N-Heterocycles

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A Flexible and Stereoselective Synthesis of Azetidin-3-ones through Gold-Catalyzed Intermolecular Oxidation of Alkynes**

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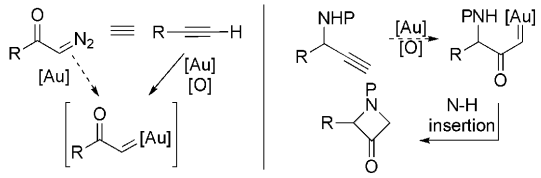
Azetidine is a strained four-membered nitrogen-containing heterocycle that can be found in various natural products[1] and compounds of biological importance. Although β-lactams (i.e. azetidin-2-ones) are a rich source of antibiotics,[2] their structural isomer (azetidin-3-ones) with the carbonyl group one carbon removed from the nitrogen atom, have not been found in nature but could serve as versatile substrates for the synthesis of functionalized azetidines.[3]

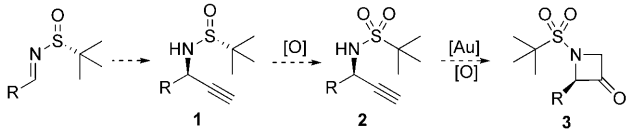
The synthesis of azetidin-3-ones[3] has been mainly realized by acid-promoted or metal-catalyzed decomposition of α-amino-α′-diazo ketones[4] and 4-*exo-tet* cyclizations of α-amino ketones. The diazo ketone approach is the most reliable in terms of substrate scopes, but it often suffers from competitive reactions and low yields;[4b,5] moreover, diazo compounds are toxic and potentially explosive.[6] For the synthesis of chiral azetidin-3-ones,[7] natural amino acids serve as a convenient and cheap chiral pool, but at the same time poses limits on substrate scope and configuration. Herein, we report a straightforward, flexible, and general sequence for the efficient synthesis of chiral azetidin-3-ones with typically >98% *ee* that bypasses toxic diazo intermediates.

Early in 2010 our research group showed for the first time[8] that reactive α-oxo gold carbenes[9] could be readily accessed by simple intermolecular oxidation[10] of terminal alkynes,[11] therefore allowing substitution of toxic α-diazo ketones with benign and readily available alkynes (Scheme 1). This approach was later applied to the preparation of oxetan-3-ones from easily available propargyl alcohols.[12] A further application of this chemistry calls for an intramolecular N–H insertion by an α-oxo gold carbene using protected propargylamines as substrates (Scheme 1).



Scheme 1. Formation of azetidin-3-ones through alkyne oxidation.

To implement this design, we anticipated that the key was to find a suitable electron-withdrawing protecting group for the basic amino group that might deactivate cationic gold catalysts. While an acyl group is in general not suitable owing to a competitive carbonyl 5-*exo-dig* cyclization,[13] the use of a tosyl group would encounter difficulty in its later removal, which is typically accomplished under harsh basic/reductive conditions.[14] We decided to use the *tert*-butylsulfonyl (Bus)[15] group as the protecting group for two reasons: 1) it can be removed under acidic conditions, and 2) it can be prepared from *tert*-butylsulfinyl by simple oxidation using *m*-CPBA. Importantly, *tert*-butylsulfinamide derivatives are easily formed in chiral forms by using Ellman's chemistry.[16] As shown in Scheme 2, this protecting-group strategy would allow us to access various *N*-*tert*-butylsulfonylpropargylamines (i.e. **2**) with high *ee* values conveniently from chiral sulfinamides **1** without additional protection and deprotection steps, and eventually a range of chiral azetidin-3-ones could be obtained (Scheme 2).



Scheme 2. Design: formation of chiral azetidin-3-ones through *tert*-butylsulfinamide derivatives.

