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Catalytic Regioselective Control in the Diastereoselective 1,3-Dipolar Cycloaddition Reactions of 1-(1-Alkynyl)cyclopropyl Ketones with Nitrones

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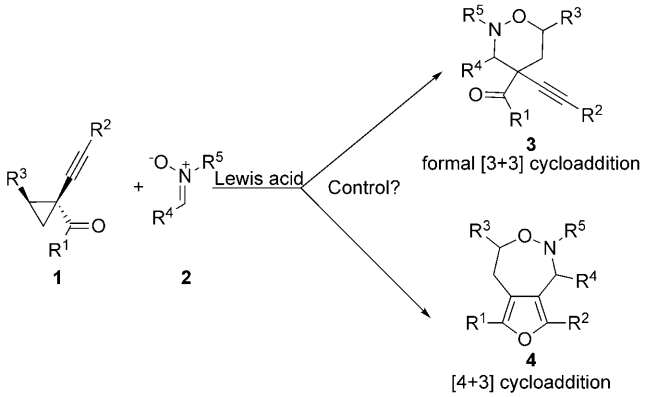
One of the challenges in modern synthesis is the creation of distinct types of complex molecules from identical starting materials by subtly altering the choice of catalyst.[1] Recently, much attention has been paid to 1-(1-alkynyl)cyclopropyl ketones due to their unique structures and reactivities. For example, Schmalz[2a] and Zhang[2b–c] have successfully developed gold-catalyzed tandem reactions of 1-(1-alkynyl)cyclopropyl ketones to efficiently construct highly substituted furans and carbobicycles. In addition, we very recently developed a Rh^{I}-catalyzed carbonylation reaction of 1-(1-alkynyl)cyclopropyl ketones that leads to fused 5,5-bicyclic furans.[3]

After our study of the gold-catalyzed cycloaddition reactions of 2-(1-alkynyl)-2-alken-1-ones with nitrones and as a continuation of our efforts to design and develop novel regiodivergent reactions,[4] we became interested in the Lewis acid catalyzed 1,3-dipolar cycloaddition reactions of 1-(1-alkynyl)cyclopropyl ketones **1** with nitrones **2**.[5] We envisaged that these reactions might provide two different types of adduct by two regioselective cycloaddition reactions (Scheme 1): 1) tetrahydro-1,2-oxazines **3** through 1,3-dipolar (formal [3+3]) cycloaddition of nitrones to the cyclopropane moiety of **1**[6,7] and 2) 5,7-fused heterobicyclic furo[3,4-*d*]-[1,2]oxazepines **4** through tandem double cyclization (formal [4+3] cycloaddition) of nitrone **2** with **1**.[8,9] How to efficiently control these two types of cycloaddition reaction



Scheme 1. Proposed reaction pattern for 1-(1-alkynyl)cyclopropyl ketones with nitrones.

is an interesting, but troublesome, issue. Herein, we report our recent result that this regioselectivity can be controlled by subtle changes in the choice of catalyst. Furthermore, a kinetic resolution study and the transformation of an optically active substrate provide evidence supporting the proposed mechanism of the gold(I)-catalyzed tandem cyclization/[4+3] cycloaddition.

This hypothesis was initially tested by reacting 1-(1-alkynyl)cyclopropyl ketone **1a** with nitrone **2a** under catalysis by a series of Lewis acids. After numerous attempts, we were pleased to find that the reaction gave tetrahydro-1,2-oxazine **3aa** in 90% isolated yield with a diastereomeric ratio of 92:8 under conditions A: $Sc(OTf)_3$ (10 mol%, Tf = triflate), 1,10-pheneanthroline (10 mol%), 4 Å molecular sieves (MS), 1,2-dichloroethane (DCE), 28–32 °C (Table 1).[10] In contrast, the corresponding 5,7-fused bicyclic furo[3,4-*d*][1,2]oxazepine **4aa** was isolated in 96% yield, as a single diastereomer (d.r. > 20:1), under the catalysis of $Ph_3PAuOTf$ (2 mol%) in CH_2Cl_2 at room temperature (conditions B). Interestingly, the reaction gave both formal [3+3] cycloadduct **3aa** (25% ^{1}H NMR yield) and [4+3] cycloadduct **4aa** (25% ^{1}H NMR yield) under the catalysis of AgOTf after 2 days with 50% conversion. Other Lewis

