Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 1579

Gold-catalyzed three-component spirocyclization: a one-pot approach to functionalized pyrazolidines†

Bernd Wagner,[a] Wolf Hiller,[a] Hiroaki Ohno[b] and Norbert Krause*[a]

Received 30th November 2015,
Accepted 15th December 2015

DOI: 10.1039/c5ob02453f

www.rsc.org/obc

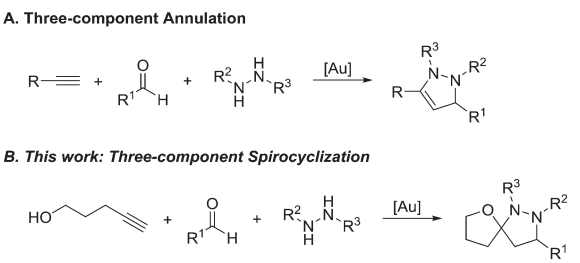
An efficient, highly atom economic synthesis of hitherto unknown spirocyclic pyrazolidines in a one-pot process was developed. The gold-catalyzed three-component coupling of alkynols, hydrazines and aldehydes or ketones likely proceeds *via* cycloisomerization of the alkynol to an exocyclic enol ether and subsequent [3 + 2]-cycloaddition of an azomethine ylide. A library of 29 derivatives with a wide range of functional groups was synthesized in up to 97% yield. With this new method, every position in the final product can be substituted which renders the method ideal for applications in combinatorial or medicinal chemistry.

Introduction

Heterocycles are a pivotal structural element of a large number of pharmaceuticals. Hence, in order to tackle new challenges in medicinal chemistry, there is a growing demand for novel types of heterocycles with tailored pharmacological properties.[1] From the preparative point of view, extensive structural variation of the heterocyclic target molecules is required using the full arsenal of modern synthetic methodology, *e.g.*, catalytic processes utilizing transition metals or organocatalysts,[2] C–H activation,[3] and multicomponent reactions (MCRs).[4]

The use of homogeneous gold catalysts in multicomponent reactions holds great promise. Due to their high reactivity towards π-systems (in particular alkynes), gold catalysts allow a distinctive control of selectivity, as well as, wide tolerance towards reactive functional groups.[5] Combining this with the advantages of MCRs (rapid assembly of complex structural motifs from small molecules with high atom economy) renders the method highly valuable in combinatorial and medicinal chemistry. Since the first publication of a gold-catalyzed coupling of aldehydes, secondary amines and alkynes by Li *et al.*,[6] the number of MCRs catalyzed by gold is continuously rising.[7] Recently, one of us (H.O.) has developed a new approach to dihydropyrazoles by gold-catalyzed three-component annulation of alkynes with hydrazines and aldehydes or ketones, a method that was applied to the one-pot synthesis of dihydroindazoles,[8] as well as, pyrazolo[4,3-*b*]indoles.[9] We now report a conceptually new gold-catalyzed three-component spirocyclization of acetylenic alcohols, hydrazines, and aldehydes or ketones which provides a diversity-oriented access to previously unknown spirocyclic pyrazolidines (Scheme 1).

Many natural products contain spiroacetals as characteristic scaffold (Fig. 1). Prominent examples are the marine toxines



Scheme 1 Gold-catalyzed three-component annulation *vs.* spirocyclization.

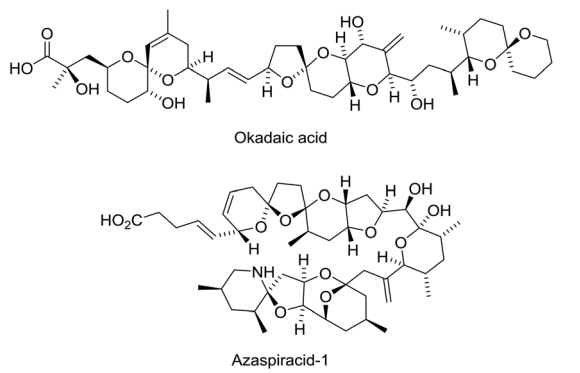


Fig. 1 Natural products containing [*O*,*O*]- and [*N*,*O*]-spiroacetals.