We set out to screen different conditions for the key gold-catalyzed oxidative cyclization of *tert*-butylsulfonamides. Using racemic sulfonamide **2a** as the substrate, some of the results are listed in Table 1. As it soon became obvious that the sulfonamide behaved very differently from its alcohol counterpart, and azetidin-3-one **3a** was formed in only 28% yield along with a significant amount of mesylate **4a** using the optimized conditions for propargylic alcohol substrates (Table 1, entry 1).[12] Interestingly, no Wolff rearrangement product[17] was observed. Varying the *N*-oxides (Table 1, entries 2–6), however, revealed that bulky and electron-deficient 2,6-dibromopyridine *N*-oxide (**5e**) was the best (Table 1, entry 5). Using this optimal oxidant, various gold catalysts were screened (Table 1, entries 5, 7–11). Those with 2-biphenylphosphine ligands generally performed better (Table 1, entries 9–11); moreover, a close comparison of the three 2-biphenylphosphine ligands revealed that the reaction was slightly more efficient with a bulkier biphenyl group (compare Table 1, entry 9 and entry 10) but less so if the

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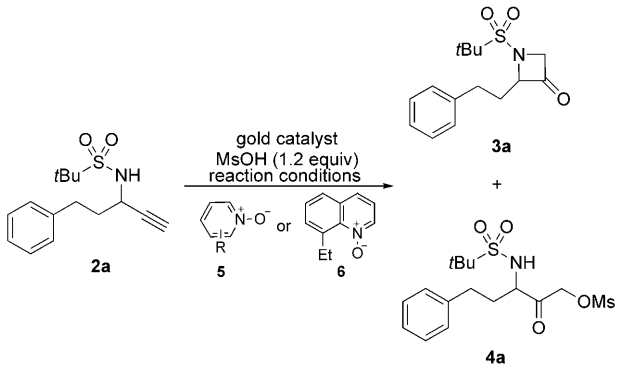
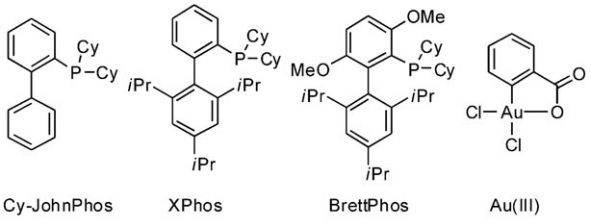
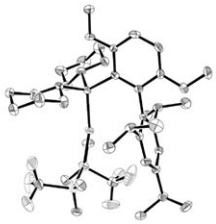
Table 1: Formation of azetidin-3-ones through oxidative cyclization: optimization of reaction conditions.[a]



Entry	Gold catalyst	Oxidant (R)	Reaction conditions	Yield [%][b]	
				3a	**4a**
1	$[Ph_3PAuNTf_2]$	**5a** (3,5-Cl_2)	RT, 4 h	28	27
2	$[Ph_3PAuNTf_2]$	**5b** (4-Ac)	RT, 12 h	21[c]	19
3	$[Ph_3PAuNTf_2]$	**5c** (4-Et)	RT, 12 h	< 5[d]	–
4	$[Ph_3PAuNTf_2]$	**5d** (2-Br)	RT, 4 h	30	29
5	$[Ph_3PAuNTf_2]$	**5e** (2,6-Br_2)	RT, 4 h	48	10
6	$[Ph_3PAuNTf_2]$	**6**	RT, 12 h	22[e]	15
7	$[IPrAuNTf_2]$	**5e** (2,6-Br_2)	RT, 12 h	50	4
8	$[(4\text{-}CF_3)_3PAuNTf_2]$	**5e** (2,6-Br_2)	RT, 4 h	42	12
9	[Cy-JohnPhosAuNTf$_2$]	**5e** (2,6-Br_2)	RT, 4 h	56	10
10	[XPhosAuNTf$_2$]	**5e** (2,6-Br_2)	RT, 4 h	58	12
11	[*t*Bu-XPhosAuNTf$_2$]	**5e** (2,6-Br_2)	RT, 4 h	50	10
12	[BrettPhosAuNTf$_2$]	**5e** (2,6-Br_2)	RT, 4 h	70	4
13	**[BrettPhosAuNTf$_2$]**	**5e (2,6-Br_2)**	**RT, 6 h**[f]	**85**[g]	–
14	Au^{III}	**5e** (2,6-Br_2)	RT, 30 min	68	< 1
15	$PtCl_2$/CO (toluene)	**5e** (2,6-Br_2)	80 °C, 12 h[f]	< 5[d]	–

[a] Reaction conditions: [**2a**] = 0.05 M, oxidant (2 equiv). [b] Estimated by ^{1}H NMR analysis using diethyl phthalate as the internal reference. [c] 20% of **2a** remained unreacted. [d] Most **2a** remained unreacted. [e] 10% of **2a** remained unreacted. [f] No acid additive, 1.2 equivalents of **5e**. [g] Yield of isolated **3a** was 82%. Cy = cyclohexyl, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene, Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

