Sustainable Heterocycle Synthesis via Gold Catalysis: Exploring Amino Acids and Water-Soluble Catalysts

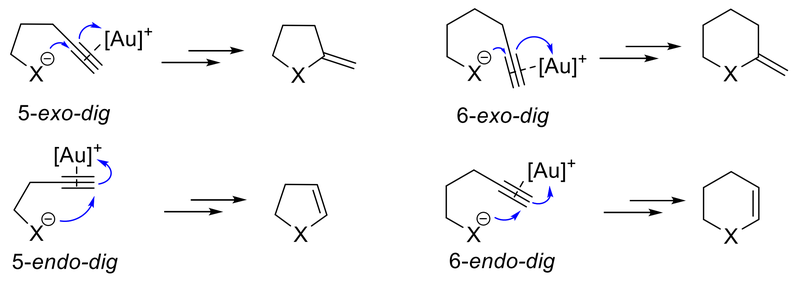
Tomás A. Dómina, Liddier O. Pérez and Sebastián A. Testero

Rosario Chemistry Institute, (IQUIR, CONICET-UNR), Organic Chemistry Division, School of Biochemical and Pharmaceutical Sciences, National University of Rosario (FCByF-UNR), Suipacha 531, S2002LRK, Rosario, Argentina.

domina@iquir-conicet.gov.ar

INTRODUCTION

Over the past twenty years, the scientific community has begun to explore the various applications of gold - a metal long considered "inert" - as a homogeneous catalyst for chemical reactions. The attractiveness of the use of gold in catalysis stems from its **high selectivity for the activation of multiple bonds**, mainly alkynes, towards nucleophilic attack.[1] This characteristic allows its use for heterocycle synthesis (**Scheme 1**). Heterocyclic ring systems are essential in drug design, serving as core structures in many approved drugs. Nitrogen- and oxygen-containing heterocycles, in particular, have become increasingly significant in recent years.[2]



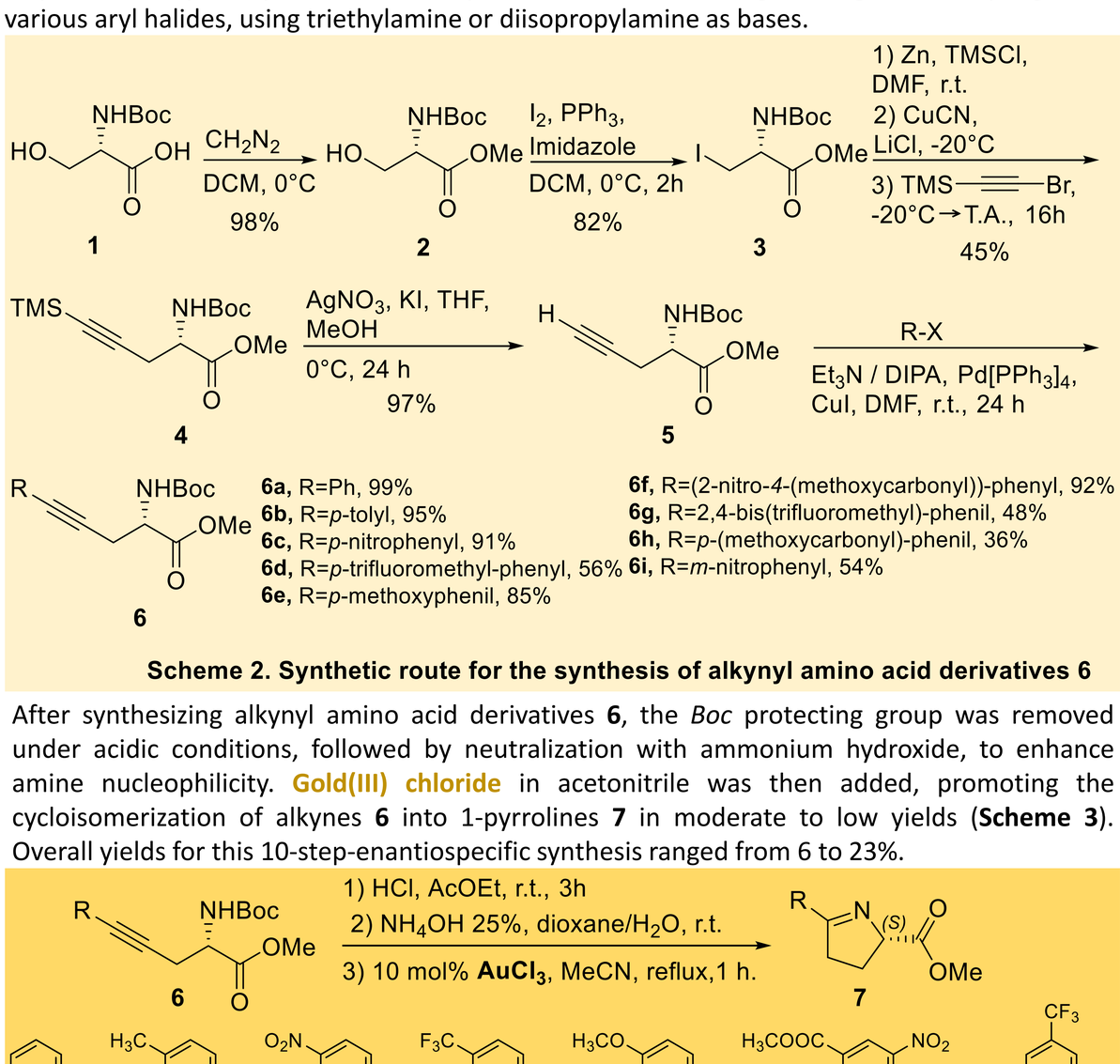
Scheme 1. Main modes of gold-catalyzed intramolecular cyclization.

