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Gold catalyzed [3+2] cycloaddition of *N*-allenyl amides with azomethine imines†

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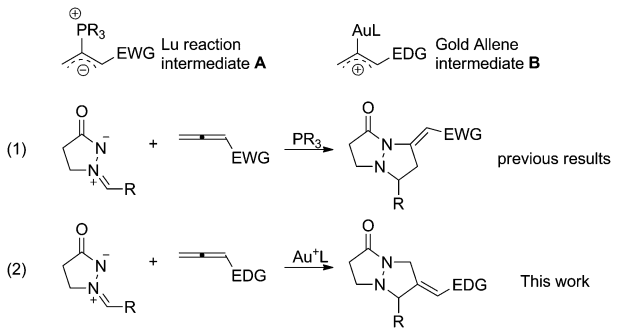
Gold(I) catalyzed [3+2] cycloaddition of azomethine imines with *N*-allenyl amides was developed to provide two types of pyrazolyl based bicyclic heterocycles. Both pyrazolidin-3-one derived and dihydroisoquinoline derived azomethine imines reacted smoothly with *N*-allenyl amides to give 6-methylene bipyrazolidin-1-ones and 1-methylene hexahydropyrazolo[5,1-a] isoquinolines in moderate to good yields.

1,3-Dipolar cycloadditions are powerful methods for constructing a variety of five-membered heterocycles. Especially, the reactions of azomethine imines with alkenes or alkynes have attracted great interest in recent years.[1,2] However, few examples of 1,3-dipolar cycloaddition of azomethine imines with allenes have been reported to date.[3]

Recent advances in gold chemistry have led to a novel pathway for the ring construction from allenes. The initial examples in this field are documented as the gold(I) catalyzed intramolecular cycloaddition of allenes with alkenes or dienes.[4] Later on, intermolecular [2+2], [4+2] cycloaddition of *N*-allenyl amides with electron rich alkenes was also illustrated.[5,6] Nevertheless, these results focused exclusively on carbocycle synthesis. Using a gold–allene complex as the dipolarphile for the synthesis of heterocycles has seldom been explored.[7] Herein we report a gold catalyzed cycloaddition reaction of *N*-allenyl amides[8] with pyrazolidin-3-one derived azomethine imines to give 6-methylene bipyrazolidin-1-ones with high diastereoselectivities.[9,10] The regioselectivity of this reaction is different from the previous reports (Scheme 1),[3] due to the divergent reactivities between intermediates **A** and **B**.[11] In addition, the reaction of *N*-allenyl amides with dihydroisoquinoline derived azomethine imines was also explored, yielding regioselectively a series of 1-methylene hexahydropyrazolo [5,1-a] isoquinolines.[3c]

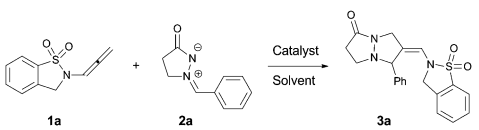
The reaction of *N*-allenyl amide **1a** with azomethine imine **2a** was chosen as the model system for our initial investigation.



Scheme 1 Allene derived intermediates and 1,3-dipolar cycloaddition with azomethine imines.

Following a previous procedure,[5a] the reaction of 1 mol equiv. of **1a** with 1.2 mol equiv. of **2a** was carried out under the condition of 5% mol equiv. of $Ph_3PAuCl/AgSbF_6$ with the addition of 100 mg 4 Å MS. The desired product 6-methylene bipyrazolidin-1-one **3a** was then obtained in 90% yield. Silver salts screening was performed, in which, $Ph_3PAuCl/AgOTf$ was found to be the best silver combination (Table 1, entry 2).[12] Removing the 4 Å molecular sieve and reducing the catalyst loading decreased the reaction yield considerably (Table 1, entries 3 and 4). In the control experiment, two substrates

Table 1 Condition optimization for the reaction of **1a** with **2a**[a]



	Catalyst (%)	Soln/temp (°C)/time (h)	**3a** Yield[b] (%)
1	$Ph_3PAuCl/AgSbF_6$ (5)	DCM/rt/2	90
2	$Ph_3PAuCl/AgOTf$ (5)	DCM/rt/2	97
3[c]	$Ph_3PAuCl/AgOTf$ (5)	DCM/rt/2	86
4	$Ph_3PAuCl/AgOTf$ (2.5)	DCM/rt/2	76
5	No catalyst	Xylene/reflux/12	Mixture

[a] Unless noted, all reactions were carried out at the 0.1 mmol scale in 2 mL solvent with the addition of 5 mol% catalyst and 100 mg 4 Å MS, (**1a**/**2a** = 1/1.2). [b] Isolated yields. [c] No 4 Å MS was added.