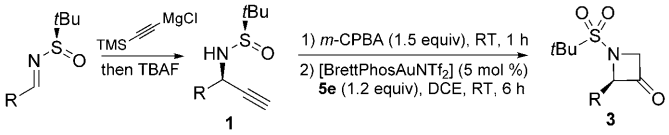



[BrettPhosAuNTf$_2$]

cyclohexyl groups were replaced with bigger *tert*-butyl groups (compare Table 1, entries 10 and 11). With this trend in mind, we decided to test dicyclohexylphosphine ligands containing even bulkier biphenyl moieties. Therefore Brettphos, a functionalized XPhos with MeO groups at the 3- and 6-positions developed by Buchwald,[18] became an apparent choice. Complex [BrettPhosAuNTf$_2$] was easily prepared by following a typical preparative procedure for cationic gold(I) complexes,[19] and its structure was confirmed by single-crystal X-ray analysis.[20] To our delight, this new cationic gold(I) complex offered a significant improvement (Table 1, entry 12). Inspired by our recent work that did not use acid additives,[11] the reaction was attempted without MsOH. Pleasingly, azetidin-3-one **2** was formed in an 85% (82% isolated) yield, and the reaction rate did not decrease to a significant extent (Table 1, entry 13). Somewhat surprisingly, dichloro(2-picolinato)gold(III) could also catalyze this reaction with an acceptable efficiency, albeit with the need of MsOH (Table 1, entry 14). However, $PtCl_2$ did not promote this reaction (Table 1, entry 15).

With the optimal reaction conditions secured, the reaction scope was then studied. Throughout this study, (*R*)-*tert*-butylsulfinamide was used as the chiral auxiliary. As shown in Table 2, chiral *N*-propargylsulfinamide derivatives were prepared in excellent diastereoselectivities by following Lin's procedure,[21] and the configuration of the propargyl center was assigned accordingly. The oxidation of the sulfinamide using *m*-CPBA and subsequent gold-catalyzed oxidative cyclization were performed without column purification of the sulfonamide intermediate, and the two-step overall yields are shown. Azetidin-3-one compounds with different substituents at the 2-position were prepared in mostly good yields. One exception was a *tert*-butyl group, where < 35% yield was observed by ^{1}H NMR analysis, presumably owing to steric hindrance; in contrast, a cyclohexyl group was readily

Table 2: Reaction scope study.[a]



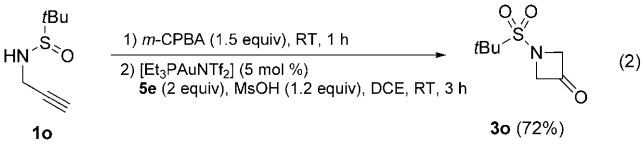
Entry	R	Sulfinamide			Azetidin-4-one		
		1[b]	Yield [%][c]	d.r.	**3**	Yield [%][c]	*ee* [%][d]
1	$PhCH_2CH_2$	**1a**	82	> 99:1	**3a**	82	99
2	*n*-propyl	**1b**	71	> 99:1	**3b**	79	99
3	cyclohexyl	**1c**	78	> 99:1	**3c**	81	> 99
4	pent-4-en-1-yl	**1d**	90	> 50:1	**3d**	80	97
5	4-bromobutyl	**1e**	74	> 99:1	**3e**	74	99
6	4-azidobutyl	**1f**	78[e]	> 99:1	**3f**	67[f]	98
7		**1g**	76[g]	> 99:1	**3g**	84	98
8		**1h**	84	> 99:1	**3h**	78	99
9	Ph	**2i**[h]	71[i]	> 99:1	**3i**	72[j]	98
10		**1j**	72	> 99:1	**3j**	78	99

[a] Reaction conditions: [**1**] = 0.05 M. [b] Configuration was assignment based on literature precedents. [c] Yield over two steps. [d] Determined using HPLC on a chiral stationary phase. [e] Prepared from **1e**. [f] The reaction was run at 40 °C for 24 h. [g] Prepared from **1f**. [h] The oxidation with *m*-CPBA was carried out before desilylation with TBAF. [i] Yield over three steps. [j] Yield for gold catalysis. Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