[a]*Organic Chemistry, Dortmund University of Technology, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany. E-mail: norbert.krause@tu-dortmund.de; Fax: (+)49 231 755 3884*
[b]*Kyoto University, Graduate School of Pharmaceutical Sciences, Sakyo-ku, Kyoto 606-8501, Japan*

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. See DOI: 10.1039/c5ob02453f

okadaic acid, isolated from the sponge *Halichondria okadai*, and azaspiracid-1, obtained from blue mussels (*Mytilus edulis*).[10]

Synthetic approaches to the most common [*O*,*O*]-spiroacetals are well developed and normally take advantage of Lewis acid, Brønsted acid, or transition metal catalysts for the spirocyclization of prefunctionalized substrates.[11] Recent examples involve an efficient gold- or palladium-catalyzed cyclization of monopropargylic triols or ketoallylic diols reported by Aponick and co-workers,[12] the first asymmetric Brønsted acid-catalyzed cyclization of enol ethers with chiral phosphoric acids developed by List and Nagorny,[13] as well as, the enantioselective synthesis of spiroacetals in a multicomponent approach disclosed by Fañanás, Rodríguez, and Gong.[14] In contrast to this, other heterocyclic spirocompounds have been relegated to a niche existence.[15] A rare exception is the recent report by Xu *et al.*[16] on the synthesis of spiroaminals and spiroketals by bimetallic relay catalysis involving a gold-catalyzed cycloisomerization of a functionalized alkyne followed by a transition metal-catalyzed hetero-Diels–Alder reaction.

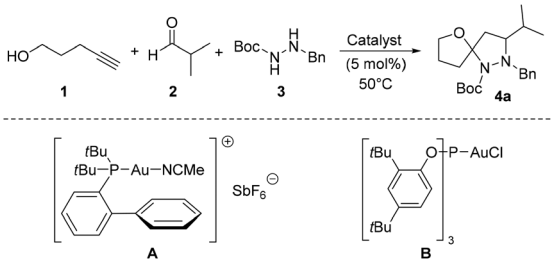
Results and discussion

Crucial to our approach towards spirocyclic pyrazolidines is the use of an acetylenic alcohol instead of a simple alkyne in the three-component reaction with a hydrazine and an aldehyde or ketone. We anticipated that the alkynol would undergo a facile cyclization in the presence of a gold catalyst[17] to afford the ether ring of the desired spiroacetal. We started our investigation with pent-4-yn-1-ol **1**, isobutyraldehyde **2** and the protected hydrazine **3**[8] in 1,2-dichloroethane with 5 mol% of $Ph_3PAuCl/AgOTf$ as catalyst at room temperature (Table 1, entry 1). After 22 h, the spiroacetal **4a** was isolated with 41% yield. A brief screening showed THF to be the best solvent (52% yield after 16 h at rt; entries 2–4). Increasing the reaction temperature to 50 °C improved the reactivity and afforded **4a** with 40% yield after only 3 h (entry 5). A change of the silver salt revealed $AgSbF_6$ to the best choice (69% yield; entries 5–7), indicating the importance of the counteranion.[5h,i]

The use of neutral gold salts AuCl and $AuCl_3$ resulted in poor conversion and formation of a gold mirror (entries 8 & 9). In contrast, cationic gold catalysts $Ph_3PAuNTf_2$ and **A** furnished good yields of **4a** (entries 10 & 11). The best results were obtained with phosphite gold complex **B** in the presence of $AgSbF_6$ (entries 12–16). By increasing the amount of alkyne **1** and aldehyde **2** from 1.2 to 2.0 equiv., the yield of spiroacetal **4a** could be raised up to 97% (entries 13 & 14). Under these conditions, the catalyst loading could be reduced from 5 to 1 mol%, resulting only in a slight decrease of reactivity and product yield (entries 15 & 16). The silver salt alone does not catalyze the spirocyclization (entry 17); the same is true for CuBr (entry 18). In contrast, $PtCl_2$ is a competent catalyst, albeit not as efficient as cationic gold (entry 19).

