



Synthetic evolutions in the nucleophilic addition to alkynes

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ABSTRACT

This short account describes our efforts to transform the simple nucleophilic addition of alkynes into a more efficient, selective and environmentally benign synthetic tool. We have circumvented the lack of regioselectivity in the gold-catalyzed triple bond addition of water through neighboring group participation and in the process we developed a 'functionalized hydration' (multiple bond formation and hydration in a one-pot process) using fluorine-engendered cationic gold catalysis. In addition, we have conducted the synthesis of *O*-heterocycles through a gold-catalyzed tandem addition/cycloisomerization sequence, the synthesis of *N*-heterocycles through a copper-catalyzed cyclization-triggered addition of alkynes, and a green synthesis of thioethers 'on water' without catalyst or initiator. These nucleophilic synthetic evolutions, catapulted by a simple addition to an alkyne, will surely contribute to provide a wider synthetic access to sophisticated biological targets.

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1. Introduction

Chemical synthesis plays a major role in medicine, agricultural and material research. Chemists need new synthetic reactions to cope with the increasing complexity of target molecules and new environmental demands. The addition of nucleophilic species to the carbon-carbon multiple bonds is arguably one of the most widely used chemical reaction for the functionalization of alkenes, alkynes and allenes. Such chemical transformations fulfill the principle of "green chemistry" since they ideally occur with 100% atom economy.

More specifically, our recent research has focused on the transformations that involve addition of nucleophilic species to alkynes. Alkynes are widely available starting materials and common synthetic intermediates. In addition, the alkyne functionality has very good functional group tolerance, that is, it is chemically inert toward various reaction conditions such as acid and base; a reaction of an alkyne usually occurs only in the presence of certain catalysts like alkynophilic coinage metals (e.g. gold or copper). This is particularly beneficial in the late steps of a synthesis. But a simple addition of nucleophiles to alkynes has its own limitations: (i) regioselectivity issues; (ii) a simple addition generates only a vinyl adduct. In this

account, we will present some recent developments in our laboratory on alkyne addition that addresses the limitations listed above.

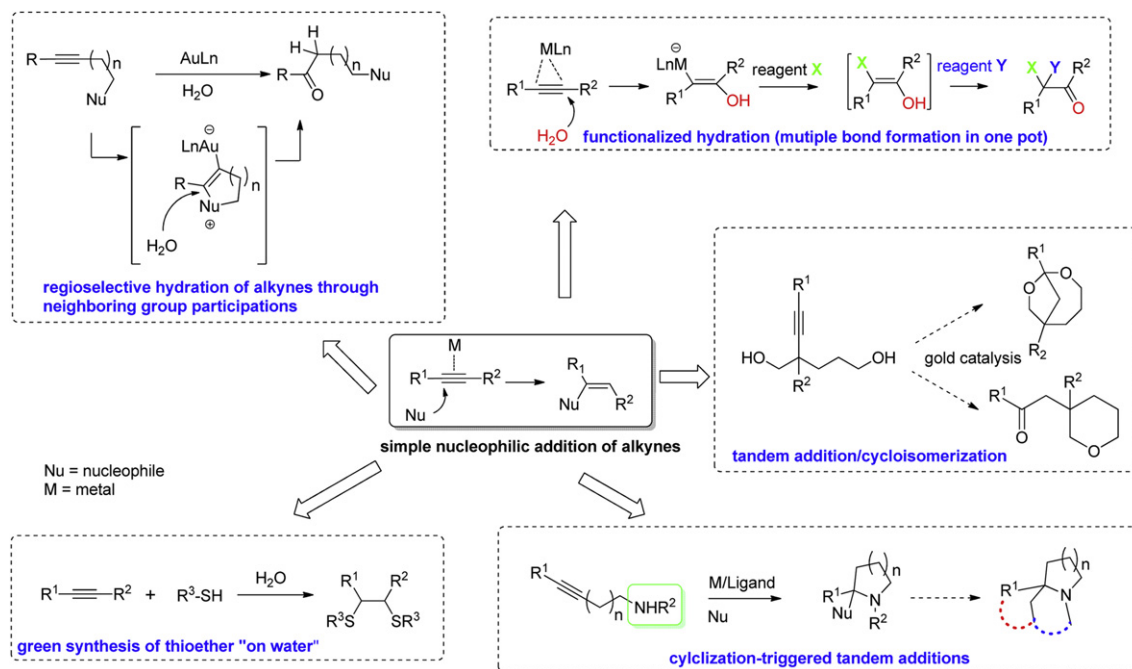
Our overarching goal is to transform the simple nucleophilic addition of alkynes into a more efficient, selective and environmentally benign synthetic tool (Scheme 1). In the following sections, we will demonstrate our approach to circumvent the regioselectivity issue through neighboring group participation; the development of 'functionalized hydration' (multiple bond formation and hydration in a one-pot process) using a fluorine-engendered cationic gold catalyst; the synthesis of *O*-heterocycles through a gold-catalyzed tandem addition/cycloisomerization sequence; the synthesis of *N*-heterocycles through a copper-catalyzed cyclization-triggered addition of alkynes; and a green synthesis of thioethers 'on water' without catalyst or initiator. These nucleophilic synthetic evolutions catapulted by a simple addition to an alkyne will contribute to a wider synthetic access to sophisticated biological targets.