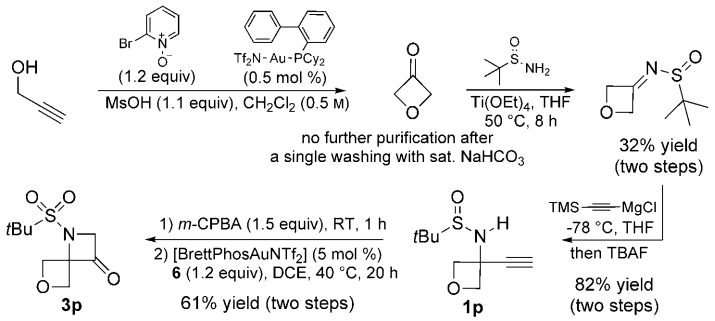
allowed (Table 2, entry 3). A range of functional groups were tolerated, including a remote C–C double bond (Table 2, entry 4), a halogen (Table 2, entry 5), and an azido group (Table 2, entry 6). In the case of a phenyl group (Table 2, entry 9), sulfinamide **1i** was not stable upon desilylation using TBAF; instead, *m*-CPBA oxidation was done before desilylation. Pleasingly, the resulting sulfonamide (i.e., **2i**) was stable and underwent the gold-catalyzed oxidative cyclization easily, and afforded azetidinone **3i** in 72% yield (Table 2, entry 9). Notably, because of the absence of any acid additive, acid-labile protecting groups such as Boc and MOM were not affected during the reaction (Table 2, entries 7 and 8). In addition, a silyl protecting group such as TBDPS was tolerated (Table 2, entry 10). In all the entries, the azetidin-4-ones were isolated with excellent *ee*, which was determined by HPLC[22] on a chiral stationary phase using racemic products as references, and essentially no epimerization was detected. The configuration of the products were assumed based on the reaction mechanism involving gold carbene N–H insertions.

Interestingly, when furan-containing sulfonamide **2k** was subjected to the gold catalysis, the desired azetidin-3-one was not observed. Instead, conjugated imine **7** was isolated as a yellow solid in 77% yield, and its structure was elucidated by single-crystal X-ray analysis (Scheme 3).[20] This transformation can be rationalized by invoking a ring opening of the azetidine intermediate **A**, facilitated by the electron-rich furan ring, and subsequent π orbital reorganization.

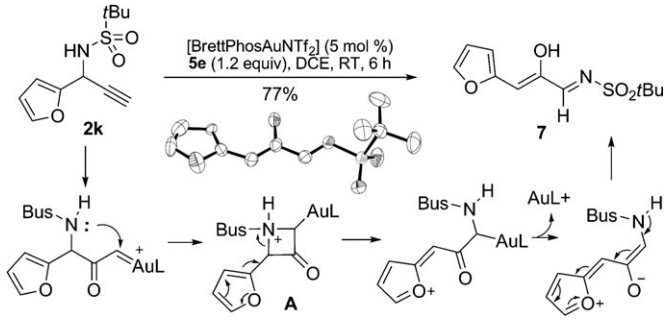
This chemistry can also be extended to the synthesis of 2,2-disubstituted azetidin-3-ones with serviceable yields [Eq. (1)], and 8-ethylquinoline *N*-oxide (**6**) was a better oxidant. Notably, **3n** was formed with 81% *ee* from the corresponding sulfinamide (d.r. 91:9),[23] Moreover, the parent *N*-*tert*-butylsulfinylazetidin-3-one **3o** was readily prepared using $[Et_3PAuNTf_2]$ as the catalyst [Eq. (2)].



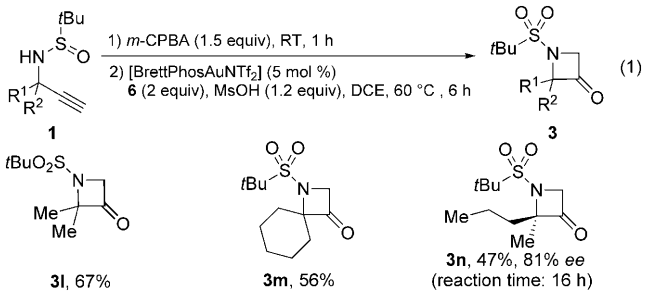
Lately, heterospiro[3.3]heptanes have been proposed as building blocks in medicinal chemistry.[24] This chemistry, in combination with our previous oxetan-3-one chemistry,[12] provided a facile synthesis of oxazaspiro[3.3]heptanone **3p**. The sequence starting from cheap propargyl alcohol is outlined in Scheme 4, and formation of the azetidine ring was achieved in a respectable 61% yield. This dual application of the α-oxo gold carbene chemistry highlights the synthetic utility of the gold-catalyzed alkyne oxidation strategy.



