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Gold(I)-Catalyzed Regio- and Stereoselective 1,3-Dipolar Cycloaddition Reactions of 1-(1-Alkynyl)cyclopropyl Oximes with Nitrones: A Modular Entry to Highly Substituted Pyrrolo[3,4-*d*][1,2]oxazepines

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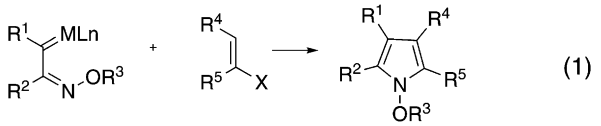
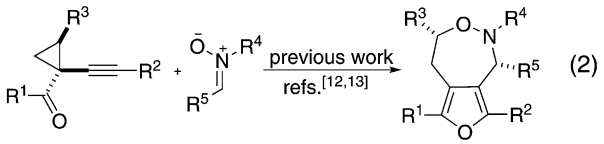
Abstract: An efficient approach for the synthesis of highly substituted pyrrolo[3,4-*d*][1,2]oxazepines has been achieved by gold(I)-catalyzed 1,3-dipolar cycloaddition reactions of 1-(1-alkynyl)cyclopropyl oximes with nitrones in good to excellent yields as a single diastereomer. A complete chirality transfer was observed in this transformation.

Keywords: cycloaddition; diastereoselectivity; enantioselectivity; gold; pyrroles

After pyrrole was discovered in the 1830s and finally isolated in 1857 by T. Anderson, it has attracted continuing interest over the years in natural products,[1] pharmaceuticals,[2] materials science[3] and supramolecular chemistry[4] due to its unique structure and properties . As a consequence, various methods for the synthesis of highly substituted pyrroles have been developed.[5] For example, in the past years, many cyclization reactions[6,7] and multi-component reactions[8] have been well established for the synthesis of pyrroles. Meanwhile, *N*-alkoxypyrroles could be used as insecticides in crop protection,[9] which makes it reasonable to develope new methods for synthesis of *N*-alkoxypyrroles. Recently, Park[10] explored a copper-catalyzed [3+2] cycloaddition of α-diazo oxime ethers with alkenes leading to highly substituted pyrroles in good to excellent yields [Eq.(1)]. However, many of the methods developed so far have several drawbacks, such as narrow substrate scope, low yield, a significant amount of by-products formed or low regioselectivity. Furthermore, the efficient synthesis of synthetically challenging fused heterobicyclic pyrroles is still highly desirable.

Recently, 1-(1-alkynyl)-cyclopropyl ketones have been used in gold-catalyzed tandem reactions to efficiently construct highly substituted furans.[11] Very recently, Wang[12] and our group[13] independently reported copper- or gold-catalyzed highly diastereoselective 1,3-dipolar cycloaddition reactions[14] of 1-(1-alkynyl)-cyclopropyl ketones with nitrones leading to heterobicyclic furo[3,4-*d*][1,2]oxazepines [Eq.(2)]. We envisaged that 1-(1-alkynyl)-cyclopropyl oximes, which could be easily prepared from the corresponding 1-(1-alkynyl)-cyclopropyl ketones, may be used to construct fused heterobicyclic pyrrolo[3,4-*d*]-[1,2]oxazepines through 1,3-dipolar cycloaddition with nitrones under the metal catalysis.

