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Efficient cyclization routes to substituted heterocyclic compounds mediated by transition-metal catalysts*

Janine Cossy

Laboratory of Organic Chemistry, ESPCI ParisTech, CNRS, 10 rue Vauquelin 75231, Paris Cedex 05, France

Abstract: Cyclizations induced by transition metals such as palladium, platinum, gold, and ruthenium can produce functionalized heterocycles such as 3-(arylmethylene)isoindolones, γ-lactones, and unsaturated δ-lactones.

Keywords: 3-(arylmethylene)isoindolones; cyclization; heterocycles; lactones; metals; metathesis.

INTRODUCTION

The use of transition metals for the synthesis of fine chemicals and complex molecules continues to be attractive and important. On our part, we were interested in synthesizing a variety of amine- and oxygen-containing heterocycles from simple starting materials through the use of different metal catalysts such as palladium, platinum, gold, or ruthenium in order to induce a cyclization step. Depending on the metal catalyst, a wide range of 3-(arylmethylene)isoindolones and lactones as well as substituted dihydropyrrolidines were obtained from ynamines. Furthermore, very efficient one-pot procedures were developed to produce functionalized lactones by using a one-pot hydrosilylation/ring-closing metathesis(RCM)/proto-desilylation sequence.

PALLADIUM CATALYSIS

Substituted 3-(arylmethylene)isoindolones **A** are present in a great variety of naturally occurring and biologically active compounds [1]. Their preparation was often achieved by nucleophilic additions to phthalimides **B** followed by a dehydration step. However, using this procedure, mixtures of regioisomers were obtained in the case of unsymmetrical substrates [1,2] (Fig. 1).

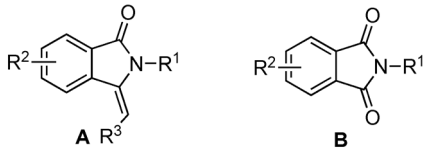

Fig. 1

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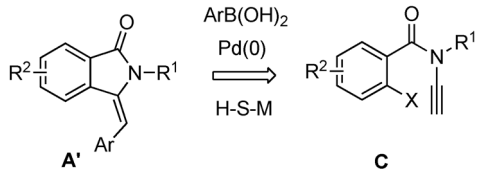
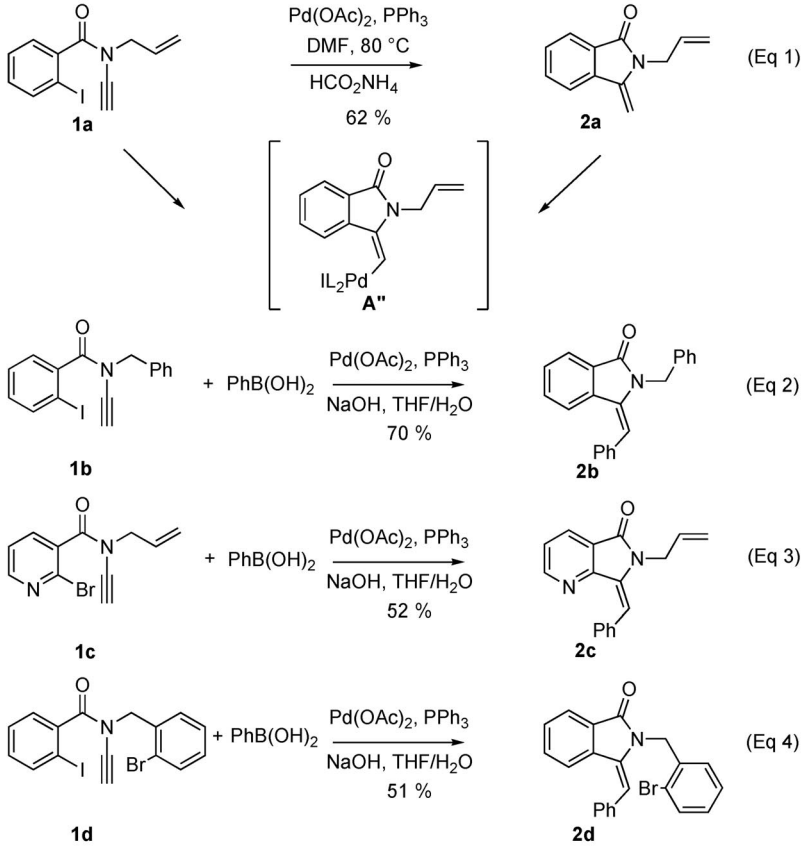
Access to compounds of type **A** was improved with the development of methods such as palladium-catalyzed carbonylation [3], heteroannulations [1,4], and Horner condensation [1,5]. An alternative strategy to access a variety of (*E*)-3-(arylmethylene)isoindolin-1-one **A'**, proceeding from ynamines **C** and diverse arylboronic acids, was envisioned. This strategy relies on a Pd(0)-catalyzed Heck–Suzuki–Miyaura (HSM) cascade reaction [6] (Scheme 1).