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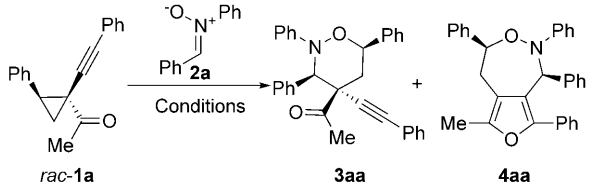
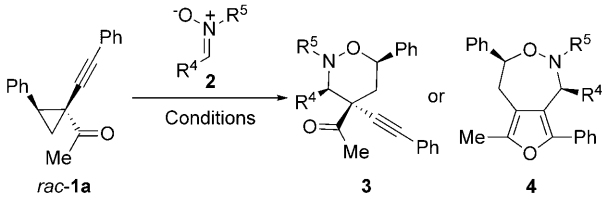
Table 1. Testing the reaction of **1a** and **2a** with various Lewis acid catalysts.[a]



Conditions	3aa		4aa	
	Yield [%]	d.r.	Yield [%]	d.r.
A	90	11.5:1	0	–
B	0	–	96	<20:1
C	25[b]	10:1	25[b]	–

[a] Conditions A: 1,10-phenanthronine (10 mol%), $Sc(OTf)_3$ (10 mol%), MS 4 Å, DCE, 28–32°C, 9.5 h; conditions B: $Ph_3PAuOTf$ (2 mol%), CH_2Cl_2, RT, 10 min; conditions C: AgOTf (10 mol%), MS 4 Å, DCE, 30°C, 2 d. [b] Yield derived from the ^1H NMR spectra.

Table 2. Tuning the regioselectivity of the 1,3-diploar cycloadditions of 1-(1-alkynyl)-cyclopropyl ketone **1a** with nitrones **2**.[a]



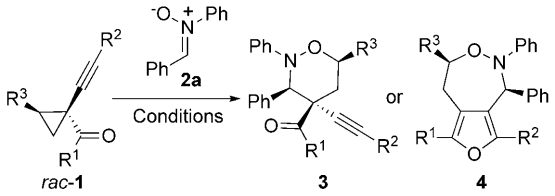
	R^4	R^5	2	Conditions	t [h]		Yield [%][b]	d.r.[c]
1	1-furanyl	Ph	**2b**	A	5.5	**3ab**	85	15.7:1
2			**2b**	B	0.3	**4ab**	93	>20:1
3	4-$NO_2C_6H_4$	Ph	**2c**	A	6.5	**3ac**	68	4.3:1
4			**2c**	B	0.3	**4ac**	85	>20:1
5	4-$MeOC_6H_4$	Ph	**2d**	A	9.5	**3ad**	97	13.3:1
6			**2d**	B	0.3	**4ad**	89	>20:1
7	styryl	Ph	**2e**	A	27	**3ae**	69	4.0:1
8			**2e**	B	0.3	**4ae**	92	>20:1
9	Ph	Bn	**2f**	A	17.5	**3af**	82	2.2:1
10			**2f**	B	6	**4af**	73	>20:1

[a] Conditions A: $Sc(OTf)_3$ (10 mol%), 1,10-phenanthroline monohydrate (10 mol%), 4 Å MS, DCE, 28–32°C; conditions B: $Ph_3PAuOTf$ (2 mol%), DCM, RT; 1.5 equivalents of the nitrone was used under conditions A and 1.1 equivalents of the nitrone was used under conditions B. [b] Isolated yield. [c] Diastereoselectivity was determined by ^1H NMR analysis of the crude product.

acids, such as $Yb(OTf)_3$, $NiClO_4$, and $Sc(OTf)_3$ without ligands were also tested and gave **3aa** in lower yields.

With the optimal reaction conditions in hand, we studied the scope of these Lewis acid catalyzed, regioselectively tunable, cycloaddition reactions (Tables 2 and 3). The gold(I)-catalyzed,[11] formal [4+3] cycloaddition reactions of ketones **1** with nitrones **2**, which form compounds **4**, are very fast and most are completed within 10–20 min, the exceptions being nitrone **2f** (Table 2, entry 10) and ketone **1j** (Table 3, entry 18). On the other hand, the $Sc(OTf)_3$-catalyzed formal [3+3] cycloaddition reactions to form compounds **3** require several hours to consume all of ketone **1**. Although the diastereoselectivity of the $Sc(OTf)_3$-catalyzed transformation is good (d.r. = 2.2–15.7:1, with most >5:1), the gold(I)-catalyzed reaction gives the cycloadducts with excellent diastereoselectivity (>20:1). It is worth noting that under both conditions A and B the cycloadditions are regiospecific, that is, no [4+3] cycloadduct was detected under conditions A and vice versa. Various functional groups, such as cyclohexenyl, cyclopropane, and esters are tolerated, which indicates that the reactions, under both sets of conditions, are highly chemoselective. Substituents on the nitrone (R^4 and R^5) have a greater impact on the diastereoselectivity of the reaction than those on the ketone (R^1, R^2, and R^3) in the $Sc(OTf)_3$-catalyzed case. However, for the substrate in which $R^3 = H$ (**1j**),

