Journal of Organometallic Chemistry 696 (2011) 269–276

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthetic evolutions in the nucleophilic addition to alkynes

Bo Xu*, Weibo Wang, Le-Ping Liu, Junbin Han, Zhuang Jin, Gerald B. Hammond*

Department of Chemistry, University of Louisville, Louisville, KY 40292, USA

ARTICLE INFO

Article history:
Received 25 August 2010
Received in revised form
7 September 2010
Accepted 8 September 2010
Available online 17 September 2010

Keywords:
Alkyne
Gold catalysis
Copper catalysis
O-heterocycles
N-heterocycles
'On water' reactions

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.

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.

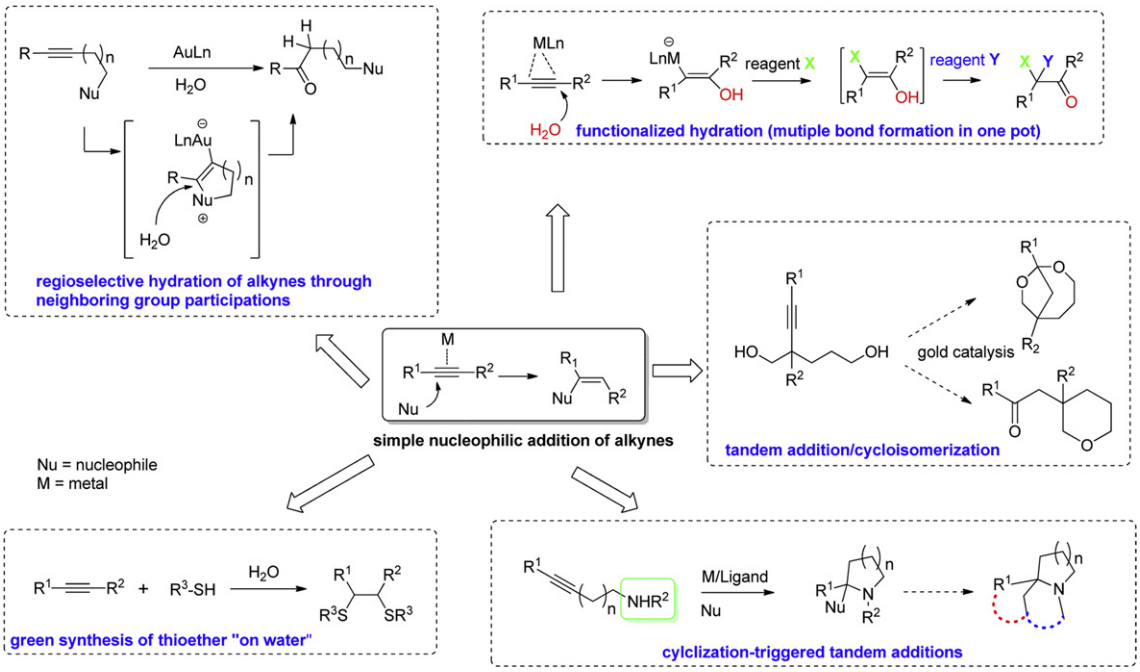
Our overarching goal is to transform the simple nucleophilic addition of alkynes into a more efficient, selective and environmentally benign synthetic tool (Scheme 1). In the following sections, we will demonstrate our approach to circumvent the regioselectivity issue through neighboring group participation; 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

* Corresponding authors.
E-mail addresses: Bo.Xu@louisville.edu (B. Xu), gb.hammond@louisville.edu (G. B. Hammond).

0022-328X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2010.09.025

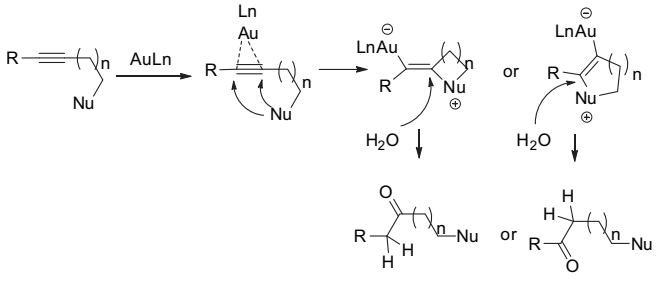


Scheme 1. Synthetic evolutions of nucleophilic addition of alkynes.

(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).

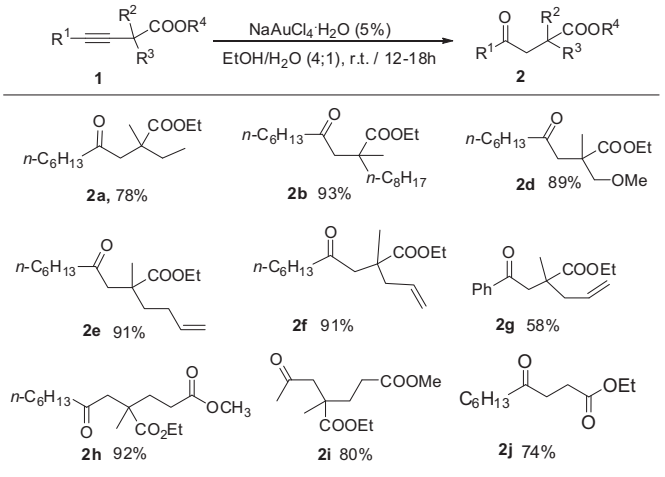
Our model reaction is the neighboring carbonyl group-assisted hydration of internal alkynes in the presence of a gold(III) catalyst that yields 1,4-dicarbonyl compounds. We chose the latter because they are convenient starting materials and intermediates in many important natural products and synthetic 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 g-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 $NaAuCl_4 \cdot 2H_2O$ (5%) in EtOH/H_2O (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.