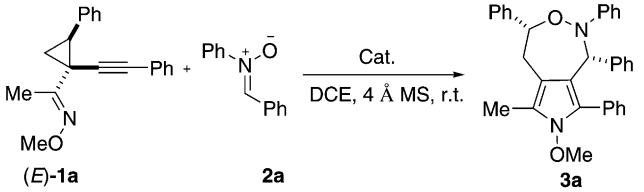


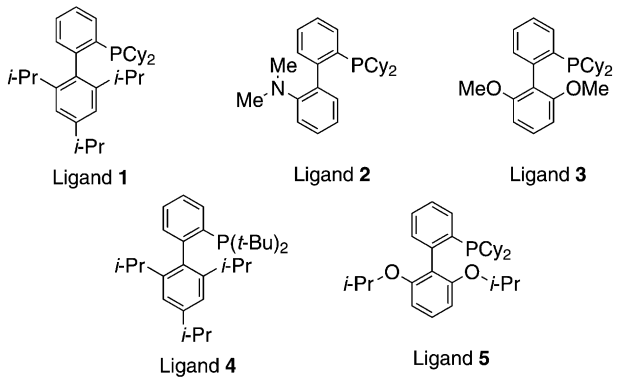


This hypothesis was initially tested by reacting of (*E*)-**1a** with nitrone **2a** in the presence of $Ph_3PAuOTf$[11a] (generated by 1:1 reaction of $Ph_3PAuCl/AgOTf$), affording the desired product **3a** in 99% yield with moderate diastereoselectivity (*dr* = 8:1), which inspired us to explore better conditions to

improve the diastereoselectivities. Changing the silver salts did not bring any obvious improvement (Table 1, entries 1–4). The reaction proceeded very slowly when Ph_3PAuCl was used as catalyst (Table 1, entry 5). AgOTf could catalyze the reaction with a little improvement in the diastereoselectivity, but AgOMs could not catalyze the reaction effectively (Table 1, entries 6 and 7). Next, we turned to investigate the effect of the ligand of the gold catalyst. To our delight, the diastereoselectivity could be effectively improved without loss of the reactivity by the use of a series of monophosphane ligands[15] (Table 1, entries 10, and 12–16). Finally, it was found that the cycloaddition reaction proceeds very smoothly in DCE at room temperature under the catalysis of 2 mol% of $(2\text{-furyl})_3PAuOTf$ (standard conditions) to give cycloadduct **3a** in 99% yield with excellent diastereoselectivity.

Table 1. Optimization studies on cycloaddition of **1a** and **2a**.[a]





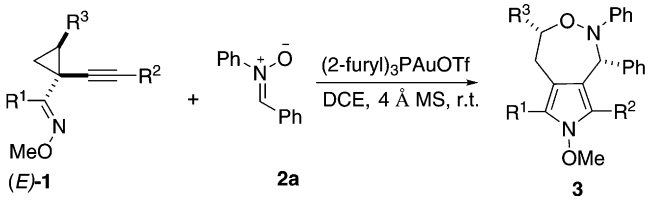
Entry	Cat.	Time [h]	Yield [%]	*dr*[e]
1[b]	$Ph_3PAuCl/AgOTf$	0.3	99	8:1
2[b]	$Ph_3PAuCl/AgSbF_6$	0.3	99	10:1
3[b]	$Ph_3PAuCl/AgNTf_2$	0.3	94	10:1
4[b]	$Ph_3PAuCl/AgOMs$	5	99	29:1
5[b,c]	Ph_3PAuCl	12	9	>50:1
6[b]	AgOTf	0.5	87	9:1
7[b]	AgOMs	21	trace	–
8[b]	IPrAuCl/AgOTf	0.3	82	8:1
9[b]	IPrAuCl/AgOMs	2.5	94	29:1
10	(L1)AuCl/AgOTf	11	94	42:1
11[d]	(L2)AuCl/AgOTf	22.5	8	46:1
12	(L3)AuCl/AgOTf	11	99	>50:1
13	(L4)AuCl/AgOTf	6	99	23:1
14	(L5)AuCl/AgOTf	6	87	>50:1
15	$(PCy_3)AuCl/AgOTf$	11	99	43:1
16	$(2\text{-furyl})_3PAuCl/AgOTf$	3	99	>50:1

[a] All reactions were carried out using **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (2 mol%) in 3 mL of DCE with 60 mg 4 Å MS at room temperature unless otherwise specified.
[b] Without 4 Å MS.
[c] 90% of **1a** was recovered.
[d] 81% of **1a** was recovered.
[e] The *dr* was determined by NMR of the crude products.