Scheme 1

Two Pd(0)-catalyzed steps, a Heck and a Suzuki–Miyaura reaction, were planned to be involved in the synthesis of 3-(arylmethylene)isoindolin-1-ones **A'** from ynamines **C**. The feasibility of the Heck reaction was first examined. Thus, when ynamine **1a** was treated with a catalytic amount of $Pd(OAc)_2$ and PPh_3 in dimethylformamide (DMF) at 80 °C in the presence of ammonium formate [to regenerate Pd(0)-catalyst from the formed intermediate α-vinyl-palladium complex **A''**], 3-(methylene)isoindolin-1-one **2a** was formed in 62 % yield (Scheme 2, eq. 1). Having demonstrated that ynamines can be in-



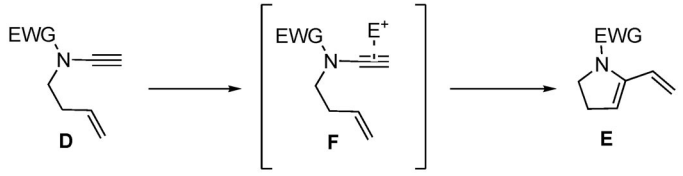
Scheme 2

volved in carbopalladation processes, the HSM cascade reaction was examined next. When ynamine **1b** was treated with phenylboronic acid in the presence of $Pd(OAc)_2$, PPh_3 and aqueous NaOH in refluxing tetrahydrofuran (THF), 3-(arylmethylene)isoindolin-1-one **2b** was obtained in 70 % yield as a single geometric isomer in the (*E*)-configuration. This reaction is general as ynamines **1c** and **1d** were transformed to corresponding 3-(arylmethylene)isoindolin-1-ones **2c** and **2d**, respectively, in good yields [6] (Scheme 2, eqs. 2–4).

Thus, from ynamines, efficient stereoselective access to (*E*)-cyclic enamines, particularly to (*E*)-3-(arymethylene)isoindolin-1-ones, using a Pd(0)-catalyzed HSM cascade reaction was developed [6].

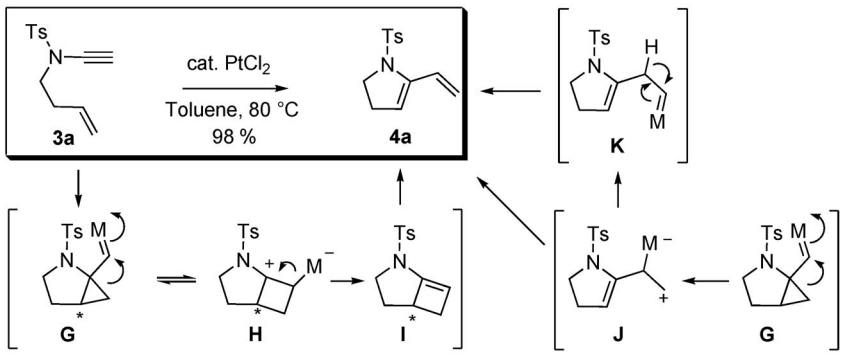
PLATINUM AND GOLD CATALYSIS

As ene-ynes can be cycloisomerized in the presence of platinum and gold catalysts [7a], these two catalysts have been considered for the synthesis of heterocyclic compounds of type **E** from ene-ynamines **D** via intermediates **F** (Scheme 3).



