Tetrahedron 71 (2015) 5800–5805

Contents lists available at ScienceDirect

Tetrahedron

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

Gold(I)-catalyzed enantioselective [3+2] and [3+3] cycloaddition reactions of propargyl acetals/ketals

Cristina Navarro, Nathan D. Shapiro, Maurizio Bernasconi, Takahiro Horibe, F. Dean Toste *

Department of Chemistry, University of California, Berkeley, CA 94720, United States

ARTICLE INFO

Article history:
Received 13 February 2015
Received in revised form 28 April 2015
Accepted 29 April 2015
Available online 6 May 2015

Keywords:
Gold
Homogeneous catalysis
Enantioselective catalysis
Cycloaddition
Propargyl acetals/ketals

ABSTRACT

An asymmetric gold(I)-catalyzed [3+2] cycloaddition of propargyl acetals/ketals and aldehydes is reported, which proceeds via stepwise migration-fragmentation of acetals/ketals and cycloaddition of the in situ generated gold-carbenoid intermediate. Various functionalized 2,5-dihydrofurans were obtained in good yields and high enantioselectivities. Furthermore, an example of the first gold(I) catalyzed [3+3] cycloaddition of secondary propargyl ketals and nitrones is presented.

1. Introduction

There is an increasing demand for the development of methods and strategies that allow the transformation of readily available precursors into target-relevant products in a rapid, economical and efficient manner. Cycloaddition reactions are synthetic tools, which fit these criteria, because they can produce a rapid increase in skeletal complexity with controlled regio- and stereoselectivities.[1] In recent years, gold complexes have emerged as excellent catalysts for novel types of cycloaddition reactions, because of their unique ability to activate carbon–carbon π-systems.[2] Gold(I) or gold(III) complexes tend to activate alkynes, alkenes or allenes in a highly selective manner. This activation mode allows for interesting reaction pathways that usually involve carbocationic intermediates. The properties of the metal can be modulated through modification of its ancillary ligand (phosphines, *N*-heterocyclic carbenes …).[3] The rapid rise in interest in gold catalysis has been accompanied by efforts to develop enantioselective variants of gold-catalyzed reactions to further increase the synthetic utility of these processes.[4]

The gold-catalyzed 1,2-rearrangement of propargyl esters has provided the basis for the development of a wide range of transformations. These reactions are hypothesized to proceed through gold-stabilized cationic intermediates that show reactivity analogous to electrophilic transition metal vinyl carbenoids.[5] As expected these cationic species can demonstrate either carbene like 1,1-reactivity (cyclopropanation) or participate in vinylogous 1,3-functionalization reactions that have typically been associated with 1,3-dipoles.[6] In the context of the latter, Iwasawa[7] first invoked a gold-containing 1,3-dipole to prepare tricyclic indole derivatives in 2006. In 2008, we also proposed gold azomethine ylides as intermediates to understand the reaction of propargylic benzoates with α,β-unsaturated imines.[5h] We obtained azepine products, through a stepwise [4+3] annulation process between the imines and the gold vinylcarbenoids, generated upon 1,2-migration of the ester group. Similarly, Zhang et al.[8] reported that migration-fragmentation of propargyl acetals/ketals allowed for a [3+2]-cycloaddition with electron-rich aromatic aldehydes to form highly functionalized 2,5-dihydrofurans, useful building blocks in organic synthesis. However, an enantioselective version of this transformation has not been reported before. Finally, in 2009 we reported a gold(III)-catalyzed [3+3]-cycloaddition of tertiary propargyl esters and azomethine imines.[9] This example of a formal cycloaddition between metal vinylcarbenoids and 1,3-dipoles was followed by a reported by Zhang et al. employing nitrones as to be effective 1,3-dipoles for gold(I)-catalyzed [3+3] cycloaddition with 2-(1-alkynyl)-2-alken-1-ones.[10] With this information in hand, we envisioned that gold(I)-catalyzed [3+3] cycloaddition of propargyl ketals and nitrones could occur, and this transformation would give us new insights in the fast growing field of gold catalysis.