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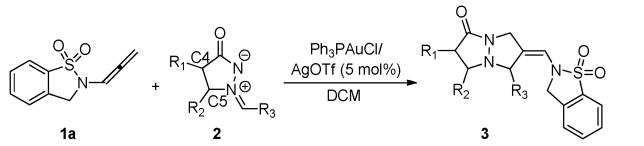
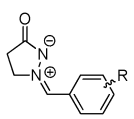
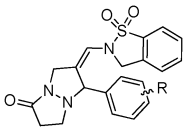
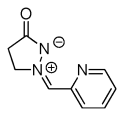
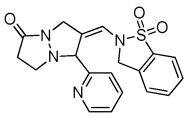
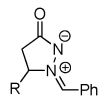
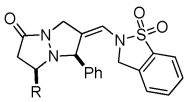
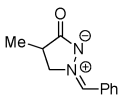
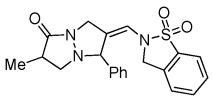
† Electronic supplementary information (ESI) available: Experimental procedures and data for all new compounds. CCDC 907213. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41258j

Table 2 The reaction of *N*-allenyl sulfonamide **1a** with a series of azomethine imines with different substitution patterns[a,b]



1a 2 3

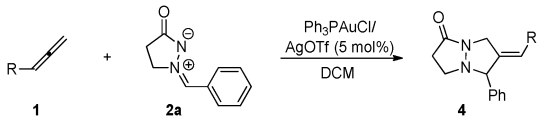
Entry	Substrate **2**	Product **3**	Reaction time (h)	Yield[c]/(dr)
				
1	**2a**, R = H	**3a**, R = H	1	97%
2	**2b**, R = *p*-OCH_3	**3b**, R = *p*-OCH_3	3	92%
3	**2c**, R = *p*-Br	**3c**, R = *p*-Br	2	95%
4	**2d**, R = *p*-F	**3d**, R = *p*-F	2	96%
5	**2e**, R = *p*-NO_2	**3e**, R = *p*-NO_2	2	82%
6	**2f**, R = *m*-Cl	**3f**, R = *m*-Cl	2	96%
				
7	**2g**	**3g**	2	83%
				
8	**2h**, R = CH_3	**3h**, R = CH_3	5	95% (10/1)
9	**2i**, R = *n*-Pr	**3i**, R = *n*-Pr	2	83% (11/1)
10	**2j**, R = *i*-Pr	**3j**, R = *i*-Pr	2	90% (12/1)
11	**2k**, R = Ph	**3k**, R = Ph	2	92% (>20/1)
				
12	**2m**	**3m**	2	96% (*syn*/*anti* = 1.2/1)

[a] Unless noted, all reactions were carried out at the 0.1 mmol scale in 2 mL CH_2Cl_2 at rt under the conditions of 5 mol% equiv. of Ph_3PAuCl/AgOTf and 100 mg 4 Å MS (the ratio of **1a/2** = 1/1.2). [b] The structure only shows relative configuration. [c] The dr value was determined using ^1H NMR spectral data.

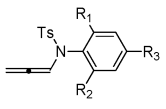
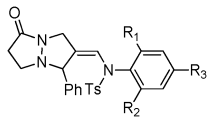
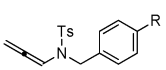
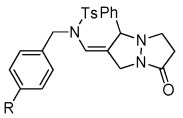
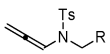
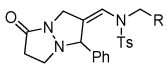
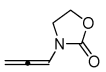
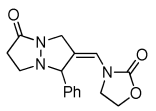
were treated in xylene under reflux conditions, which gave a mixture of undetermined products (Table 1, entry 5).‡

Next, we explored different substrate structures. A series of pyrazolidinone derived azomethine imines **2a–2f** were tested under the optimized reaction conditions (Table 1, entry 2). As shown in Table 2, both electron donating and electron withdrawing phenyl substituents (Table 1, entries 1–6) worked very well to provide the desired 6-methylene bipyrazolidin-1-one adducts **3a–f** in high yields. The pyridine group, which could coordinate with the Au(I) cation competitively, did not affect the reaction yield (Table 1, entry 7). C-4 or C-5 substituted pyrazolidinone derived azomethine imines **2h–2m** were also studied. Increasing the steric hindrance of the C-5 substituent enhanced the stereoselectivity (Table 2, entries 9–11), in which, *syn*-**3k** was obtained as a single isomer. Nevertheless, C-4 substituted substrate **2m** gave **3m** in a low *syn*/*anti* selectivity (Table 2, entry 12).[12]

Table 3 The reaction of azomethine imine **2a** with various *N*-allenyl amides[a]



1 2a 4

Entry	Substrate **2**	Product **4**	Reaction time (h)	Yield (%)
				
1	**1b**, R_1, R_2, R_3 = H	**4b**, R_1, R_2, R_3 = H	2	90
2	**1c**, R_1, R_2, R_3 = CH_3	**4c**, R_1, R_2, R_3 = CH_3	3	78
				
3	**1d**, R = H	**4d**, R = H	2.5	96
4	**1e**, R = F	**4e**, R = F	2	81
				
5	**1f**, R = *n*-Pr	**4f**, R = *n*-Pr	2	65
6	**1g**, R = 2-tetrahydrofuryl	**4g**, R = 2-tetrahydrofuryl	2	71
				
7	**1h**	**4h**	2	94

[a] Unless noted, all reactions were carried out at the 0.1 mmol scale in 2 mL CH_2Cl_2 at rt under the conditions of 5 mol% equiv. of Ph_3PAuCl/AgOTf and 100 mg 4 Å MS (the ratio of **1/2a** = 1/1.2).