With the optimized conditions (Table 1, entry 14) in hand, we investigated the scope of the gold-catalyzed three-component spirocyclization (Scheme 2). A wide variety of aliphatic

Table 1 Optimization of the gold-catalyzed spirocyclization[a]

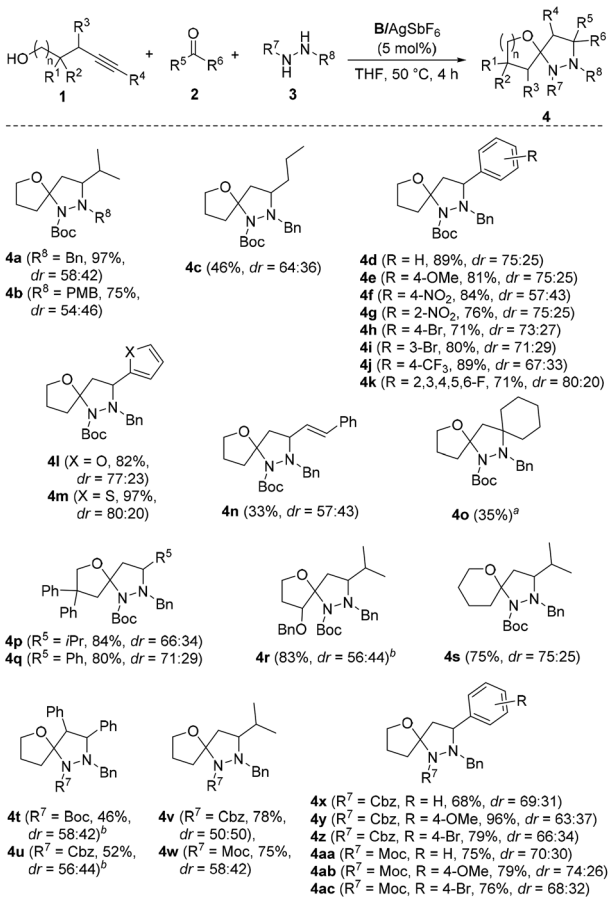


Entry	Catalyst	Solvent	Time[b]	Yield[c]
1[d]	$Ph_3PAuCl/AgOTf$	1,2-DCE	22 h[e]	41%
2[d]	$Ph_3PAuCl/AgOTf$	Toluene	16 h[e]	37%
3[d]	$Ph_3PAuCl/AgOTf$	DCM	16 h[e]	43%
4[d]	$Ph_3PAuCl/AgOTf$	THF	16 h	52%
5	$Ph_3PAuCl/AgOTf$	THF	3 h	40%
6	$Ph_3PAuCl/AgBF_4$	THF	3 h	58%
7	$Ph_3PAuCl/AgSbF_6$	THF	3 h	69%
8	AuCl	THF	7 h[e]	Traces
9	$AuCl_3$	THF	7 h[e]	Traces
10	$Ph_3PAuNTf_2$	THF	4 h	75%
11	**A**	THF	4 h	65%
12	**B**/$AgSbF_6$	THF	4 h	77%
13	**B**/$AgSbF_6$[f]	THF	4 h	89%
14	**B**/$AgSbF_6$[g]	THF	4 h	97%
15	**B**/$AgSbF_6$[g,h]	THF	4 h	85%
16	**B**/$AgSbF_6$[g,i]	THF	6 h	84%
17	$AgSbF_6$	THF	4 h[e]	Traces
18	CuBr[j]	THF	14 d[e]	Traces
19	$PtCl_2$[j]	THF	24 h	57%

[a] Reactions performed on a 0.45 mmol scale (0.15 M solution) with 1.2 equiv. each of **1** and **2** + 1.0 equiv. of **3**. Product **4a** was obtained with dr = 58 : 42 in all cases. [b] Time required to reach completion. [c] Isolated yield. [d] At rt. [e] Incomplete conversion. [f] With 1.5 equiv. each of **1** and **2** + 1.0 equiv. of **3**. [g] With 2.0 equiv. each of **1** and **2** + 1.0 equiv. of **3**. [h] With 2 mol% catalyst. [i] With 1 mol% catalyst. [j] With 10 mol% catalyst.

(**4a–c**), aromatic (**4d–k**), and heteroaromatic aldehydes (**4l/m**) is tolerated. With butyraldehyde, extensive enolization took place, resulting in a diminished yield (46%) of product **4c**. Aromatic aldehydes bearing various substituents (including nitro groups) afforded the spirocyclic pyrazolidines **4d–k** with high yield (71–89%). Notably, fluorinated aryl groups (**4j/k**), as well as, bromide (**4h/i**) can be introduced without difficulty, the latter offering a handle for further functionalization. Whereas heteroaromatic aldehydes work exceptionally well (products **4l/m**), cinnamic aldehyde afforded product **4n** with only 33% yield. Attempts to extend this method to ketones revealed a pronounced reactivity issue. With an excess of cyclohexanone in the presence of 4 Å molecular sieves, bis-spirocycle **4o** was isolated with only 7% yield. This could be improved to 35% by adding $Yb(OTf)_3$ as Lewis-acidic activator of the ketone.