Table 3. Tuning the regioselectivity of the 1,3-diploar cycloadditions of 1-(1-alkynyl)-cyclopropyl ketones **1** with nitrone **2a**.[a]



	R^1	R^2	R^3	1	Conditions	t [h]		Yield [%][b]	d.r.[c]
1	Me	cyclopropyl	Ph	**1b**	A	7	**3ba**	73	6.1:1
2				**1b**	B	0.3	**4ba**	99	>20:1
3	Me	n-C_4H_9	Ph	**1c**	A	48	**3ca**	52	6.7:1
4				**1c**	B	0.3	**4ca**	81	>20:1
5	Me	1-cyclohexenyl	Ph	**1d**	A	21	**3da**	73	13.3:1
6				**1d**	B	0.3	**4da**	94	>20:1
7	Me	$AcOC_2H_4$	Ph	**1e**	A	8	**3ea**	65	7.3:1
8				**1e**	B	0.25	**4ea**	71	>20:1
9	Me	1-naphthyl	Ph	**1f**	A	21	**3fa**	84	5.3:1
10				**1f**	B	0.3	**4fa**	73	>20:1
11	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**1g**	A	5	**3ga**	72	9.0:1
12				**1g**	B	0.6	**4ga**	86	>20:1
13	Me	Ph	4-$MeOC_6H_4$	**1h**	A	5.5	**3ha**	93	1.5:1
14				**1h**	B	0.25	**4ha**	85	>20:1
15	Ph	Ph	Ph	**1i**	A	3.5	**3ia**	40	9.0:1
16				**1i**	B	0.3	**4ia**	81	>20:1
17	Et	Ph	H	**1j**	A	24	**3ja**	0	–
18				**1j**	B	1	**4ja**	62	>20:1

[a] Conditions A: $Sc(OTf)_3$ (10 mol%), 1,10-phenanthroline monohydrate (10 mol%), 4 Å MS, DCE, 28–32°C; conditions B: $Ph_3PAuOTf$ (2 mol%), CH_2Cl_2, RT. [b] Isolated yield. [c] Diastereoselectivity was determined by ^1H NMR analysis of the crude product.

the reaction did not occur at all under conditions A, but did give the [4+3] cycloadduct **4ja** in 62% yield under conditions B (Table 2, entries 17 and 18). The structures and relative stereochemistries of **4ga** and the major diastereomer of **3ga** were further confirmed by single-crystal X-ray diffraction analysis (Figure 1).[12]