Scheme 3

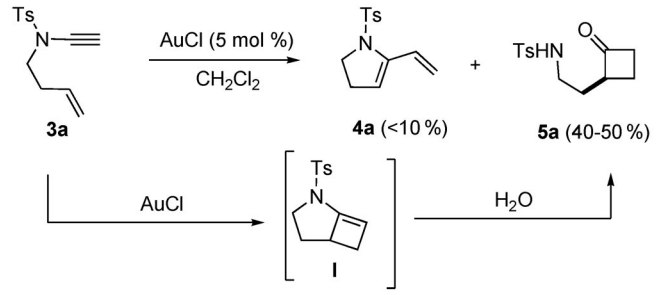
When **3a** was treated with $PtCl_2$ in refluxing toluene, the "formal metathesis product" **4** was isolated in 98 % yield [8] (Scheme 4). This compound was assumed to arise from cyclopropyl platinum carbene intermediate **G** [9], which underwent ring expansion to cyclobutyl cation **H**, stabilized by the nitrogen atom [10], and then a demetalation afforded cyclobutene intermediate **I**. This latter intermediate underwent an electrocyclic ring opening to produce 1,3-diene **4a**. However, recent mechanistic studies suggest that **4a** can come from the cyclopropylmetal carbene **G** via intermediates **J** and **K** [9].



Scheme 4

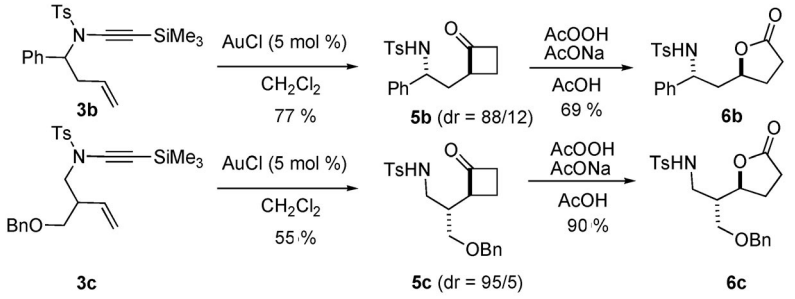
By using $PtCl_2$, the stereocenter generated during the cycloisomerization of the ene-ynamine is lost during the electrocyclic ring opening of **I**. In order to avoid the loss of this stereogenic center, the electrocyclic ring opening of the cyclobutene intermediate was avoided by using milder conditions. To this end, we decided to investigate the gold-catalyzed cycloisomerization of 1,6-ene-ynamines. When

3a was treated with AuCl (5 mol %) in CH_2Cl_2 at rt, a different reactivity was observed as 1,3-diene **4a** was detected as a minor product (<10 %) and cyclobutanone **5a** was the major compound, isolated in 40–50 % yield (Scheme 5). Although, the reaction was achieved under anhydrous conditions, exposure to atmospheric moisture during the work-up was sufficient to promote the hydrolysis of the presumed cyclobutene intermediate **I** [7a,7b].



Scheme 5

The reaction is general as **3b** and **3c** were transformed to the corresponding cyclobutanones **5b** and **5c** in good yields and with excellent diastereoselectivities when a stereogenic center was present either at the α or β position to the nitrogen atom (dr ≈ 90/10) (Scheme 6). The sensitive cyclobutanones **5b** and **5c** were transformed into oxygenated heterocycles, e.g., to the corresponding functionalized γ-lactones **6b** and **6c**, respectively, by using a stereospecific Baeyer–Villiger reaction [7] (Scheme 6).