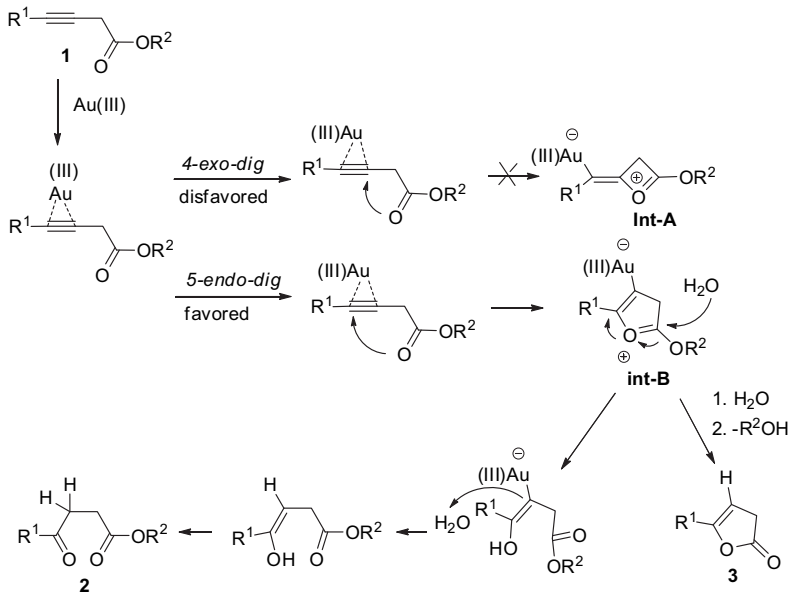
The proposed mechanism for the reaction, based on similar systems, is shown in Scheme 3. First, the gold(III) catalyst coordinates with alkyne **1**, activating the triple bond, and triggering the participation of the carbonyl group nearby; this acts as a nucleophile, attacking the triple bond to form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



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

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



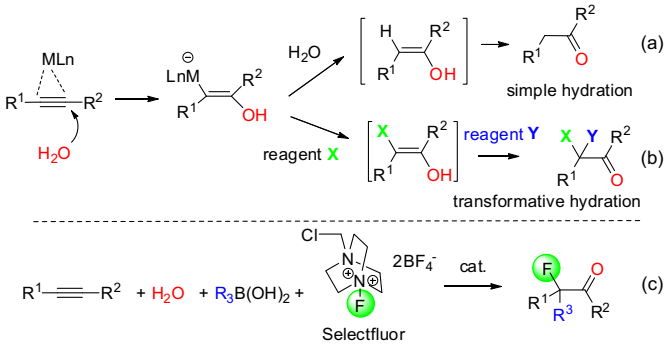


Scheme 3. Proposed mechanism for the hydration of 3-alkynoates.

[3], if the carbonyl oxygen attacks the β-carbon, it is considered a *4-exo-dig* process, which is disfavored. But if the carbonyl oxygen attacks the γ-carbon, it would then be a *5-endo-dig* attack, which is regarded as favored. Thus, **int-B** should be the predominating intermediate. Water attack on **int-B** furnished the g-keto ester **2**. A competing side reaction, namely the elimination of R^2OH from **int-B**, is also possible. This would account for the trace amounts of cyclic byproduct **3** obtained in some cases.

3. Functionalized hydration of alkynes [11]

A major shortcoming of the transition metal-catalyzed hydration of alkynes is that it only adds the elements of H_2O to an alkyne [11] (Scheme 4a). We propose that the vinyl metal complex hydration intermediate can react further during the hydration process to give an α,α-disubstituted ketone (Scheme 4b) in a one-pot reaction. We coined this process 'functionalized hydration'. We speculated that if a vinyl gold intermediate could react with an organoboronic acid (reagent X) and an electrophilic fluorine source such as Selectfluor (reagent Y) it would afford α-aryl-α-fluoroketone in one-pot (Scheme 4b). Our proof of principle was the synthesis of functionalized α-fluoroketones—well-known targets and important synthetic intermediates [12–22]. Tertiary α-fluorinated ketones have received much attention recently because compounds having an α-fluorocarbonyl moiety are biologically



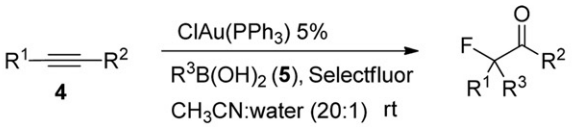
Scheme 4. Concept of functionalized hydration.