[3+2] Cycloaddition of **2a** with several *N*-allenyl amides were subsequently investigated. Phenyl and benzyl substituted *N*-allenyl amides **1b–d** afforded **4b–d** in moderate to good yields (Table 3, entries 1 and 2). While alkylamine derived substrates **1f** and **1g** afforded the desired products in slightly lower yields (Table 3, entries 5 and 6). The reaction of 2-oxazolidinone derived substrate **1h** with **2a** proceeded smoothly to provide the corresponding bicyclic adduct **4h** in 94% yield (Table 3, entry 7).

The structure of **4h**, as shown in Fig. 1, was determined to be an *N*-vinylamide containing bicyclic pyrazolo [1,2-a] pyrazole structure as identified by X-ray crystallography (Fig. 1).[13]

The gold catalyzed reaction of 3,4-dihydroisoquinoline derived azomethine imine **5** with *N*-allenyl amides was also tested.[3c] As shown in Table 4, the cyclic and phenyl substituted *N*-allenyl amides **1a** and **1b** gave **6a** and **6b** in good yields, while its 2,6-diisopropyl-phenyl analog **1i** afforded the desired product **6c** in a relatively lower

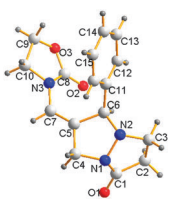
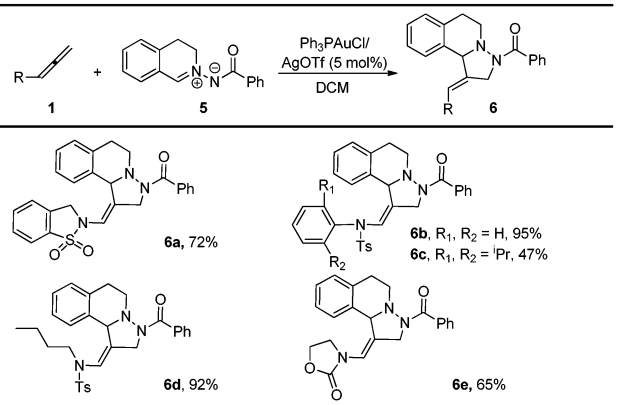
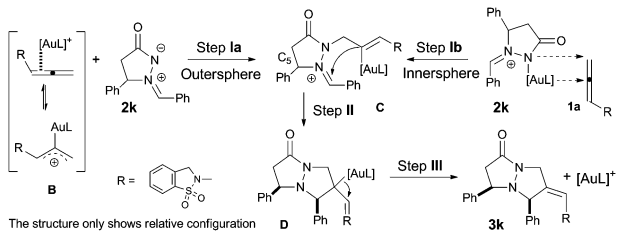


Fig. 1 X-ray structure of compound **4h**.

Table 4 The reaction of 3,4-dihydroisoquinoline derived azomethine imine **5** with various *N*-allenyl amides[a]



[a] Unless noted, all reactions were carried out at the 0.1 mmol scale in 2 mL CH_2Cl_2 at rt.



Scheme 2 A plausible mechanism for gold catalyzed [3+2] cycloaddition of *N*-allenyl amides with azomethine imines.

yield (Table 4).[12] Alkylamine substrate **1f** and 2-oxazolidinone substrate **1h** also worked very well, providing the corresponding cycloadducts **6d-e** in moderate to good yields.

Based on previous reports, two gold activation mechanisms were proposed. As shown in Scheme 2, the reaction could be started from the outer-sphere nucleophilic addition of **2k** to the gold–allene complex **B** to give intermediate **C** (step **Ia**, Scheme 2).[14] Alternatively, coordination of azomethine imine **2k** with gold catalyst followed by an inner-sphere nucleophilic addition could also lead to intermediate **C** (step **Ib**, Scheme 2).[15] Step **Ia** is preferred because of formation of the allene dimerization side products while reducing azomethine imine's equivalence.[5a] Subsequent intramolecular cyclization of intermediate **C** yielded another iminium intermediate **D** (step II), in which the vinylamine unit attacks the cationic azomethine imine from the opposite side of the C-5 phenyl group to give a *syn*-configuration cycloadduct. Deauration *via* elimination provided the [3+2] cycloadduct **3k** and regenerated the cationic gold catalyst. Steps **II** and **III** might be a concerted process to give *Z*-configuration product selectivity.

Notes and references

‡ General procedure for the [3+2] cycloaddition reaction: a solution of $Ph_3PAuCl/AgOTf$ (5 mol%) in dry CH_2Cl_2 (2 mL) with the addition of 100 mg activated 4 Å MS was stirred for three minutes. Then, *N*-allenyl amide **1a** (0.1 mmol) and azomethine imine **2a** (0.12 mmol) were added. The reaction mixture was stirred at rt until complete consumption of the starting material (TLC monitoring). Concentration of the reaction mixture in vacuum followed by flash column chromatography over SiO_2 (hexane/EtOAc = 1/5) afforded **3a** as a colorless oil in 97% yield.

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