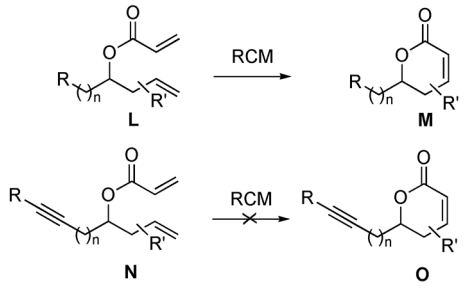


Scheme 6

RUTHENIUM CATALYSIS

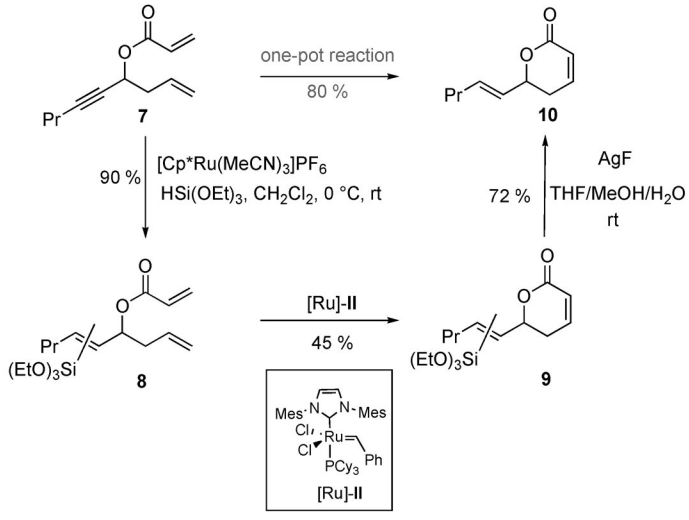
Given our results with γ-lactones, we were also interested in synthesizing functionalized six-membered ring lactones as these structural features are present in a great variety of biologically active compounds such as the phoslactomycins, callystatin, and pironetin. In order to access these latter lactones, the utilization of an RCM using ruthenium complexes was envisioned.

While RCM has proven to be a useful reaction to access α,β-unsaturated lactones **M** from dienes **L** [11], it appears useless when applied to alkyne-containing substrates such as **N** [12] (Scheme 7). This failure is probably due to chelation that occurs between the alkyne moiety and the catalyst, yielding an inactive complex. One way to avoid the deactivation of the catalyst is to protect the triple bond. This can be realized either by the introduction of a very bulky silyl group [13] or by complexating the alkyne moiety with hexacarbonyl dicobalt [14]. However, these methods require either harsh conditions, which are not compatible with many substrates [15], or unnecessary steps.



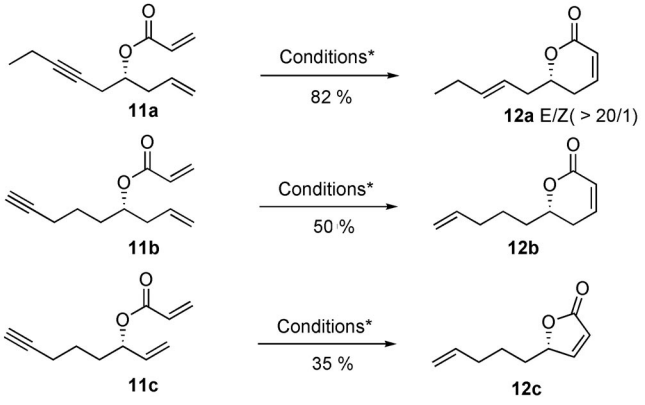
Scheme 7

As the development of simple, chemoselective, and efficient one-pot procedures for obtaining complex molecules is one of our goals, a one-pot procedure featuring a hydrosilylation/RCM/protodesilylation has been developed. In order to prove the viability of the sequence, each step was carried out separately on **7** (Scheme 8). At first, compound **7** was hydrosilylated using $HSi(OEt)_3$ in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ in CH_2Cl_2 [16] to produce **8** in 90 % yield as a mixture of regioisomers but with complete chemoselectivity. Then, **8** was subjected to RCM conditions (Ru-**II**, CH_2Cl_2, 40 °C) to afford the corresponding α,β-unsaturated lactone **9** in a moderate yield of 45 %. Finally, **10** was protodesilylated using AgF in a $MeOH/H_2O/THF$ (1/1/10) mixture [17] at rt to afford the desired (*E*)-ω-alkyl α,β-unsaturated lactone **10** (72 % yield). Thus, compound **10** was obtained in three steps with an overall yield of 20 %. In order to avoid the loss of material associated with the purification of the intermediates, a one-pot three-step process was carried out. Thus, when **7** was treated with $[Cp^*Ru(MeCN)_3]PF_6$ in the presence of $HSi(OEt)_3$, after complete conversion of the starting material [Ru]-**II** was added to the reaction mixture (CH_2Cl_2, 40 °C), and when the RCM was done, the reaction mixture was treated with AgF. To our delight, (*E*)-alkenyl α,β-unsaturated lactone **10** was isolated in 80 % yield, showing the power of this one-pot process [18].