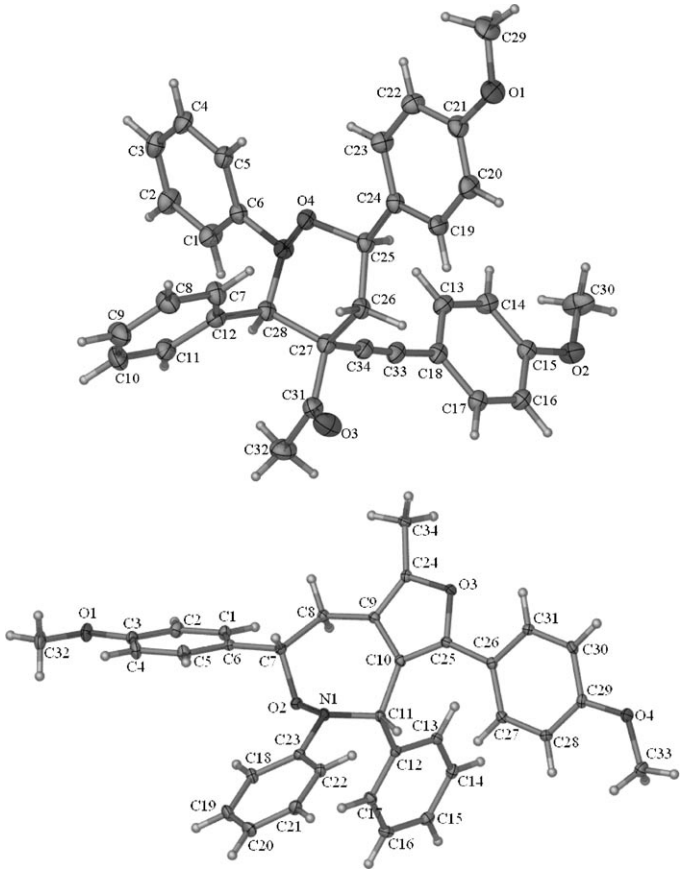
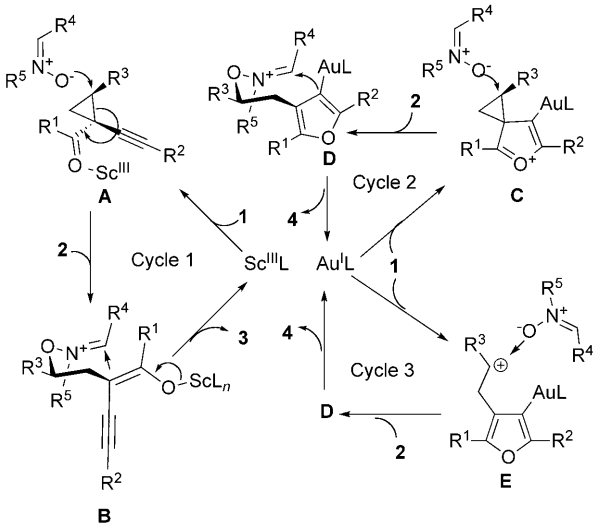


Figure 1. X-ray crystal structures of compounds **3ga** (upper) and **4ga** (lower).

Furthermore, the gold-catalyst loading can be reduced to only 0.2 mol% and the reaction still proceeds smoothly with no reduction in either the yield, or the diastereoselectivity of a 2.5 mmol scale reaction, which makes this method more practical. For example, the formal [4+3] cycloaddition reaction of **1a** (2.5 mmol) with **2a** (2.75 mmol) can be performed in 10 min to give a 94% yield of **4aa**.

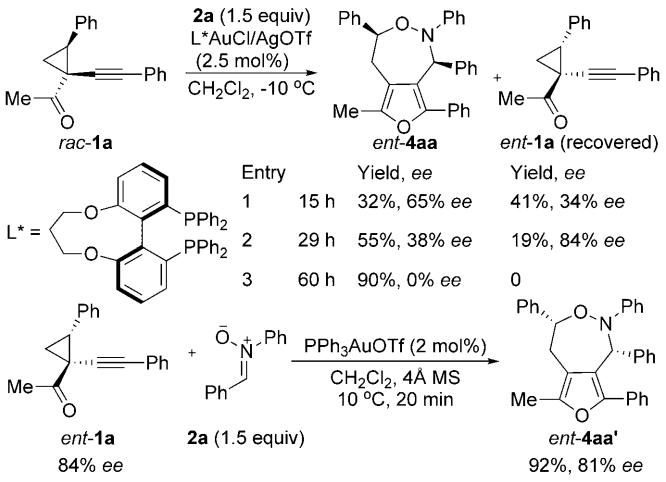
Plausible mechanisms that account for these regioselectively tunable cycloadditions are depicted in Scheme 2. Under conditions A (cycle 1), the $Sc(OTf)_3$/1,10-phenanthroline complex coordinates selectively to the carbonyl group giving intermediate **A**, which makes the cyclopropane reactive enough to regioselectively react with the nitrone and form enolate intermediate **B**.[6] Subsequent ring closure gives the formal [3+3] cycloadduct and regenerates the catalyst. The major diastereomer may be formed from the more favorable chair-like conformation of intermediate **B**. In contrast, the cationic gold(I) species preferentially binds to the



Scheme 2. Plausible mechanisms for this catalytically tunable, regioselective 1,3-dipolar cycloaddition.

alkyne,[14] rather than the carbonyl, and, thus, mediates nucleophilic attack to give oxonium-containing vinyl–gold intermediate **C** (cycle 2). This is followed by the regioselective homo-Michael addition of nitrone **2** at the more substituted position of the cyclopropyl ring,[6,2a,15] which produces furanyl–gold intermediate **D**; in turn, this, upon ring closure, gives the formal [4+3] cycloadduct and regenerates the gold catalyst. The high diastereoselectivity of this reaction may result from the more favorable chair-like conformation of intermediate **D**. An alternative, plausible catalytic cycle (cycle 3) for the formation of the formal [4+3] cycloadduct, could not be ruled out by the results described so far. In this catalytic cycle, a key carbocationic furanyl–gold intermediate **E** would be formed. Subsequent nucleophilic addition of the nitrone to the carbocation would produce intermediate **D**, which, in turn, would give the final product by the same ring closure step as in cycle 2.