PART 1. SYNTHESIS OF *N*-CONTAINING HETEROCYCLES FROM AMINO ACIDS EMPLOYING GOLD CATALYSIS

Amino acids are inexpensive and accessible starting materials for synthesizing complex heterocycles. By incorporating alkyne functions into these molecules, gold catalysis facilitates cycloisomerization reactions, leading to the formation of 1-pyrrolines and tetrahydropyrazinones, which have significant potential in drug design and development. These heterocycles also serve as scaffolds for the creation of more complex molecules with enhanced biological activity.

RESULTS

1-pyrroline synthesis. Starting from L- or D-serine, we designed and optimized a synthetic sequence to obtain enantiopure alkynyl amino acid derivatives **6**, which then underwent a **gold-catalyzed cycloisomerization** (**Scheme 2**). After protecting the *N*- and *C*-termini, compound **3** was obtained via iodination. This iodinated intermediate was converted to alkyne **4** through organozinc formation, copper(I) transmetalation, and cross-coupling with 1-bromo-2-(trimethylsilyl)acetylene. The TMS group in **4** was removed with $AgNO_3$ and KI, yielding terminal alkyne **5**. Finally, compounds **6** were synthesized from **5** through Sonogashira couplings with various aryl halides, using triethylamine or diisopropylamine as bases.

