 ^b
8		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgOTf	14		42
9		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgOTf	14		86
10		10 mol %AuCl ₃ , 10 mol %PPh ₃ , 30 mol %AgSbF ₆	1		65

^a Isolated yield.

^b 60% conversion.

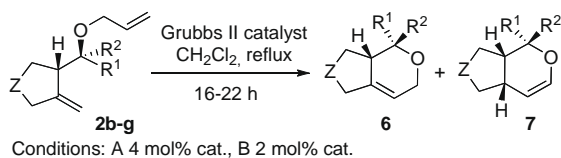
conditions at room temperature and isolated in 70% and 53% yields, respectively. No reactivity was observed for aryl-substituted enyne **1f** (Table 1, entry 6). The reaction of methyl-substituted prop-2-enyl substrates **1g**, **1h** (Table 1, entries 7 and 8) was more sluggish,

with several unidentified by-products being observed. The ether **2g** was isolated in 26% yield. In the case of crotyl-substituted derivative **1h**, as previously reported,^{5c} the reaction led selectively to the six-membered ether **2h**, which was obtained in 42% yield.



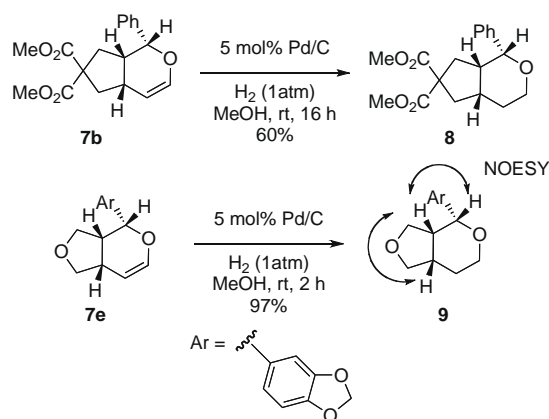
The allyloxycyclization reaction of 1,7-enyne **1i** afforded the desired ether in a modest 33% yield, the major product **3** resulting from the formal hydration of the alkyne moiety (Table 1, entry 9). We also prepared a chiral 1,6-enyne **1j** starting from commercially available (*R*)-but-1-yn-3-ol via a classical Williamson reaction. We were pleased to find that the tandem addition/cyclization smoothly occurred and led to the formation of two diastereomers **2j** and **2j'** in 65% yield and in a 86/14 ratio. The stereochemistry of the major isomer was determined by NMR NOESY experiment.

Table 2
Ruthenium-catalyzed metathesis reaction of dienes **2b–g**



Entry	2	Cond.	Products	Yield ^a (%)
1	2c	A		64
2	2d	A		64
3	2e	A B	 6e : 7e (1:4) 6e : 7e (46:54)	76 74
4	2b	A		99
5	2b	B	 6b : 7b (79:21)	99
6	2g	A		80

^a Isolated yield. Ar = 2,3-(CH₂OCH₂)₂-C₆H₃



We also examined the possibility of introduction of propargylic alcohol, which would potentially allow an enyne metathesis process. The addition of propargylic alcohol to the enyne **1b** gave rise to the degradation of the starting material, either in the presence of allylic alcohol as the solvent or in a 6:1 mixture of dioxane/propargylic alcohol. The introduction of trimethylsilylpropargylic alcohol was successful and led to a mixture of **4** and **5** in 44% overall yield (Scheme 2). This mixture was directly engaged in a desilylation process under classical conditions, which afforded **4** in 43% yield. Other attempts to introduce trimethylsilylpropargylic alcohol on enynes **1a** or **1e** unfortunately did not give the desired products.

Our efforts next focused on the Ru-catalyzed metathesis reaction of the cyclopentadienes **2** in the presence of Grubbs II catalyst (2 or 4 mol %).⁴ The carbo- and heterocyclic ethers **2c** and **2d** reacted smoothly in the presence of 4 mol % of Grubbs II catalyst and the expected alkenes **6c** and **6d** were isolated in 64% yield (Table 2, entries 1 and 2). The reactivity of **2e** was particularly interesting as an isomerized derivative **7e** was isolated in 40% yield (Table 2, entry 3). The diastereoselectivity of this isomerization was further demonstrated after the hydrogenation reaction step on derivative **9**. Ru-catalyzed isomerization of olefins has been recently highlighted and was firstly described by Nishida, Cossy, and Alcaide groups in the presence of Grubbs II catalyst.¹⁰

The **6e/7e** ratio was showed to depend on the catalyst loading. The use of 2 mol % of catalyst led to a quasi equimolar quantity of alkenes **6e** and **7e** (Table 2, entry 3). The reactivity of enyne **1b** followed the same trend (Table 2, entries 4 and 5). The completely isomerized derivative **7b** was isolated in 99% yield in the presence of 4 mol % catalyst (Table 2, entry 4), whereas a 80:20 **6b/7b** mixture was obtained in the presence of 2 mol % of Grubbs II catalyst (Table 2, entry 5). The ring-closing metathesis of **2g** was also successful and afforded the tetrahydro-1*H*,3*H*-isochromene derivative **6g** in 80% yield (Table 2, entry 6). The enyne metathesis was attempted on substrate **5**, no conversion was observed after 102 h.

We then envisaged synthesizing completely saturated **5/6** bicyclic derivatives via the catalytic hydrogenation of the alkene moiety (Scheme 3). The classical hydrogenation of **7b** and **7e**, conducted in the presence of 5 mol % Pd/C in methanol at room temperature under 1 atm pressure H₂ afforded the corresponding bicyclic adducts **8** and **9** in 60% and 97% yields, respectively. The diastereoselectivity of the tandem gold-catalyzed reaction and the Ru-catalyzed ring-closing metathesis/isomerization process was fully demonstrated at this stage by NMR NOESY experiment on compound **9**.

In conclusion, we have developed a sequential catalytic preparation of polycyclic heterocycles based on a gold-catalyzed cycloisomerization reaction followed by a Ru-catalyzed ring-closing

metathesis, leading efficiently to tetrahydro furo- or cyclopentapyran, hexahydropyrano pyrrolidine and tetrahydroisochromene skeletons. The second catalytic step was accompanied in some cases with an isomerization of the alkene moiety leading diastereoselectively to cis tetrahydrocyclopenta[c]pyran and tetrahydro-1H-furo[3,4-c]pyran. The catalytic hydrogenation reactions of these tetrahydropyrans led to the formation of polycyclic-functionalized saturated compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.001.

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