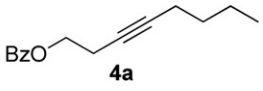
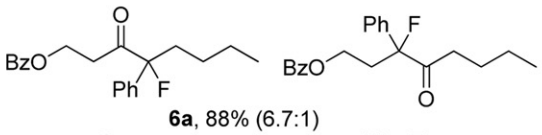
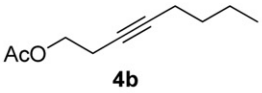
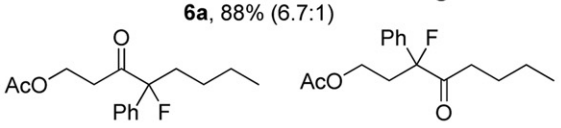
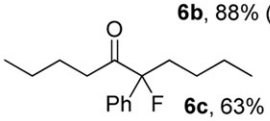
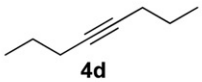
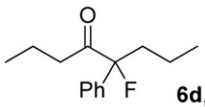
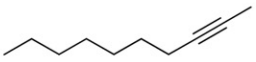
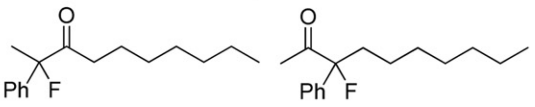
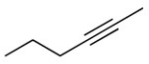
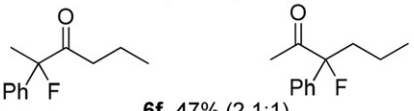
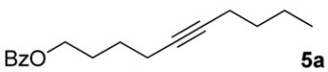
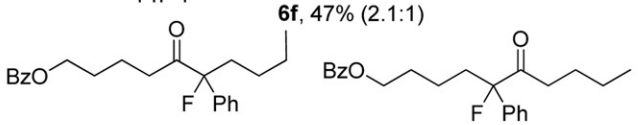
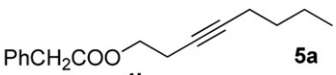
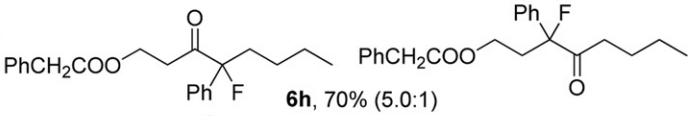
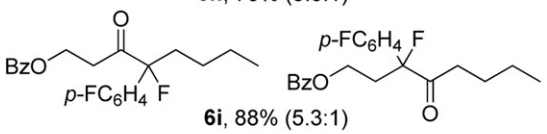
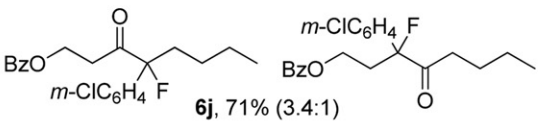
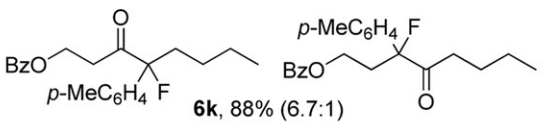
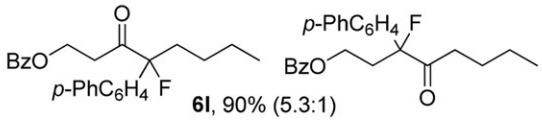
active, they are effective mimics of α-hydroxy ketones, useful probes in various biological processes, and enzyme inhibitors [12,14]. They also provide configurationally stable substituents for molecules containing a tertiary chiral carbon atom next to a carbonyl group, an important structural motif in medicinal chemistry [14]. This one-pot tandem addition/oxidative coupling/fluorination sequence—using readily available starting materials (alkyne, water, organoboronic acid and Selectfluor)—has clear advantages over literature methods, all of which require multiple synthetic steps [23–26].

We first examined the reaction of **4a** with phenyl boronic acid (Table 2). Various metal catalysts were screened. Gold(I) catalyst (Ph_3PAuCl) gave the best result, and other transition metals like copper, silver or palladium could not catalyze this transformation under similar conditions. On exploring the scope of this novel functionalized hydration, we found that functionalized and unfunctionalized internal alkynes reacted with aryl boronic acid, giving very good yields of α-substituted ketones, with moderate regioselectivity (Table 2, entries 1–12). With electron-rich 4-methoxy or 3,4-dimethoxyphenylboronic acids, we observed by-products arising from fluorination or oxidation of the electron-rich aromatic rings by Selectfluor [27,28]. Steric and electronic effects determine the regioselectivity [2,29]. For internal alkynes possessing a nucleophilic site nearby (e.g. the ester group in **4a**), this site may influence the regioselectivity through neighboring group participation [1,2,29].

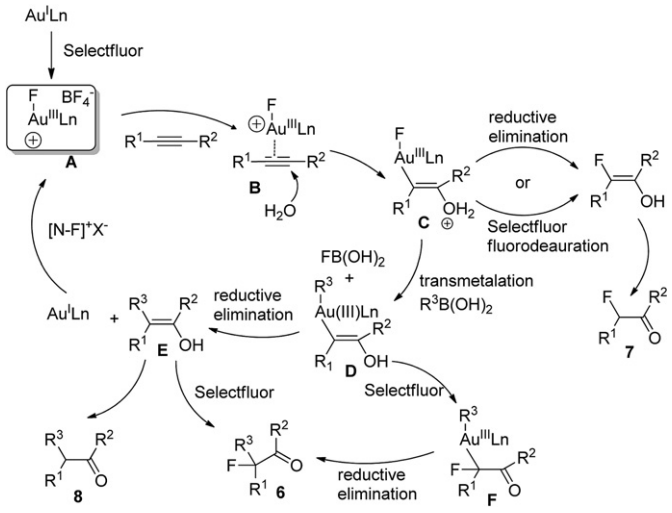
Our proposed mechanism is shown in Scheme 5. Initially, water attacks the gold-activated alkyne to form a vinyl gold complex **C** [30], which reacts with a metal reagent RM (e.g., $PhB(OH)_2$) through a transmetalation process, to give intermediate **D**. We believe that the strong B–F bond and the weak Au–F bond are the driving forces behind this transmetalation. Reductive elimination of **D** gives **E**. And **E** may be fluorinated by Selectfluor to give the functionalized ketone **6** [31]. Because we had never isolated **8** in all cases, it is also possible that intermediate **D** reacts with Selectfluor first to give **F**, and, following reductive elimination, gives the final product **6**. The transmetalation of Au^I–Cl complex with boronic acid has been demonstrated by Hashmi and coworkers in a recent paper [32]. Zhang and others have also proposed the transmetalation of Au–F with boronic acid in their gold-catalyzed oxidative-coupling reactions [33–37].