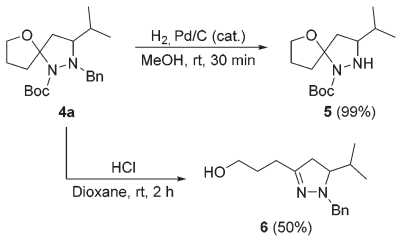
Structural variations of the alkynol **1** were rewarding as well. Introduction of substituents at the tether connecting triple bond and hydroxy gave products **4p–r**. Interestingly, only two diastereomers were formed in the case of the richly functionalized 6-oxa-1,2-diazaspiro[4.4]nonane **4r**. Extension of the tether by one carbon atom allowed the smooth formation of the 6-oxa-1,2-diazaspiro[4.5]decane **4s** with good yield of 75%.



Scheme 2 Scope of the gold-catalyzed three-component spirocyclization. Conditions according to Table 1, entry 14. Diastereomeric ratios determined by ^{1}H-NMR. Moc = methoxycarbonyl. [a] With 8 equiv. of cyclohexanone, 10 mol% of $Yb(OTf)_3$ and 4 Å molecular sieves. [b] Only two diastereomers observed.

Nicely, the spirocyclization is not restricted to terminal alkynols; use of internal acetylenic alcohols furnished the products **4t**/**u** with a fully substituted pyrazole ring, albeit with reduced yield (46/52%). Analogous to **4r**, only two of four possible diastereomers were obtained. Finally, variation of the protecting groups at the hydrazine **3** is also possible. For a successful three-component transformation, the hydrazine has to bear an electron-rich and an electron-deficient group.[8,18] The former can be benzyl or *p*-methoxybenzyl (product **4b**); for the latter, various carbamates can be employed: Boc, Cbz (spirocycles **4u–v**, **4x–z**), or Moc (products **4w**, **4aa–ac**). This opens up different options for further transformation of the spirocycles. For example, hydrogenative debenzylation of **4a** furnished the monoprotected pyrazolidine **5** with almost quantitative yield (Scheme 3). In contrast, removal of the Boc group under acidic conditions led to a mixture containing 50% of the ring-opened product **6**. Obviously, the presence of a protecting group at the hemiaminal nitrogen is important for the stability of the spirocyclic pyrazolidine.

In most cases, the spirocyclic pyrazolidines **4** were formed with diastereomeric ratios between 2 : 1 and 3 : 1. Generally,



Scheme 3 Deprotection of spiroacetal **4a**.

aromatic and heteroaromatic aldehydes give higher diastereoselectivites (up to 4 : 1) than their aliphatic counterparts (Scheme 2). The catalyst did not have an impact on the diastereoselectivity. The relative configuration of the major diastereomer of product **4h** was determined by X-ray crystal structure to be (3*RS*,5*SR*). The diastereoselectivities and the configuration of the major isomer are analogous to those observed previously in the gold- and Brønsted acid-catalyzed three-component coupling of alkynols, anilines, and glyoxalic acid.[14a]

From the mechanistic point of view, there appear be exist two possible pathways for the formation of the spirocyclic pyrazolidines **4** from the components **1–3** which differ in the order of events. Following the proposal made previously by one of us (H.O.) for the gold-catalyzed three-component annulation to dihydropyrazoles, a Mannich-type coupling of the aldehyde with the hydrazine would afford a propargyl hydrazine; cyclization to a dihydropyrazole would then be followed by an intramolecular hydroalkoxylation to give the spiroacetal.[8] Alternatively, the reaction might be initiated by gold-catalyzed cyclization of the alkynol to an exocyclic enol ether[17] which then undergoes a [3 + 2]-cycloaddition with an azomethine ylide formed from the hydrazine and the aldehyde. Following the reaction of by ^{1}H-NMR spectroscopy revealed a rapid consumption of the alkynol within 5 min whereas the hydrazine is consumed at a slower rate (Fig. 2). Moreover, an