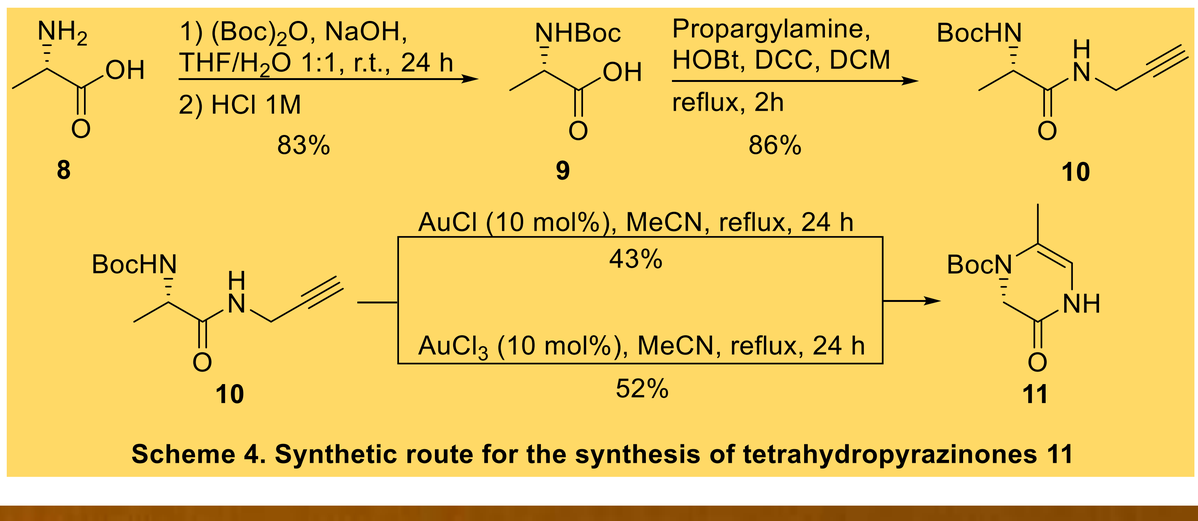


Scheme 2. Synthetic route for the synthesis of alkynyl amino acid derivatives 6

After synthesizing alkynyl amino acid derivatives **6**, the *Boc* protecting group was removed under acidic conditions, followed by neutralization with ammonium hydroxide, to enhance amine nucleophilicity. **Gold(III) chloride** in acetonitrile was then added, promoting the cycloisomerization of alkynes **6** into 1-pyrrolines **7** in moderate to low yields (**Scheme 3**). Overall yields for this 10-step-enantiospecific synthesis ranged from 6 to 23%.

Scheme 3. 1-pyrrolines synthesized

Tetrahydropyrazinone synthesis. We have designed and are still optimizing a synthetic sequence starting with the *N*-protection of L-Alanine, with other amino acids also viable as starting materials. The alkyne functionality is then introduced through an amide coupling with propargylamine, yielding compound **10**. Cycloisomerization using gold(I) or gold(III) chloride affords tetrahydropyrazinone **11** in moderate yields (**Scheme 4**).



Scheme 4. Synthetic route for the synthesis of tetrahydropyrazinones 11

PART 2. HYDROSOLUBLE, RECYCLABLE NHC-GOLD (I) CATALYSTS FOR LACTONE SYNTHESIS.

*Water is a versatile and green solvent, valued for its low cost, safety, renewability, and non-flammability. Water-soluble NHC-based transition metal catalysts have proven to be stable and reactive tools for conducting catalytic reactions in aqueous media.[3] In this context, we utilized five Au(I)–NHC complexes with sulfonate groups (**C1-C5**, **Figure 1**) to efficiently synthesize γ-alkylidene lactones from alkynyl amino acid derivatives using a biphasic toluene-water medium. The biphasic medium allows the product to be soluble in the organic layer, enabling isolation through simple phase separation. The hydrophilic catalyst remains in the aqueous phase, facilitating the recycling and reuse of the active gold species (**Figure 2**).*

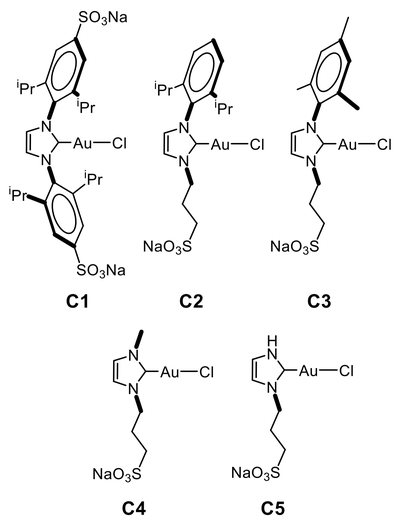


Figure 1. Au(I)–NHC catalysts C1–C5.

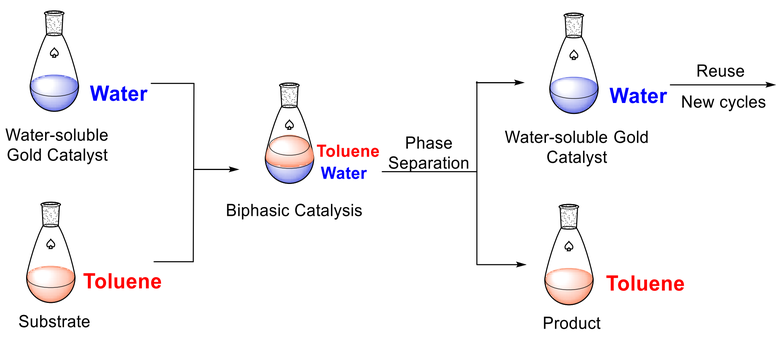
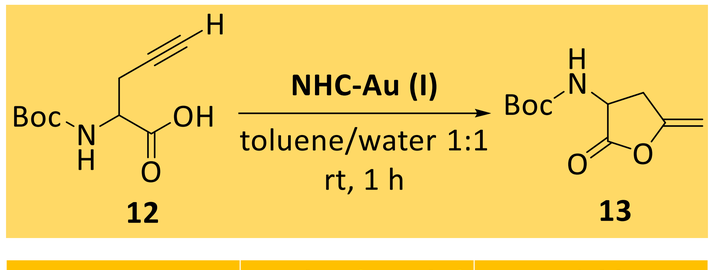


Figure 2. Biphasic catalysis using water soluble gold complexes.