Table 2
Scope of the functionalized hydration.[a]

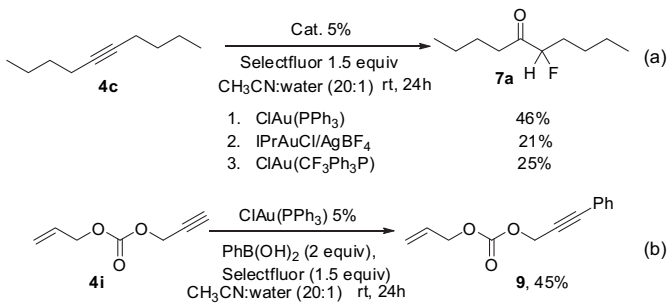


entries	1	2 ($R^3B(OH)_2$)	products
1	 **4a**	$PhB(OH)_2$ **5a**	 **6a**, 88% (6.7:1)
2	 **4b**	**5a**	 **6b**, 88% (4.6:1)
3	 **4c**	**5a**	 **6c**, 63%
4	 **4d**	**5a**	 **6d**, 79%
5	 **4e**	**5a**	 **6e**, 85% (2.2:1)
6	 **4f**	**5a**	 **6f**, 47% (2.1:1)
7	 **4g**	**5a**	 **6g**, 83%(5:1)
8	 **4h**	**5a**	 **6h**, 70% (5.0:1)
9	**4a**	$p\text{-F-}C_6H_4\text{-}B(OH)_2$ **5b**	 **6i**, 88% (5.3:1)
10	**4a**	$m\text{-Cl-}C_6H_4\text{-}B(OH)_2$ **5c**	 **6j**, 71% (3.4:1)
11	**4a**	$p\text{-Me-}C_6H_4\text{-}B(OH)_2$ **5d**	 **6k**, 88% (6.7:1)
12	**4a**	$p\text{-Ph-}C_6H_4\text{-}B(OH)_2$ **5e**	 **6l**, 90% (5.3:1)

[a] **4** (0.4 mmol), **5** (0.8 mmol), Selectfluor (1.0 mmol), $ClAuPPh_3$ (5%), 3 mL CH_3CN/water (20:1), rt, 18−24 h. Selectfluoro: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]-octane bis(tetrafluoroborate).



Scheme 5. Proposed mechanism for the functionalized hydration.



Scheme 6. Synthesis of fluoroketones and oxidative coupling of alkynes.

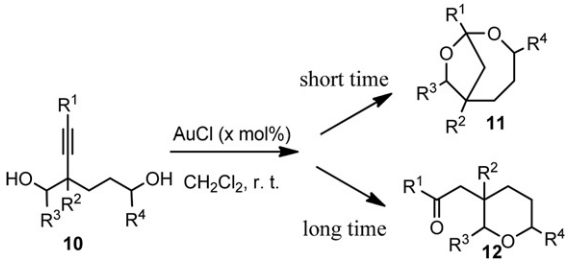
To probe our proposed mechanism, we conducted two control experiments (Scheme 6). According to Scheme 5, fluoroketones **7** could be formed in the absence of a coupling partner R^3M, in which case, the vinyl metal complex **C** undergoes reductive elimination or fluorodemetalation[15] to give fluoroketone **7**. This was the case experimentally, although so far only moderate yields have been obtained. The reaction of terminal alkyne **4i** with **5a** gives the oxidative-coupling product **9** [38]. The formation of **6** hints toward a tandem mechanism that involves fluorination of the gold complex, transmetalation with boronic acid or terminal alkyne, and reductive elimination. It is interesting to note that gold catalysts undergo transmetalation and reductive elimination readily, although they are not able to undergo oxidative insertion – as Pd does in coupling reactions.

The key step of this mechanism is the generation of cationic gold species **A** by fluorination (Scheme 5). Our preliminary experiments show that Selectfluor did react with gold(I) complex at room temperature. For example, when CH_3CN was used as solvent, AuCl readily reacted with Selectfluor at room temperature; the net result should be the transfer of fluorine from Selectfluor to gold (Scheme 5). The change of oxidation state of gold has been verified by X-ray photoelectron spectroscopy (XPS) and high resolution ESI-mass spectroscopy [11].

4. Synthesis of *O*-heterocycles through a tandem addition/cycloisomerization sequence [39]

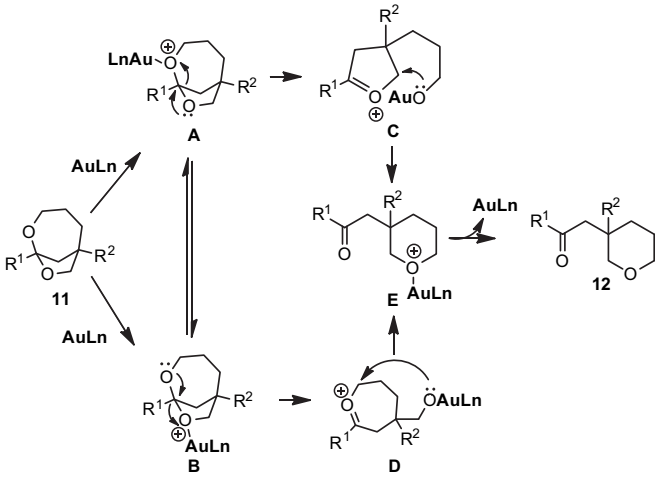
Bicyclic *O*-heterocycles like ketals or their heterobicyclic counterparts [40] are intriguing structural motifs, not only from the perspective of chemical diversity or biological potential, but

Table 3
Gold-catalyzed transformation of diols 10 to ketals 11 or tetrahydropyrans **12**.[a]

