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Gold-Catalyzed [3+3]-Annulation of Azomethine Imines with Propargyl Esters

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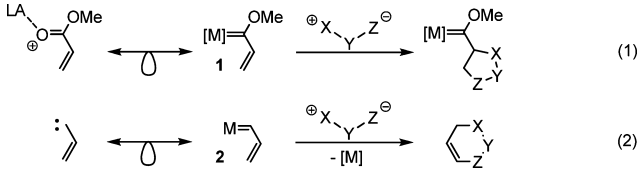
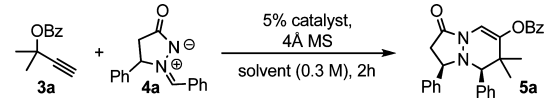
The reactions of alkenyl Fischer carbenes **1** with 1,3-dipoles typically proceed via a concerted-asynchronous [3+2] cycloaddition (eq 1). Considering the orbitals involved in these transformations, the isolobal analogy allows the comparison of the reactivity of **1** to that of Lewis acid complexed acrylates.[1] In contrast, the LUMO of alkenyl metal carbenoids of type **2** may be approximated as singlet vinylcarbenes (eq 2).[2,3] Given this analogy, a [3+3]-cycloaddition between 1,3-dipoles and carbenoids of type **2** would be predicted. Unfortunately, free electrophilic vinylcarbenes undergo rapid rearrangement to cyclopropenes, and intermolecular cycloadditions of these species are typically low yielding.[4,5] This problem has been circumvented through the use of alkenyl metal-carbenoids **2**, which are typically generated in situ from metal-catalyzed diazo decomposition;[6] however, cycloaddition reactions of 1,3-dipoles with carbenoids[7] of type **2** have yet to be reported. We report herein a gold(III)-catalyzed [3+3]-cycloaddition[8] of propargyl esters and azomethine imines, which is proposed to proceed via stepwise cycloaddition with a gold(III)-carbenoid intermediate of type **2**.[9−11]



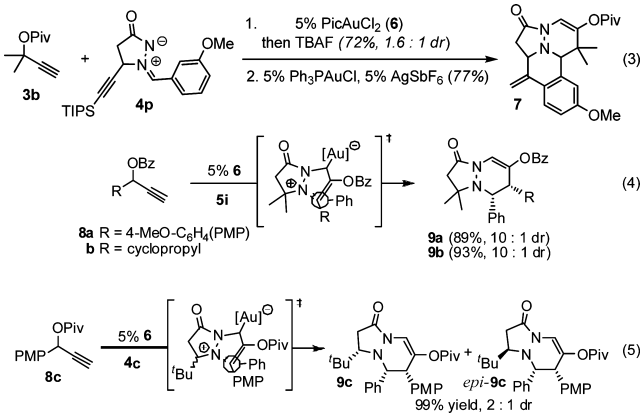
Beginning with our previously optimized reaction conditions,[9d] we were delighted to find that bicyclic [3+3] cycloadduct **5a** was formed in 90% yield and with 6:1 *cis*:*trans* diastereoselectivity in the Au(III)-catalyzed reaction of ylide **4a** with propargyl ester **3a** (Table 1, entry 1).[12,13] While varying the solvent failed to provide an increase in the diastereoselectivity (entries 2−4), lowering the temperature to 0 °C improved the ratio of *cis*:*trans* to 8:1 (entry 5).[14] Other Au(III) chloride salts also catalyzed the reaction with only slightly diminished yields (entries 6−7); however, Au(III) bromide and various Au(I) catalysts failed to provide any of the desired product (entries 8−9).[15]

Table 1. Reaction Optimization



entry	catalyst	solvent	temp	conversion	yield[a]	dr (*cis*:*trans*)
1	$PicAuCl_2$ (**6**)[b]	CD_2Cl_2	rt	100%	90%	(6:1)
2[c]	**6**	MeCN	rt	48%	44%	(6:1)
3[c]	**6**	NO_2Me	rt	71%	61%	(5:1)
4	**6**	C_6D_6	rt	–[d]	49%	(3:1)
5[c]	**6**	CD_2Cl_2	0 °C	100%	89% (79%[e])	(8:1)
6	$NaAuCl_4$	CD_2Cl_2	rt	100%	73%	(6:1)
7	$AuCl_3$	CD_2Cl_2	rt	100%	85%	(6:1)
8	$AuBr_3$	CD_2Cl_2	rt	20%	<5%	–
9	$Ph_3PAuCl/AgSbF_6$	CD_2Cl_2	rt	<5%	<5%	–

[a] Yield and diastereomeric ratio determined by ^1H NMR versus an internal standard. [b] Pic = 2-picolinate. [c] Reaction time was 4 h. [d] The starting ylide was partially insoluble in 0.3 M C_6D_6. [e] Isolated yield of analytically pure *cis* **5a**.



With optimal conditions in hand (entry 5), the substrate scope of the gold-catalyzed [3+3]-cycloaddition reaction was examined. As demonstrated in the reaction of β-phenyl substituted azomethine imine **4a**, substitution of the β-position of the pyrazolidinone generally provides bicyclic product **5a** with high *cis* selectivity (*vida infra*). Alkyl substituents are also tolerated at this position (Table 2, entries 1−2), with larger substituents giving increased selectivity (20:1 for *tert*-butyl versus 8:1 for methyl). Remarkably, even an alkynyl substituent is sufficient to provide high selectivity (7:1, entry 3). Moreover, this reaction was readily extended to the synthesis of tetracycle **7** (eq 3). Following the initial [3+3] cycloaddition of azomethine imine **4p**, the alkyne was deprotected with TBAF and subjected to Au(I)-catalyzed hydroarylation conditions to deliver **7**.[16]

The azomethine imine can also be substituted at the α-position, although in this case the product (**5e**) was formed with 1.3:1 *cis*:*trans* diastereoselectivity (entry 4). On the other hand, the cycloaddition of azomethine imine **4f**, having both α- and β-substituents, remained highly selective (10:1, entry 5). Finally, the backbone need not be substituted (entry 7) but can also accommodate quaternary carbons in either position (entries 8−9).