A new cycle can be initiated by adding fresh substrate and toluene to the aqueous phase containing the Au–NHC catalyst.

RESULTS

All of the catalysts (**C1–C5**) successfully promoted the **cycloisomerization reaction of alkynyl amino acid derivatives into γ-alkylidene lactones** (**Table 1**). Nevertheless, the results obtained showed that an increase in steric hindrance on the substituent directly attached to the NHC ring resulted in enhanced catalytic activity of the gold(I) complexes, with **the bulkier NHC complex (C1) being the most effective catalyst in the studied reaction**. This increased efficiency is further demonstrated by **C1**'s superior performance in aqueous medium. Notably, its loading could be reduced to 0.01 mol% without a significant loss of activity, achieving a Turnover Frequency (TOF) of 4829 h^{-1} at 0.01 mol%, as shown in **Figure 3**.



Entry	Catalyst (1 mol%)	Yield
1	C1	95
2	C2	87
3	C3	94
4	C4	95
5	C5	98

Table 1. Cycloisomerization of alkynyl amino acid derivatives 12 into γ-alkylidene lactones 13 and yields with catalysts C1-C5.

To evaluate the reusability of the catalysts under optimized conditions, we conducted a recycling study (**Figure 4**). Remarkably, **the gold(I) catalyst C1 could be recycled and reused at least 15 times** without any loss of activity. In contrast, catalysts C2, C3, C4 and C5 began to lose efficiency after the 6th or 7th cycle, leading to the formation of inactive purple colloidal gold. Based on these results, and to the best of our knowledge, **C1 is the water-soluble gold(I)–NHC catalyst with the highest reported recyclability.**[4]

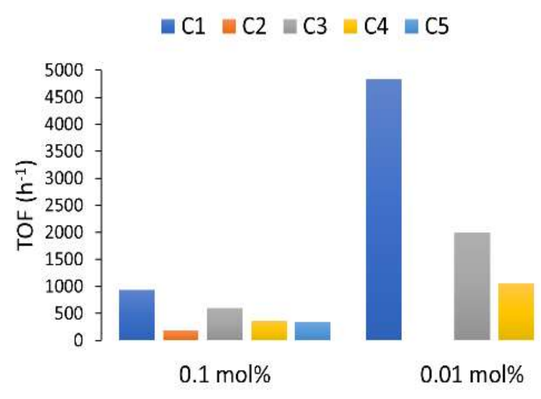


Figure 3. Relative effectiveness of our water-soluble catalysts C1-C5.

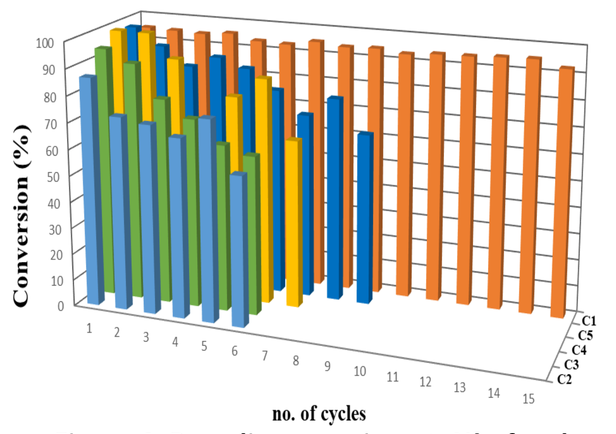


Figure 4. Recycling experiment. N° of cycles vs conversion % of different [Au] complexes.

CONCLUSIONS

We successfully designed and optimized two synthetic sequences that convert the simple amino acids serine and alanine into more complex heterocycles—1-pyrrolines and tetrahydropyrazinones, respectively—using gold catalysis in the key cycloisomerization step, which was achieved in moderate yields.

Hydrosoluble catalysts C1-C5 were active for the cycloisomerization reaction of alkynyl amino acids into γ-alkylidene lactones. Catalyst C1 showed the highest catalytic capacity and robustness in the aqueous system, with its loading being reduced to 0.01 mol% and allowing for 15 consecutive reuse cycles without a decrease in catalytic activity.

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