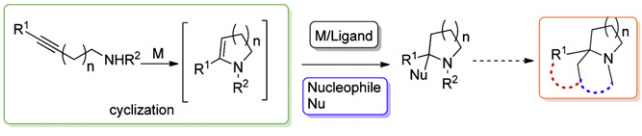


Entry	$R^1/R^2/R^3/R^4$	*x* mol%/Time	Yield [%][b,c]
1	*n*-C_6H_{13}/Me/H/H **10a**	6 mol%/24 h	**12a**, 91
2	*t*-Bu/Me/H/H **10b**	2 mol%/10 min	**11b**, 52(99)
3	**10b**	6 mol%/24 h	**12b**, 52
4	CypCH_2/Me/H/H **10c**	2 mol%/10 min	**11c**, 87(99)
5	**1c**	6 mol%/24 h	**12c**, 83
6	C_6H_5/Me/H/H **10d**	2 mol%/10 min	**11d**, 84(99)
7	**10d**	6 mol%/24 h	**12d**, 88
8	*p*-$CH_3OC_6H_4$/Me/H/H **10e**	2 mol%/10 min	**11e**, 80(99)
9	**10e**	6 mol%/24 h	**12e**, 86
10	*p*-ClC_6H_4/Me/H/H **10f**	2 mol%/10 min	**11f**, 77(99)
11	**10f**	6 mol%/24 h	**12f**, 65
12	*n*-C_6H_{13}/Et/H/H **10g**	2 mol%/10 min	**11g**, 86(99)
13	*n*-C_6H_{13}/Me/C_6H_5/H **10h**	2 mol%/10 min	**11h**,[d] 68(99)
14	*n*-C_6H_{13}/Me/H/Me **10i**	2 mol%/10 min	**11i**,[e] 79(99)
15	Me/Me/H/H **10j**	2 mol%/10 min	**11j**, 46(99)
16	*i*-Pr/Me/H/H **10k**	2 mol%/10 min	**11k**, 75(99)
17	Bn/Me/H/H **10l**	2 mol%/10 min	**11l**, 82(99)

[a] General conditions: 2-alkynyl-1,5-diols **10** 0.20 mmol, AuCl 1.0 mg (2 mol%), CH_2Cl_2 1.0 mL; or 2-alkynyl-1,5-diols **10** 0.20 mmol, AuCl 3.0 mg (6 mol%), CH_2Cl_2 1.0 mL.
[b] Isolated yields.
[c] NMR yields.
[d] Mixture of diaseteroisomers in 1.4:1 ratio.
[e] Mixture of diaseteroisomers in 1:1 ratio.

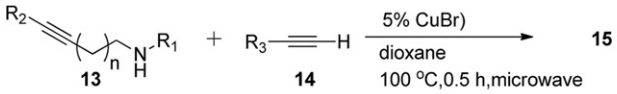


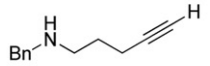
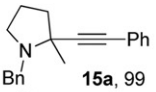
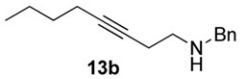
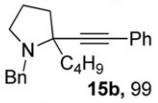
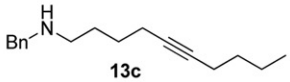
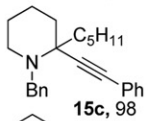
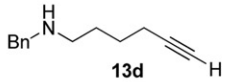
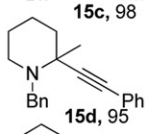
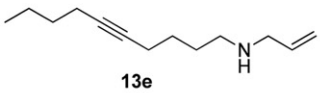
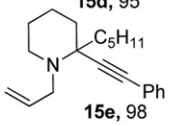
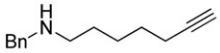
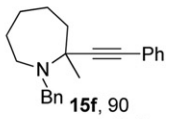
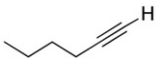
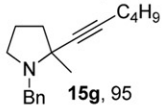
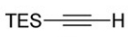
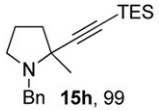
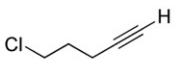
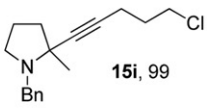
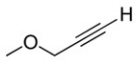
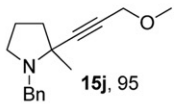
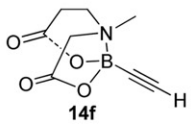
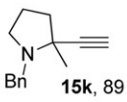
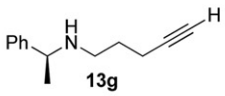
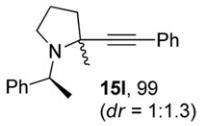
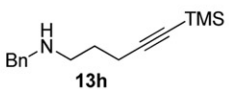
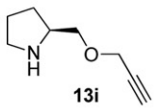
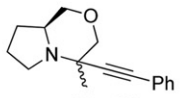
Scheme 7. Plausible mechanism for the transformation of **11** to **12**.



Scheme 8. Cyclization-triggered alkynylation.