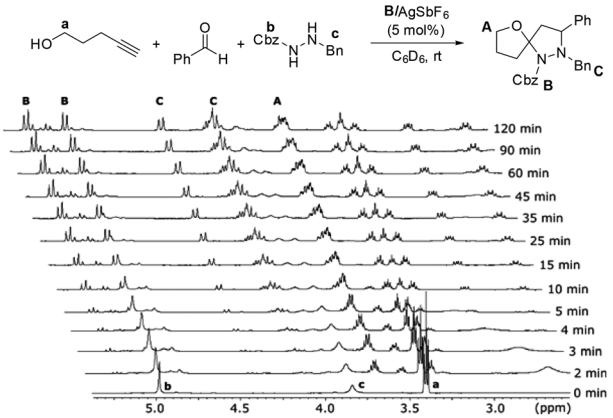
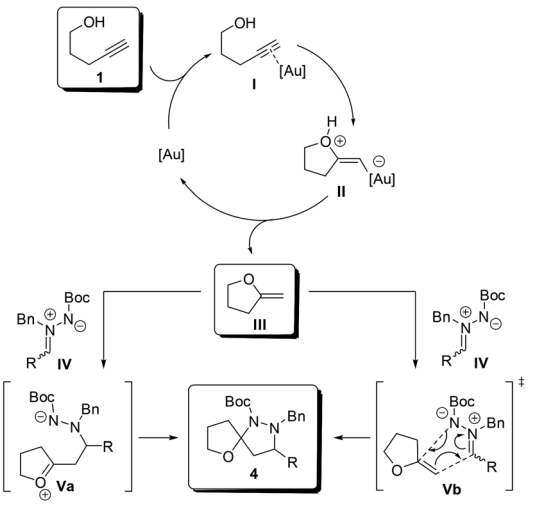
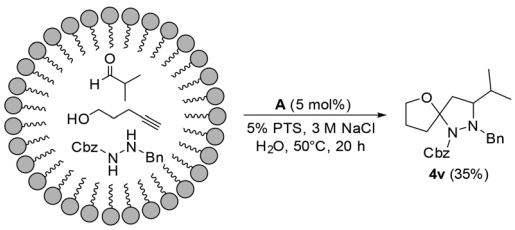


Fig. 2 Kinetic ^{1}H-NMR study of the gold-catalyzed three-component coupling.



Scheme 4 Proposed mechanism for the gold-catalyzed three-component spirocyclization.



Scheme 5 Gold-catalyzed three-component spirocyclization in micelles (PTS = polyoxyethanyl α-tocopheryl sebacate).

intermediate was observed in the ^{1}H-NMR at δ ~3.5 which may be attributed to an enol ether.

Accordingly, we assume that the transformation starts with the gold-catalyzed cycloisomerization of alkynol **1** to enol ether **III** *via* intermediates **I** and **II** (Scheme 4).[14a,17] The subsequent [3 + 2]-cycloaddition with azomethine ylide **IV** may follow a stepwise (*via* intermediate **Va**) or concerted pathway (*via* transition state **Vb**). There is a limited number of examples for gold-catalyzed [3 + 2]-cycloadditions involving azomethine ylides;[14a,19] thus, the gold catalyst may be involved also in the final step towards spirocycles **4**. Unfortunately, attempts to perform the [3 + 2]-cycloaddition with preformed enol ethers have failed due to the instability of these substrates.[17b]

Conclusions and outlook

We have developed an efficient, highly atom economic and general synthesis of hitherto unknown spirocyclic pyrazolidines in a one-pot fashion based on simple starting materials. The gold-catalyzed three-component coupling of alkynols, hydrazines and aldehydes or ketones likely proceeds *via* cycloisomerization of the alkynol to an exocyclic enol ether and subsequent [3 + 2]-cycloaddition of an azomethine ylide. We have synthesized a library of 29 derivatives with a wide range of functional groups in up to 97% yield. With this new method, every position in the final product can be substituted as required for applications in combinatorial or medicinal chemistry. Further work devoted to a better mechanistic understanding, as well as, to an improved substrate scope, reactivity, sustainability, and stereoselectivity of the three-component spirocyclization is in progress. Gratifyingly, initial experiments to perform the reaction in micelles with water as bulk solvent were successful.[20] Reaction of isobutyraldehyde, pent-4-yn-1-ol, and benzyl/Cbz-protected hydrazine with cationic gold catalyst **A** in an aqueous medium containing 5% polyoxyethanyl α-tocopheryl sebacate (PTS) and 3 M NaCl afforded spiroacetal **4v** with 35% yield after 20 h at 50 °C (Scheme 5). Even though further optimization is required, this result demonstrates that even highly demanding multicomponent reactions can be carried out under the challenging conditions of micellar catalysis.

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