Scheme 4. Synthesis of oxazaspiro[3.3]heptane **3p**. THF = tetrahydrofuran.

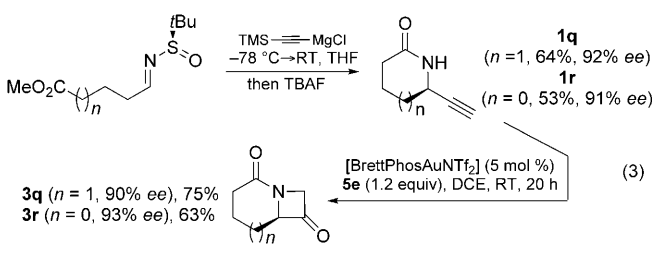


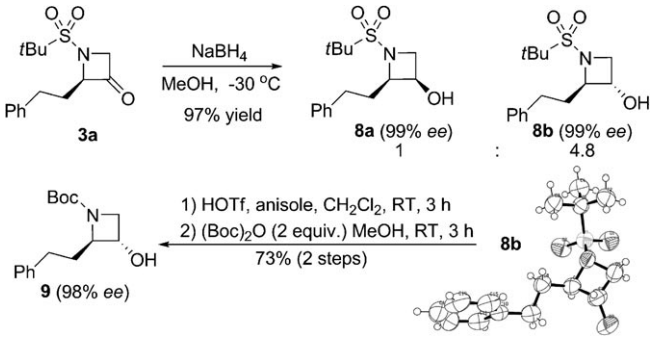
Scheme 3. Formation of imine **7**.



Although linear *N*-propargylcarboxamides are not suitable substrates due to competitive 5-*exo*-*dig* cyclization by its acyl group,[13] lactams such as **1q** and **1r** with the acyl group tied back by the ring structure can avoid this issue. Indeed, these substrates underwent smooth oxidative cyclization, and led to strained bicyclic lactams **3q** and **3r** in fairly good yields and good enantiomeric excesses [Eq. (3)].

Removal of the Bus group was then examined using **3a** as the model substrate (Scheme 5). Direct deprotection under acidic conditions resulted in a complex mixture, which may be attributed to the reaction of the carbonyl group with the newly revealed amine moiety. Consequently, the ketone





Scheme 5. Removal of the Bus group.

moiety was reduced with $NaBH_4$. The resulting diastereomeric diols were separated, and the *trans* configuration of the major isomer (i.e. **8b**) was confirmed by single-crystal X-ray analysis.[20] To our delight, the Bus group in **8b** was smoothly removed under acidic conditions.[15] To facilitate isolation of the product, the free amine was capped with a Boc group.

In summary, a practical and flexible synthesis of chiral azetidin-3-ones has been developed. The key reaction is a gold-catalyzed oxidative cyclization of chiral *N*-propargylsulfonamides. Mechanistically, reactive α-oxo gold carbenes are generated as intermediates through intermolecular alkyne oxidation and subsequent intramolecular N–H insertion. The use of *tert*-butylsulfonyl as the protecting group takes advantage of the chiral *tert*-butylsulfinimine chemistry and avoids additional unnecessary deprotection and protection steps. Moreover, the Bus group can be easily removed from the azetidine ring under acidic conditions. The extension of this chemistry using other sulfonyl protecting groups is currently being examined.

Experimental Section

General procedure for the gold-catalyzed oxidative cyclization**:** To a solution of the sulfonamide, generated as a crude residue by *m*-CPBA oxidation of sulfinamide **1** in DCE (6 mL), were added *N*-oxide **5e** (0.36 mmol) and [BrettPhosAuNTf$_2$] (15.3 mg, 0.015 mmol) at RT. Upon completion of the reaction (as evident by TLC), the reaction mixture was treated with 1N HCl (15 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired azetidin-3-one **3**.

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