Table 4
Scope of the tandem amination/alkynylation reaction.[a]



entry	13	14	15 (yield %)
1	 **13a**	 **14a**	 **15a**, 99
2	 **13b**	**14a**	 **15b,** 99
3	 **13c**	**14a**	 **15c,** 98
4	 **13d**	**14a**	 **15d,** 95
5	 **13e**	**14a**	 **15e,** 98
6	 **13f**	**14a**	 **15f**, 90
7	**13a**	 **14b**	 **15g**, 95
8	**13a**	 **14c**	 **15h**, 99
9	**13a**	 **14d**	 **15i**, 99
10	**13a**	 **14e**	 **15j**, 95
11	**13a**	 **14f**	 **15k**, 89
12	 **13g**	**14a**	 **15l**, 99 (*dr* = 1:1.3)
13	 **13h**	**14a**	**15m**, 0
14	 **13i**	**14a**	 **15n**, 85 (*dr* = 1:7.8)

[a] **13** (0.5 mmol), **14** (2.0 mmol), 1 mL dioxane.

also because of the stimulating transformations that they could engender. During our investigations on the regioselective functionalization of allenoates [41–46], we pondered whether these could also open up a manifold of non-trivial transformations. Taking a cue from Genet and coworkers' gold-catalyzed cycloisomerization of bis-homopropargylic diols to strained dioxabicyclic ketals [47], and using **10** – promptly obtained by LAH reduction of the parent diester [46] – as our substrate, we screened various gold salts. To our satisfaction, with gold(I) chloride, the reaction proceeded very smoothly in dichloromethane at room temperature, and was completed in 10 min; the desired ketal **11**, was isolated in excellent yield (Table 3). During our investigation, we found that tetrahydropyran derivative **12** accompanied the formation of **11** when the reaction time was prolonged. Initially, we thought that this rearrangement could be induced by acidic conditions, but no tetrahydropyran was observed when various Brønsted acids were employed to catalyze the conversion of **11** to **12**. We were positively surprised to discover that tetrahydropyran **12** could be obtained in good to excellent yields by simply increasing the gold catalyst loading and prolonging the reaction time, as summarized in Table 3.

A plausible mechanism for the gold-catalyzed transformation of dioxabicyclo[4.2.1] ketal **11** to tetrahydropyran **12** is outlined in Scheme 7. Gold activates one of the oxygen atoms to form the intermediate **A** or **B**, which may rearrange to the oxonium intermediate **C** or **D**. These intermediates undergo an intramolecular attack to give intermediate **E,** which produces the tetrahydropyran product **12** and regenerates the gold catalyst.

5. Synthesis of *N*-heterocycles through a cyclization-triggered addition of alkynes [48]

In the search for bioactivity, *N*-heterocycles of different ring sizes, with different substitution patterns, are among the most important structure classes [48–53]. A large percentage of drugs in the market contain one or more *N*-heterocycles. Although the synthesis of heterocycles has been around for over a century and a variety of well-established methods are available, there are still unmet needs for concise and efficient synthesis of structurally more complex *N*-heterocycles, especially when larger amounts of material are required for extensive biological studies or clinic trials [54]. The desire to map new chemical spaces through tandem or cascade reactions in atom-economical fashion inspired us to develop a strategy to access biologically important heterocycles through alkynophilic coinage metals capable of catalyzing tandem additions/cyclization of alkynes. This new tandem strategy may enable us to rapidly generating biological important *N*-heterocycles like cyclic amino-acids with a facility unmatched by previous methodologies.

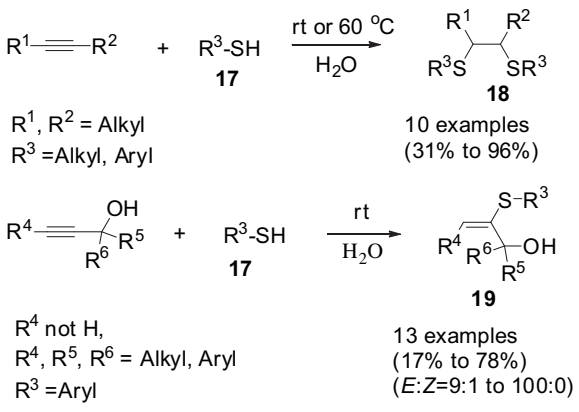
The transition metal-catalyzed intramolecular amination (cyclization) of alkene/allene/alkyne is a well-established method to generate *N*-heterocycles, but this method doesn't introduce new functionality to the heterocycles for further manipulation. We proposed a flexible strategy to generate *N*-heterocycles in tandem fashion: first, an intramolecular hydroamination of amino-alkynes **13** generates an activated enamine or imine *in situ*, capable of reacting with a functionalized carbon nucleophile to give double addition products (Scheme 8) in one pot. In this manner, we not only accomplished the construction of *N*-heterocycles, but also introduced a new functional group onto the ring system through a carbon–carbon forming reaction, this being particularly advantageous when constructing complex ring systems.

Che and coworkers have reported a gold(I)-catalyzed tandem synthesis of pyrrolo[1,2-a]quinolines [55,56], but their reaction requires aromatic amines and terminal alkynes. The gold-catalyzed one-pot synthesis of 1,2-dihydroquinoline derivatives from amines, internal alkynes, and terminal alkynes have also been reported by Bertrand et al. [57]. On the other hand, Li et al. have reported the tandem addition of an amine and alkyne to a,b-unsaturated esters through an iminium intermediate [58]. We envisioned a broader scope for our tandem hydroamination/alkynylation process, namely, the amination of inactive alkynes (terminal or internal) in the presence of a single metal catalyst operating on both, the hydroamination and alkynylation steps.