Under the optimized conditions, the scope and limitations of this transformation were next explored by variation of the 1-(1-alkynyl)-cyclopropyl *O*-methyloximes (*E*)-**1**. Firstly, the substituent effect of R^2 was studied by introduction of different alkynyl groups (Table 2, entries 1–7), affording the corresponding **3** in high yields with excellent diastereoselectivities, and there is no obvious substituent effect for those substituted alkynes. Moreover, not only (*E*)-**1i** and (*E*)-**1j** with aryl-substituted R^3 but also (*E*)-**1k** with *n*-butyl-substituted R^3 are applicable to these reaction conditions, affording the corresponding cycloadducts **3i–k** in 94–99% yields as single stereoisomer (Table 2, entries 8–10). However, a relatively low yield of **3l** was obtained with $R^3 = H$, indicating that the R^3 substituent has a slight effect on yield (Table 2, entry 11).

Afterwards, we turned our attention to the effect of R^1. Using the same method, *E* and Z-isomers of **1m** were isolated from the reaction of corresponding ketone with methoxyamine. When they were added

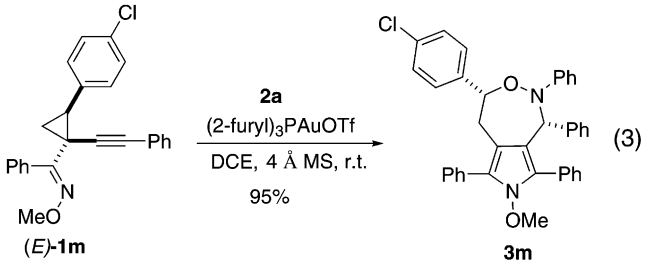
Table 2. The cycloaddition of **1** with **2a**.

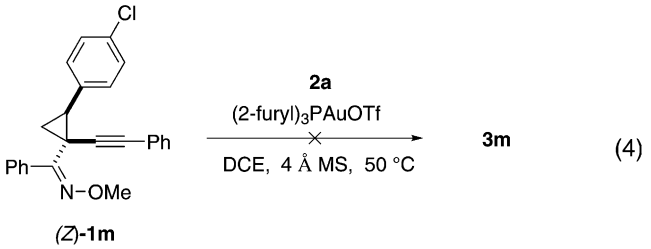


Entry	$R^1/R^2/R^3$ (**1**)	Time [h]	**3**	Yield[a] [%]
1	Me/4-$MeOC_6H_4$/Ph (**1b**)	2.5	**3b**	99
2	Me/4-MeC_6H_4/Ph (**1c**)	15	**3c**	99
3	Me/4-BrC_6H_4/Ph (**1d**)	11	**3d**	92
4	Me/1-cyclohexenyl/Ph (**1e**)	4	**3e**	95
5	Me/cyclopropyl/Ph (**1f**)	4	**3f**	98
6	Me/$AcOC_2H_4$/Ph (**1g**)	10	**3g**	99
7	Me/n-C_4H_9/Ph (**1h**)	15	**3h**	95
8	Me/Ph/4-$MeOC_6H_4$ (**1i**)	10	**3i**	99
9	Me/Ph/4-MeC_6H_4 (**1j**)	4.5	**3j**	99
10	Me/Ph/*n*-C_4H_9 (**1k**)	2.5	**3k**	94
11[b]	Me/Ph/H (**1l**)	22	**3l**	84

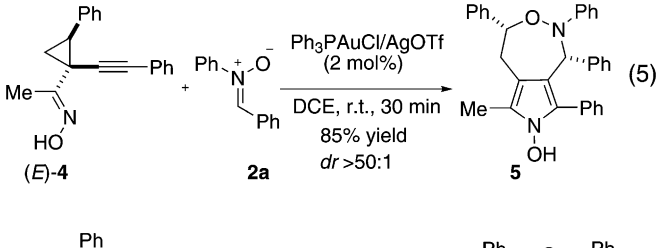
[a] Isolated yield and only one diastereomer was formed, which was detected by NMR.
[b] The reaction was carried out at 50 °C.