* Corresponding author. Tel.: +1 510 642 2850; e-mail address: fdtoste@berkeley.edu (F.D. Toste).

http://dx.doi.org/10.1016/j.tet.2015.04.109
0040-4020/

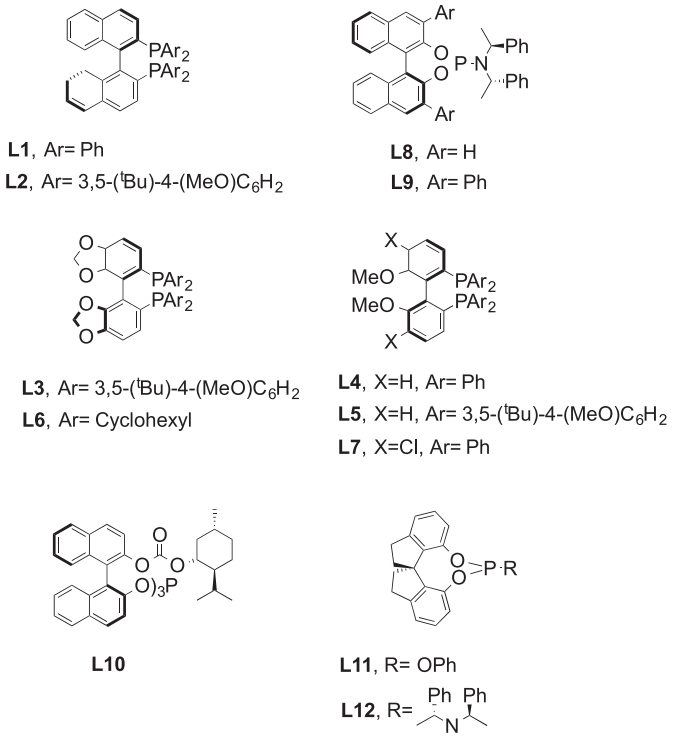


Fig. 1. Chiral ligands used for the cycloaddition reactions.

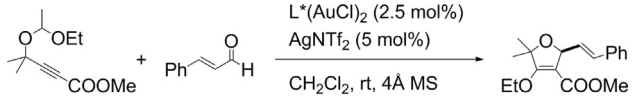
We report herein the first asymmetric gold(I)-catalyzed [3+2] cycloaddition of propargyl acetals and aldehydes, which proceeds via stepwise migration-fragmentation of the acetal and cycloaddition of the in situ generated gold-carbenoid intermediate. Furthermore, we present an example of the first gold(I)-catalyzed [3+3]-cycloaddition reaction of secondary propargyl ketals and nitrones and the corresponding enantioselective version. Fig. 1.

2. Gold(I)-catalyzed [3+2] cycloaddition reactions between propargyl acetals/ketals and aldehydes

2.1. Optimization of the reaction conditions

We began our investigation using propargyl ester **1a** and *trans*-cinnamaldehyde **2a** as suitable test substrates for this [3+2] cycloaddition. We examined different cationic gold(I) catalysts bearing chiral bisphosphine ligands (Table 1, entries 1–5). In all cases the gold complexes were activated by $AgNTf_2$ and afforded desired product **3aa** in good yields. The use of phosphine ligand **L1**=(*R*)-BINAP (Table 1, entry 1) induced moderated enantioselectivities in the formation of 2,5-dihydrofuran **3aa**. More bulky **L2**=(*R*)-DTBM-BINAP (Table 1, entry 2) afforded **3aa** almost as racemic mixture. **L3**=(*R*)-DTBM-SEGPHOS gave **3aa** in higher yields but similar enantioselectivity as **L1**=(*R*)-BINAP. (90% yield, 77% ee; Table 1, entry 3). **L4**=(*R*)-MeO-BIPHEP afforded **3aa** in 91% yield but almost as a racemic mixture. (3% ee; Table 1, entry 4) However, more bulky (*R*)-DTBM-MeO-BIPHEP provided 2,5-dihydrofuran **3aa** in good yields and very high levels of enantioinduction (80% yield, 95% ee; Table 1, entry 5).

