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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 carbenoids⁷ of type **2** have yet to be reported. We report herein a gold(III)-catalyzed [3+3]-cycloaddition⁸ of propargyl esters and azomethine imines, which is proposed to proceed *via* stepwise cycloaddition with a gold(III)-carbenoid intermediate of type **2**.^{9,10,11}

(1)

(2)

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

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

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 (*vide 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 (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).

(3)

(4)

(5)

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 (entries 12–13), but provide the cycloadducts with significantly lower diastereoselectivity. 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 *cis*-imine geometry and the preferred *trans* geometry of the proposed gold-carbenoid intermediate.^{9d} 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. The major isomer was assigned to be *cis* by X-ray crystallography (see supporting information).
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19. This substrate combination was chosen to aid in characterization of the products. Nearly identical selectivities 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.

Table 1

Reaction optimization.

entry	catalyst	solvent	temp.	conversion	yield ^d	dr (cis:trans)
1	PicAuCl ₂ (6) ^b	CD ₂ Cl ₂	rt	100%	90%	(6:1)
2 ^c	6	MeCN	rt	48%	44%	(6:1)
3 ^c	6	NO ₂ Me	rt	71%	61%	(5:1)
4	6	C ₆ D ₆	rt	— ^d	49%	(3:1)
5 ^c	6	CD ₂ Cl ₂	0 °C	100%	89% (79% ^e)	(8:1)
6	NaAuCl ₄	CD ₂ Cl ₂	rt	100%	73%	(6:1)
7	AuCl ₃	CD ₂ Cl ₂	rt	100%	85%	(6:1)
8	AuBr ₃	CD ₂ Cl ₂	rt	20%	<5%	—
9	Ph ₃ PAuCl/AgSbF ₆	CD ₂ Cl ₂	rt	<5%	<5%	—

^aYield and diastereomeric ratio determined by ¹H-NMR versus an internal standard.

^bPic = 2-picolinic acid

^cReaction time was 4 hours.

^dThe starting ylide was partially insoluble in 0.3M C₆D₆

^eIsolated yield of analytically pure *cis* **5a**.

Table 2

Azomethine imine scope.

entry		product	yield (<i>cis:trans</i>)
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'=H	82% ^a
8		5i R = Me, R' = H	82% ^{a,b}
9		5j R = H, R' = Me	88% ^a

entry	product	yield (<i>cis:trans</i>)
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.