In order to gain an insight into the mechanism of the formation of compounds **4**, a control experiment without the addition of the nitrone was performed. This showed that the cycloisomerization of 1-(1-alkynyl)cyclopropyl ketone **1a** into the trisubstituted furan is very slow under conditions B, indicating that the nitrone is involved in the cyclopropyl ring-opening step, which is consistent with Schmalz's work.[2a] Further studies (Scheme 3) on the kinetic resolution[6f] of a racemic mixture of **1a** and the transformation of optically active *ent*-**1a** provided further strong supporting evidence for the proposed cycle (cycle 2, Scheme 2). For example, the reaction of racemic **1a** with nitrone **2a** under the catalysis of the (*R*)-C_3-TunePhos-derived[16] gold complex was quenched, before completion, after 29 h and gave a 55% yield of *ent*-**4aa** in 38% *ee* and 19% of *ent*-**1a**, in 84% *ee*, was recovered. However, if the reaction was allowed to go to completion a racemic mixture of cycloadduct **4aa** was formed. Interestingly, optically active *ent*-**1a** reacted smoothly with nitrone **2a** under the catalysis of



Scheme 3. Kinetic resolution of *rac*-**1a** and transformation of the recovered *ent*-**1a**; L* = (*R*)-C_3-TunePhos.

Ph_3PAuCl/AgOTf to give the optically active *ent*-**4aa′** in high yield with the same level of enantiomeric purity as the starting materials. With these results, the reaction pathway through carbocationic furanyl–gold intermediate **E** (cycle 3) can be ruled out.

In summary, we have developed a Lewis acid catalyzed, regioselective, 1,3-dipolar cycloaddition of nitrones to 1-(1-alkynyl)cyclopropyl ketones, in which the cycloaddition pattern can be tuned by the selection of the catalyst. In the presence of the $Sc(OTf)_3$/1,10-phenanthroline catalyst, the reaction undergoes formal [3+3] cycloaddition to afford highly substituted, multifunctionalized tetrahydro-1,2-oxazines in moderate to excellent yields with up to 15.7:1 diastereomeric ratio, whereas 5,7-fused bicyclic furo[3,4-*d*]-[1,2]oxazepines can be obtained in good to excellent yields with excellent diastereoselectivity from a gold-catalyzed formal [4+3] cycloaddition. Further studies, including kinetic resolution and synthetic applications, are ongoing in our laboratories and will be reported in due course.

Experimental Section

For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

Synthesis of 3aa (conditions A): In a glove box, $Sc(OTf)_3$ (0.025 mmol, 12.3 mg), 1,10-phenanthroline monohydrate (0.025 mmol, 5.0 mg), 4 Å MS (50 mg), and DCE (2 mL) were added to a dry Schlenk tube. After the solution was stirred for 15 min, nitrone **2a** (74.0 mg, 0.375 mmol) and ketone **1a** (0.25 mmol, 65.0 mg) were added. Following stirring for 7 h at 28–32 °C, the reaction was complete, as determined by TLC analysis. Filtration and concentration under reduced pressure provided the residue, which was purified by flash column chromatography on silica gel (hexanes/diethyl ether = 30:1) to afford the pure product **3aa** (103.0 mg, d.r. = 11.5:1) in 90 % yield.

Synthesis of 4aa (conditions B): A solution of $Ph_3PAuOTf$ (1 mL, 0.01 M in CH_2Cl_2, 2 mol %) was added to a solution of ketone **1a** (130 mg, 0.5 mmol) and nitrone **2a** (102.9 mg, 0.55 mmol, 1.1 equivalents) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred for 10 min at room temperature until the reaction was complete, as determined by TLC analysis. After filtration and concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexanes/diethyl ether = 50:1) to afford the pure product **4aa** (219.1 mg, d.r. = > 20:1) in 96 % yield as a white solid.

Acknowledgements

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Keywords: cycloaddition · cyclopropane · Lewis acids · regioselectivity · stereoselectivity

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