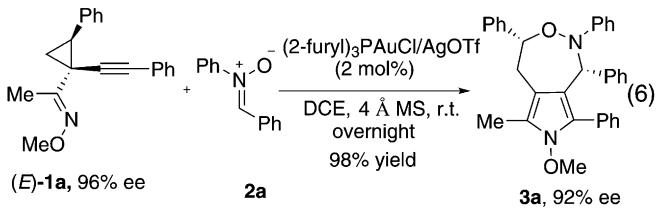
to the reaction system, only the (*E*)-isomer of **1m** could react with nitrone **2a** to give the desired product **3m** in 95% yield [Eq.(3)], the (*Z*)-**1m** remained untouched even when the reaction temperature was raised to 50 °C [Eq.(4)].





Polysubstituted 1*H*-pyrrol-1-ol **5** was afforded from the corresponding unprotected oxime (*E*)-**4** with nitrone **2a** under the catalysis of $Ph_3PAuCl/AgOTf$ in 30 min [Eq.(5)]. Moreover, optically active pyrrolo-[3,4-*d*][1,2] oxazepine (1*R*,4*R*)-**3a** was obtained in the yield of 98% with 92% *ee* from the enantioenriched *E*-(1*R*,2*S*)-**1a** under our standard conditions [Eq.(6)], indicating that chirality transfer takes place in this transformation. Thus, the reaction should proceed *via* an S_N2 reaction pathway.[13b]





The structure and relative stereochemistry of **3** were established by single-crystal X-ray diffraction analysis of **3d** (Figure 1)[16]. The structures and seterochemistry of **1a–1l** were further confirmed by a single-crystal X-ray diffraction analysis of (*E*)-**4**, which reacted with MeI under the basic conditions leading to the same product (*E*)-**1a** as that from the correponding cyclopropyl ketone and $CH_3ONH_2{\cdot}HCl$. The isomer of **1m** which could react with nitrone **2a**, was inferred as (*E*)-**1m**, and the other unreactive isomer was inferred as (*Z*)-**1m**.

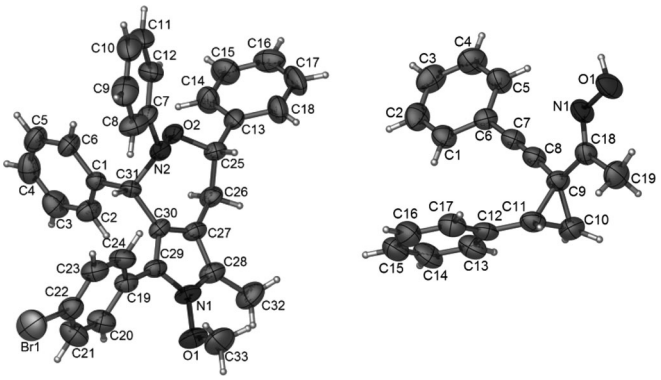
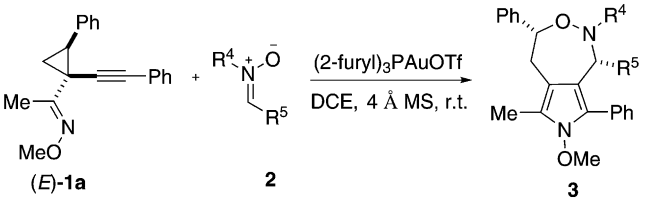


Figure 1. X-ray crystal structures of compounds **3d** (*left*) and (*E*)-**4** (*right*).

After studying the scope of oximes **1**, the substituent effect of nitrones **2** was investigated. Gratifyingly, both electron-deficient and electron-rich aryl substituents R^5 on nitrones **2** were compatible to the present transformation, affording the corresponding cycloadduct **3** in excellent yields as a single diastereomer, except for **3o** and **3p** (Table 3, entries 1–7). In addition, a benzyl group as R^4 on nitrone **2i** was also compatible, yielding **3u** in 99% yield (Table 3, entry 8).