Among the various coinage metal catalysts screened, copper catalyst was the best, and Cu(I) catalyst was better than Cu(II). The scope of this tandem amination/alkynylation reaction is outlined in Table 4. The reaction worked extremely well in all cases producing near quantitative chemical yields of five-, six-, and seven-membered ring compounds. Complete regioselectivity was observed in all cases. When *N*-methyliminodiacetic acid (MIDA) boronate [59] alkyne **14f** was used, the terminal alkyne product **15k** was obtained (Table 4, entry 11); this may be due to cleavage of MIDA boronate during the reaction. The regioselectivity obeyed Baldwin's rules [3]. The cyclization of 3-yn-amine **13b** and **13a** gave five-membered ring products through *5-endo-dig* and *5-exo-dig* processes [60]. And the reactions of 5-yn-amine (e.g., **13c**) and 6-yn-amine (e.g., **13e**) yielded six-membered and seven-membered rings, through *6-exo-dig* and *7-exo-dig* processes, respectively. The cycloisomerization of 1,*n*-enynes and 1,*n*-diynes is currently a highly competitive field in organic synthetic chemistry [61]. Our newly found method provides direct entry to functionalized 1,*n*-enynes, as showcased by the synthesis of 1,6-enyne (**15e**) in high yield in a single step (Table 4, entry 5).

6. Green synthesis of vicinal dithioethers and alkenyl thioethers from the reaction of alkynes and thiols in water [62]

Thioethers have become increasingly important as the role of sulfur is probed deeper in biological processes, new materials, and chemical synthesis in general [62,63]. One of the most straightforward syntheses of thioethers is the addition of thiol to alkynes (Scheme 9). Due to the increasing environmental consciousness among the scientific community, we chose water as our reaction medium. It was surprising to us that water was able to speed-up this addition considering that both, starting material and product, are virtually insoluble in water. And this reaction doesn't need any catalyst or initiator. According to Sharpless and co-workers, reaction rates that are accelerated when insoluble reactants are stirred in aqueous suspension are denoted as "on water" conditions [64]. Thus, this reaction could be considered as an 'on water' reaction.



Scheme 9. Green synthesis of vicinal dithioethers and alkenyl thioethers.

Various alkynes reacted with thiols in water to give vicinal dithioethers **18** in good yields, and non-terminal propargyl alcohols reacted with phenyl thiols to produce a highly regio and stereoselective monohydrothiolation product, *E*-alkenyl thioether **19** (Scheme 9).

7. Concluding remarks

The nucleophilic addition of alkyne is a synthetic tool that is evolving to meet the needs for more efficient and environmentally benign synthesis of synthetic targets. We have demonstrated that the regioselectivity can be controlled by the formation of cyclic intermediates, and that tandem chemistry can enable quick access to a diverse set of oxygen and nitrogen heterocycles. Developing the full potential of these reactions, including their asymmetrical versions is currently a priority in our laboratory.

Acknowledgment

We are grateful to the National Science Foundation for financial support (CHE-0809683).