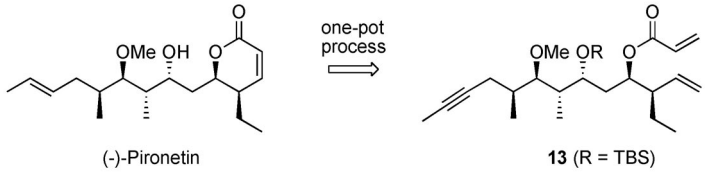
Scheme 8

These conditions were then applied to compounds **11a–c**, which were transformed into the corresponding ω-alkenyl α,β-unsaturated lactones **12a–c** in yields varying from 35 to 82 % [18] (Scheme 9).



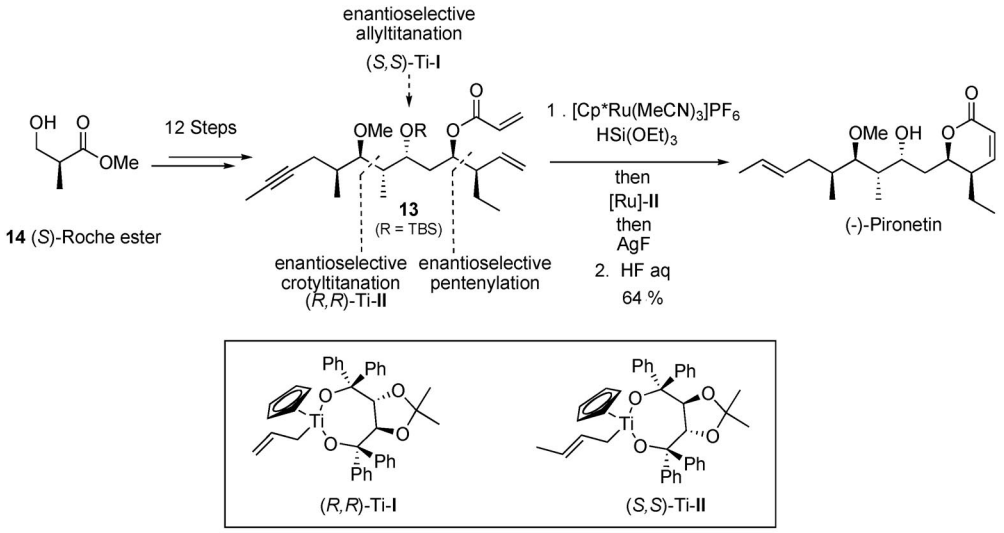
Scheme 9

Following these results, we were particularly interested in applying this one-pot process to α,β-unsaturated γ-lactone-containing natural products, particularly (–)-pironetin. (–)-Pironetin displays plant-growth regulatory [20] as well as immunosuppressive activities, and recently this compound has been identified as a strong antitumor agent by inhibiting the polymerization of tubulin [21]. Due to its limited availability and its interesting biological activity, the synthesis of pironetin was very attractive and several total syntheses have been reported [22]. Our strategy involved the one-pot process previously described. Thus, access to (–)-pironetin was envisioned from **13** by using the hydrosilylation/RCM/protodesilylation process in order to build the γ-lactone moiety (Scheme 10).



Scheme 10

The unsaturated ester **13** was prepared from (*S*)-Roche ester **14** in 12 steps (Scheme 11). Control of the stereogenic center at C7 was achieved by using the highly face-selective allyltitatium complex (*S*,*S*)-Ti-**I** [23]. The stereocontrol at C8 and C9 was achieved by using the crotyltitanium agent (*R*,*R*)-Ti-**II** [23]. The establishment of the stereogenic centers at C4 and C5 was carried out by utilizing a highly stereoselective boron-mediated pentenylation that has been previously developed in our group [24]. This 12-step sequence set the stage for our one-pot hydrosilylation/RCM/protodesilylation process that was successfully applied to **13**. After deprotection of the hydroxy group at C6 using aqueous HF, (–)-pironetin was isolated in 64 % yield (for the last two steps) [25]. The spectroscopic and physical



Scheme 11

data of the synthesized (–)-pironetin were in accordance with those reported for the natural product [19–21].

By using very simple procedures and depending on the metal catalyst used, a diversity of functionalized heterocyclic compounds was obtained from very simple starting materials and in good yields.

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