2. Regioselective hydration of alkynes through neighboring group participation [1]

The addition of water to alkynes generates carbonyl compounds such as ketones or aldehydes [1]. Unlike other syntheses of carbonyl compounds, the hydration of alkynes is an atom-economical addition of water without energy-intensive redox chemistry [2]. But the hydration of internal alkynes is sluggish and non-regioselective. Usually only terminal alkynes show good regioselectivity

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Scheme 1. Synthetic evolutions of nucleophilic addition of alkynes.

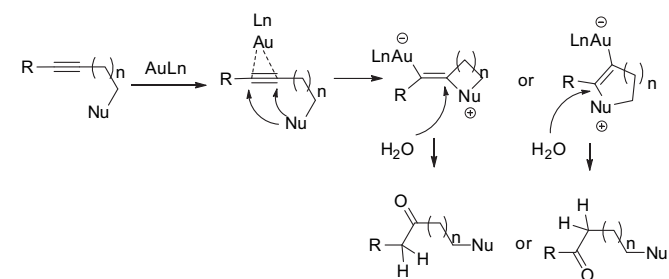
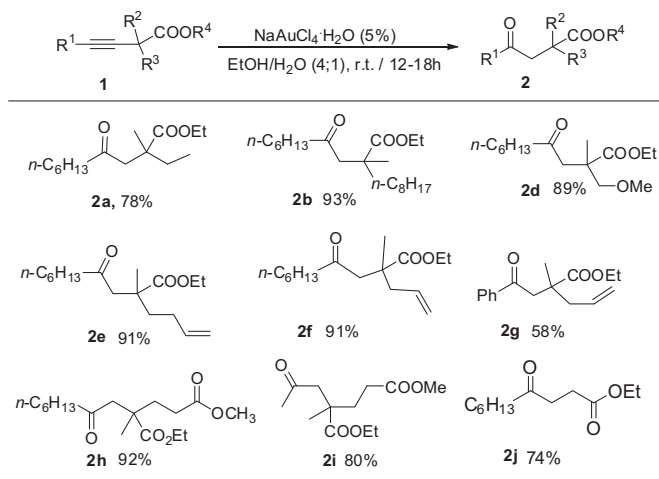
(Markovnikov products), and most reactions need elevated temperatures or strong acid co-catalysts. In general, the regioselective hydration of internal alkynes may only proceed in the presence of a directing functionality—heteroatoms or aromatic rings in close proximity [2]. We proposed that with internal alkynes possessing a nucleophilic site Nu nearby (Scheme 2), this nucleophilic site could attack a metal (e.g. gold)-activated triple bond to form two regioisomeric cyclic intermediates. Although both carbons in the triple bond are prone to nucleophilic attack, one cyclic intermediate may be favored over the other according to Baldwin's rules [3]. The subsequent nucleophilic attack by water yields a single hydration product (Scheme 2).

Our model reaction is the neighboring carbonyl group-assisted hydration of internal alkynes in the presence of a gold(III) catalyst that yields 1,4-dicarbonyl compounds. We chose the latter because they are convenient starting materials and intermediates in many important natural products and synthetic drug syntheses [4–8], but, unlike their 1,3 or 1,5-counterparts, the disconnection of 1,4-dicarbonyl compounds, especially of highly substituted 1,4-dicarbonyl compounds such as γ -keto- α,α -substituted esters, is not trivial [4–10]. A tactical approach that enables a one-step disconnection of highly substituted γ -keto esters is the direct hydration of

3-alkynoates **1**, provided this transformation can be carried out regioselectively, under mild conditions, and with good functional group tolerance [1]. After screening various metal and solvent combinations, we concluded that NaAuCl₄·2H₂O (5%) in EtOH/H₂O (4:1) offered the best conditions for the hydration of alkyne **1**. The hydration proceeded smoothly in high yield and regioselectivity, and was tolerant of ether, double bond, and other ester functionalities (Table 1). Indeed, only one regioisomer was detected in all the crude products examined.

The proposed mechanism for the reaction, based on similar systems, is shown in Scheme 3. First, the gold(III) catalyst coordinates with alkyne **1**, activating the triple bond, and triggering the participation of the carbonyl group nearby; this acts as a nucleophile, attacking the triple bond to form a cyclized vinyl gold intermediate of type **int-A** or **int-B**. According to Baldwin's rules

Table 1
Au(III)-catalyzed hydration of internal 3-alkynoates.



Scheme 2. Directed gold-catalyzed hydration of alkynes through neighboring group assistance.

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