References

[1] W. Wang, B. Xu, G.B. Hammond, J. Org. Chem. 74 (2009) 1640–1643.
[2] L. Hintermann, A. Labonne, Synthesis (2007) 1121–1150.
[3] J.E. Baldwin, J. Chem. Soc., Chem. Commun (1976) 734–736.
[4] A.G. Csaky, J. Plumet, Chem. Soc. Rev. 30 (2001) 313–320.
[5] G. Piancatelli, M. D'Auria, F. D'Onofrio, Synthesis (1994) 867–889.
[6] Y. Kubota, H. Nemoto, Y. Yamamoto, J. Org. Chem. 56 (1991) 7195–7196.
[7] S. Aoki, E. Nakamura, Tetrahedron 47 (1991) 3935–3946.
[8] S. Aoki, E. Nakamura, Synlett (1990) 741–742.
[9] S. Muthusamy, P. Srinivasan, Tetrahedron Lett. 47 (2006) 6297–6300.
[10] A.I. Meyers, R.H. Wallace, M. Harre, R. Garland, J. Org. Chem. 55 (1990) 3137–3143.
[11] W. Wang, J. Jasinski, G.B. Hammond, B. Xu, Angew. Chem. Int. Ed. 49 (2010) 7247–7252.
[12] Y. Guo, B. Twamley, J.N.M. Shreeve, Org. Biomol. Chem. 7 (2009) 1716–1722.
[13] K.-Y. Kim, B.C. Kim, H.B. Lee, H. Shin, J. Org. Chem. 73 (2008) 8106–8108.
[14] G.K.S. Prakash, P. Beier, Angew. Chem., Int. Ed. 45 (2006) 2172–2174.
[15] E.C. Burger, B.R. Barron, J.A. Tunge, Synlett (2006) 2824–2826.
[16] F.A. Davis, W. Han, C.K. Murphy, J. Org. Chem. 60 (1995) 4730–4737.
[17] V. Reutrakul, T. Kruahong, M. Pohmakotr, Tetrahedron Lett. 35 (1994) 4853–4856.
[18] W.R. Dolbier Jr., S.K. Lee, O.I.V. Phanstiel, Tetrahedron 47 (1991) 2065–2072.
[19] E. Differding, G.M. Ruegg, R.W. Lang, Tetrahedron Lett. 32 (1991) 1779–1782.
[20] C. Tarnus, M.J. Jung, J.M. Remy, S. Baltzer, D.G. Schirlin, FEBS Lett. 249 (1989) 47–50.
[21] P. Bravo, E. Piovosi, G. Resnati, J. Chem. Res., Synop. (1989) 134–135.
[22] P. Bravo, G. Resnati, J. Chem. Soc., Chem. Commun. (1988) 218–219.
[23] R.S. Neale, J. Am. Chem. Soc. 86 (2002) 5340–5342.
[24] L. Benati, P.C. Montevecchi, P. Spagnolo, Tetrahedron Lett. 29 (1988) 2381–2384.
[25] K. Tamao, K. Maeda, Tetrahedron Lett. 27 (1986) 65–68.
[26] G.E. Heasley, C. Codding, J. Sheehy, K. Gering, V.L. Heasley, D.F. Shellhamer, T. Rempel, J. Org. Chem. 50 (2002) 1773–1776.
[27] P.T. Nyffeler, S.G. Duron, M.D. Burkart, S.P. Vincent, C.-H. Wong, Angew. Chem., Int. Ed. 44 (2005) 192–212.
[28] M. Schueler, Spec. Chem. Mag. 26 (2006) 20.
[29] N. Marion, R.S. Ramon, S.P. Nolan, J. Am. Chem. Soc. 131 (2009) 448–449.
[30] L.-P. Liu, B. Xu, M.S. Mashuta, G.B. Hammond, J. Am. Chem. Soc. 130 (2008) 17642–17643.
[31] D. Enders, M.R.M. Hüttle, Synlett (2005) 991 The fluorination of a ketone bearing aromatic ring has been reported:.
[32] A.S.K. Hashmi, T.D. Ramamurthi, F. Rominger, J. Organomet. Chem. 694 (2009) 592–597.
[33] G. Zhang, Y. Peng, L. Cui, L. Zhang, Angew. Chem., Int. Ed. 48 (2009) 3112–3115.
[34] P. Garcia, M. Malacria, C. Aubert, V. Gandon, L. Fensterbank, ChemCatChem 2 (2010) 493–497.
[35] A.D. Melhado, W.E. Brenzovich, A.D. Lackner, F.D. Toste, J. Am. Chem. Soc. 132 (2010) 8885–8887.
[36] W.E. Brenzovich, D. Benitez, A.D. Lackner, H.P. Shunatona, E. Tkatchouk, F.D. Toste, Angew. Chem., Int. Ed. 49 (2010) 5519–5522.
[37] G. Zhang, L. Cui, Y. Wang, L. Zhang, J. Am. Chem. Soc. 132 (2010) 1474–1475.
[38] F. Yang, Y. Wu, Eur. J. Org. Chem. 2007 (2007) 3476–3479.
[39] L.-P. Liu, G.B. Hammond, Org. Lett. 11 (2009) 5090–5092.
[40] (a) P.A. Bartlett, M. Entzeroth (Eds.), Exploiting chemical diversity for drug discovery, Royal Society of Chemistry, Cambridge, UK, 2006;
(b) P.-C. Kuo, T.-H. Kuo, A.G. Damu, C.-R. Su, E.-J. Lee, T.-S. Wu, R. Shu, C.-M. Chen, K.F. Bastow, T.-H. Chen, K.-H. Lee, Org. Lett. 8 (2006) 2953.
[41] B. Xu, G.B. Hammond, Synlett 2010 (2010) 1442–1454.
[42] J.C. Aponte, G.B. Hammond, B. Xu, J. Org. Chem. 74 (2009) 4623–4625.
[43] H. Yang, B. Xu, G.B. Hammond, Org. Lett. 10 (2008) 5589–5591.
[44] B. Xu, G.B. Hammond, Angew. Chem., Int. Ed. 47 (2008) 689–692.
[45] W. Wang, B. Xu, G.B. Hammond, Org. Lett. 10 (2008) 3713–3716.
[46] L.-P. Liu, B. Xu, G.B. Hammond, Org. Lett. 10 (2008) 3887–3890.
[47] S. Antoniotti, E. Genin, V. Michelet, J.-P. Genet, J. Am. Chem. Soc. 127 (2005) 9976–9977.
[48] J. Han, B. Xu, G.B. Hammond, J. Am. Chem. Soc. 132 (2010) 916–917.
[49] C. Zhang, C.K. De, R. Mal, D. Seidel, J. Am. Chem. Soc. 130 (2008) 416–417.
[50] B.M. Trost, N. Maulide, R.C. Livingston, A. Ruthenium-Catalyzed, J. Am. Chem. Soc (2008) 16502–16503.
[51] S. Fustero, J. Moscardo, D. Jimenez, M.D. Perez-Carrion, M. Sanchez-Rosello, C. Del Pozo, Chemistry 14 (2008) 9868–9872.
[52] J.L. Vicario, D. Badia, L. Carrillo, New methods for the asymmetric synthesis of nitrogen heterocycles 2005. Research Signpost, Kerala, India, 2005.
[53] E.S.H. El Ashry, A. El-Nemr, Synthesis of naturally occurring nitrogen heterocycles from carbohydrates. Blackwell Publications, Oxford, UK, Ames, Iowa, 2005.
[54] N.T. Patil, Y. Yamamoto, Chem. Rev. 108 (2008) 3395–3442.
[55] X.-Y. Liu, C.-M. Che, Angew. Chem., Int. Ed. 47 (2008) 3805–3810.
[56] X.-Y. Liu, C.-M. Che, Angew. Chem., Int. Ed. 48 (2009) 2367–2371.
[57] X. Zeng, G.D. Frey, R. Kinjo, B. Donnadieu, G. Bertrand, J. Am. Chem. Soc. 131 (2009) 8690–8696.
[58] L. Zhou, H.-F. Jiang, C.-J. Li, Adv. Synth. Catal. 350 (2008) 2226–2230.
[59] E.P. Gillis, M.D. Burke, J. Am. Chem. Soc. 129 (2007) 6716–6717.
[60] X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, Angew. Chem. Int. Ed. 49 (2010) 942–945.
[61] V. Michelet, P.Y. Toullec, J.-P. Genet, Angew. Chem., Int. Ed. 47 (2008) 4268–4315.
[62] Z. Jin, B. Xu, G.B. Hammond, Eur. J. Org. Chem (2010) 168–173.
[63] R.J.W. Cremlyn, An Introduction to Organosulfur Chemistry. Wiley, Chichester, New York, 1996.
[64] A. Chanda, V.V. Fokin, Chem. Rev. 109 (2009) 725–748.