Table 1
Optimization of the gold-catalyzed enantioselective [3+2] cycloaddition reaction[a]



1a **2a** **3aa**

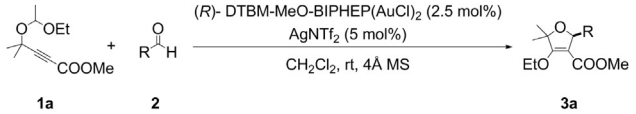
Entry	Ligand (L*)	Yield[b] (%)	ee[c] (%)
1	**L1**=(*R*)-BINAP	60	72
2	**L2**=(*R*)-DTBM-BINAP	77	2
3	**L3**=(*R*)-DTBM-SEGPHOS	89	77
4	**L4**=(*R*)-MeO-BIPHEP	91	3
5	**L5**=(*R*)-DTBM-MeO-BIPHEP	80	95

[a] Reaction conditions: 2.5 mol% gold catalyst, 5 mol% $AgNTf_2$, 0.15 mmol (1 equiv) of **1a**, 0.23 mmol (1.5 equiv) of *trans*-cinnamaldehyde **2a**, 10 mg of 4 Å molecular sieves (MS), 0.8 mL CH_2Cl_2, 1.5 h.
[b] Isolated yields.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using *rac*-BINAP$(AuCl)_2$ as gold catalyst.

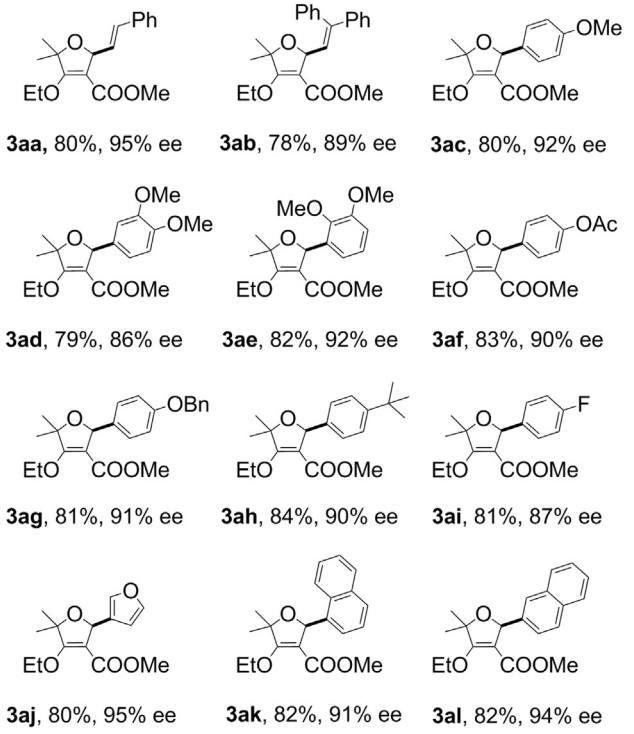
2.2. Aldehyde scope

With optimal conditions in hand (Table 1, entry 5), we explored the scope of the gold(I)-catalyzed enantioselective cycloaddition. The reaction is general for a wide range of aldehydes (**2a**–**2l**). (Table 2). More bulky enal **2b** afforded **3ab** in 78% yield and 89% ee. Electron rich aromatic aldehydes **2c**, **2d** and **2e** afforded **3ac**, **3ad**

Table 2
Asymmetric [3+2] cycloaddition reaction: aldehyde scope[a,b,c,d]



1a **2** **3a**



[a] Reaction conditions: 2.5 mol% gold catalyst, 5 mol% $AgNTf_2$, 0.15 mmol (1 equiv.) of **1a**, 0.23 mmol (1.5 equiv.) of aldehyde **2**, 10 mg of 4 Å molecular sieves (MS), 0.8 mL CH_2Cl_2, 1.5 h.[d] Reaction between substrate **1a** and 3-Phenylpropanal afforded the desired product **3a** with 30% conversion. This lack of reactivity of aliphatic aldehydes was also observed as well by Zhang *et.al.*[8]
[b] Isolated yields.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using rac-BINAP$(AuCl)_2$ as gold catalyst.