The aldehyde-derived substituent of the azomethine imine can also be varied. Both electron-rich and electron-deficient aryl groups are well tolerated in the gold(III)-catalyzed cycloaddition (entries 10−11). Ortho-substituted aryl groups are also accommodated but provide the cycloadducts with significantly lower diastereoselectivity (entries 12−13). Finally, the cycloaddition reaction of ylides derived from aliphatic aldehydes generally proceeded in lower yield (entry 14).

An additional stereocenter is generated when secondary propargyl esters are employed (eqs 4, 5). In this case, regardless of whether the cycloaddition is concerted or stepwise (as depicted),[17] the high 1,2-*cis* diastereoselectivity can be rationalized as resulting from the

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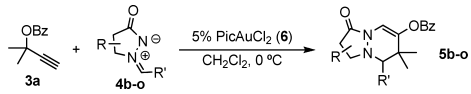
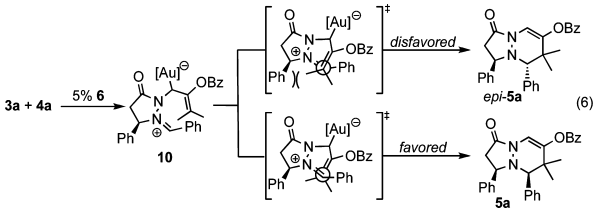
Table 2. Azomethine Imine Scope



entry	product	yield (*cis*:*trans*)
1	**5b** R = Me	98% (8 : 1)
2	**5c** R = ^{t}Bu	92% (20 : 1)
3	**5d** R = C≡CTIPS	96% (7 : 1)
4	**5e** (R = H)	94% (1.3 : 1)
5	**5f** (R = Me)	83% (10 : 1)
6	**5g**	90% (>20:1)
7	**5h** R = R' = H	82% [a]
8	**5i** R = Me, R' = H	82% [a,b]
9	**5j** R = H, R' = Me	88% [a]
10	**5k** R = Ph, R' = 3,4,5-(MeO)$_3$-C$_6$H$_2$	80% (6 : 1)
11	**5l** R = Ph, R' = 4-CN-C$_6$H$_4$	94% (5 : 1)
12	**5m** R = Ph, R' = 3-pyridyl-2-Cl	98% (1.7 : 1)
13	**5n** R = Me, R; = 2-I-C$_6$H$_4$	72% (1.8 : 1)
14	**5o** R = Ph, R' = cyclopropyl	41% [a] (2.8 : 1)

[a] Reaction performed at room temperature. [b] 2 mmol scale.

cis-imine geometry and the preferred *trans* geometry of the proposed gold-carbenoid intermediate.[9d,18] To gain further insight into the origin of the 1,2-*cis* stereoselectivity, secondary propargyl ester **8c** was reacted with *tert*-butyl substituted azomethine imine **4c** (eq 5).[19] In this case, a 2:1 mixture of diastereomers with respect to the pyrazolidinone substituent, and favoring the 1,3-*trans* isomer of **9c**, was formed.[20] Furthermore, the high diastereoselectivity in the gold-catalyzed reactions of **3a** can be rationalized by minimization of unfavorable steric interactions between the propargyl ester methyl groups and the β-substituent in the ring closing transition state (eq 6). These results suggest that the diastereoselectivity is determined during ring closing, rather than in the formation of allylgold intermediate **10**.[13]



In conclusion, we have developed a gold(III)-catalyzed synthesis of diazabicycles from readily available starting materials.[21] This report represents the first example of a formal cycloaddition between alkenyl metal carbenoids and 1,3-dipoles. In contrast to the previously reported cycloadditions,[9d,10f] this reaction highlights the difference in the reactivity of alkenyl Fischer carbenes and the alkenyl Au-carbenoids generated from the rearrangement of propargyl esters. Further studies exploring and exploiting this difference are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures, compound characterization data (PDF), and X-ray structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Employing a different propargyl ester (acetate or pivolate) provided no change in selectivity.
(15) HCl, $PtCl_2$, $PdCl_2(PPh_3)_2$, $[IrCl(cod)]_2$, and $[RuCl_2(CO)_3]_2$ failed to promote this reaction.
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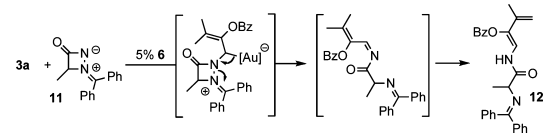
(17) Additional evidence for a stepwise mechanism was obtained in the reaction of azomethine imine **11**, which furnished enamine **12** after ring fragmentation and tautomerization.



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(19) This substrate combination was chosen to aid in characterization of the products. Nearly identical selectivites were observed in reactions employing either **8a** or **8c**.
(20) The configuration of the minor isomer was confirmed by X-ray crystallography (see Supporting Information).
(21) For further synthetic transformations of the diazabicycles, see the Supporting Information.

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