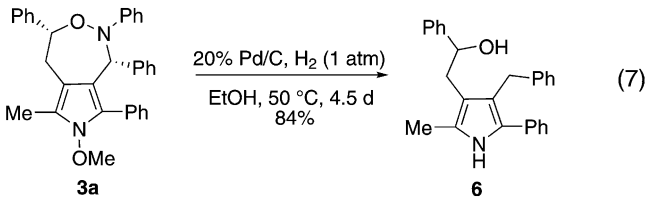
To show the potential synthetic applications of the product, heterobicyclic **3a** was reduced by hydrogenation in EtOH at 50 °C catalyzed by Pd/C under an H_2 atmosphere [Eq (7)], affording pyrrole **6** in 84% yield. In this transformation, it is noteworthy that not

Table 3. The cycloaddition of **1a** with various **2**.



Entry	R^4/R^5	Time [h]	**3** (Yield [%])	*dr*
1	Ph/2-furyl (**2b**)	2.5	**3n** (99)	>50:1
2	Ph/4-$MeOC_6H_4$ (**2c**)	2.5	**3o** (99)	10:1
3	Ph/styryl (**2d**)	7.5	**3p** (99)	16:1
4	Ph/1-naphthyl (**2e**)	3	**3q** (99)	>50:1
5	Ph/4-$NO_2C_6H_4$ (**2f**)	7.5	**3r** (96)	>50:1
6	Ph/4-BrC_6H_4 (**2g**)	3.5	**3s** (98)	>50:1
7	Ph/3-ClC_6H_4 (**2h**)	3.5	**3t** (88)	>50:1
8	Bn/Ph (**2i**)	2.5	**3u** (99)	>50:1

only two N–O bonds but also one C–N bond were reduced.



(7)

In summary, we have developed an efficient synthesis of highly substituted pyrrolo[3,4-*d*][1,2]oxazepines from 1-(1-alkynyl)-cyclopropyl oximes with nitrones by gold-catalyzed 1,3-dipolar cycloaddition reactions under mild reaction conditions This gold(I)-catalyzed cycloaddition is regiospecific and highly diastereoselective. An enantioselective synthesis of chiral pyrrolo[3,4-*d*][1,2]oxazepine could be also achieved from the corresponding optically active substrate and a complete chirality transfer was observed, indicating the reaction procceeds *via* a S_N2 reaction pathway. Further studies including synthetic applications in our laboratories are under way and will be reported later.

Experimental Section

Typical Procedure for the Synthesis of 1-(1-Alkynyl)-cyclopropyl *O*-Methyloxime 3a

A solution of $(2\text{-furyl})_3$PAuOTf (2 mol%) generated from 1:1 mol mixture of $(2\text{-furyl})_3$PAuCl/AgOTf in 3 mL DCE and activated molecular sieves 4 Å (60 mg) were added to a dry Schlenk tube under argon. After stirring for 0.5 h, *O*-methyloxime (*E*)-**1a** (86.7 mg, 0.30 mmol) and nitrone **2a** (70.9 mg, 0.36 mmol) were added to the mixture. After being stirred for another 3 h at room temperature, 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/acetic ether/DCM = 50:1:1) to afford the pure product **3a**; yield: 145.0 mg (0.29 mmol, 99%).

Supporting Information

Experimental details and copies of $^1H/^{13}C$ NMR spectra of all new compounds are available as Supporting Information.

Acknowledgements

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[16] CCDC 875044 (**3d**) and CCDC 8750450 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

6 Gold(I)-Catalyzed Regio- and Stereoselective 1,3-Dipolar Cycloaddition Reactions of 1-(1-Alkynyl)cyclopropyl Oximes with Nitrones: A Modular Entry to Highly Substituted Pyrrolo[3,4-*d*][1,2]oxazepines

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