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Intermolecular Gold-Catalyzed Diastereo- and Enantioselective [2+2+3] Cycloadditions of 1,6-Enynes with Nitrones**

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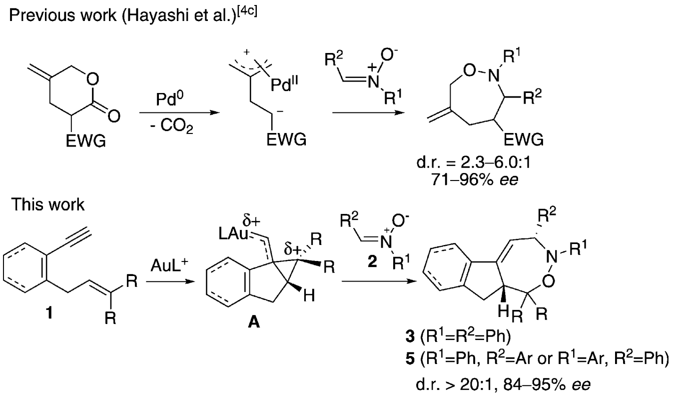
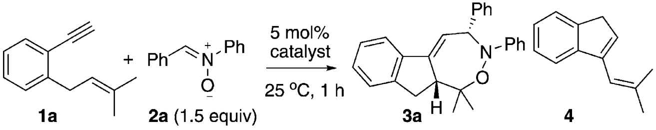
Metal-mediated cycloaddition reactions are a powerful tool for accessing carbo- and heterocyclic frameworks.[1] Nitrones serve as three-atom building units in various [3+2] and [3+3] cycloadditions with suitable dipolarophiles to access five- and six-membered nitrogen heterocycles.[2,3] The utility of such reactions is manifested not only in the easy access to natural products,[2a] but also in the development of many enantioselective cycloadditions. We are aware of few reports of nitrone cycloadditions for the synthesis of seven-membered heterocycles.[4] The reported examples are exclusively focused on [4+3] nitrone cycloadditions,[4–6] as shown by the work of Hayashi and co-workers (Scheme 1).[4c] We report herein the gold-catalyzed cyclization/[2+2+3] cycloaddition cascade[5,6] between nitrones and the readily available 1,6-enynes **1** to give the highly substituted 1,2-oxazepane derivatives **3** and **5** with satisfactory diastereo- and enantioselectivity. The importance of this reaction is reflected by the occurrence of 1,2-oxazepane moieties in several bioactive molecules.[7]



Scheme 1. Cycloaddition reactions for nitrones.

For 1,6-enynes, the interception of the 1,4-dipole equivalent **A** is challenging because of its intrinsic reactivity toward cycloisomerization.[8,9] Echavarren and co-workers attempted to intercept **A** with carbonyl compounds in an intermolecular fashion,[10a,c,11] but those reactions were inevitably accompanied by a significant amount of side products.[10a] Helmchen[10b] studied the same cycloaddition using unsubstituted 1,6-enynes, but carbonyl compounds other than 2-nitrobenzaldehyde were used in large excess (20 equiv). The use of 1,6-enynes as efficient 1,4-dipole equivalents is only feasible in intramolecular system.[10c]

Table 1: Nitrone cycloaddition with various catalysts.



Entry	Catalyst[a]	Solvent	3a[b] Yield [%]	4[b] Yield [%]
1	$AgSbF_6$	DCE	–	46
2	$AgNTf_2$	DCE	–	43
3	$[PPh_3AuCl]/AgSbF_6$	DCE	39	15
4	$[PPh_3AuCl]/AgNTf_2$	DCE	35	20
5	$[LAuCl]/AgSbF_6$	DCE	95	–
6	$[LAuCl]/AgNTf_2$	DCE	86	–
7	$[IPrAuCl]/AgSbF_6$	DCE	75	15
8	$[IPrAuCl]/AgNTf_2$	DCE	72	18
9	$[LAuCl]/AgSbF_6$	DCM	87	–
10	$[LAuCl]/AgSbF_6$	1,4-dioxane	82	–
11	$[LAuCl]/AgSbF_6$	toluene	71	–

[a] L = P(*t*Bu)$_2$(*o*-biphenyl), [substrate] = 0.19 M. [b] Product yields are reported for compounds isolated after purification on silica gel. DCE = 1,2-dichloroethane, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl.

We sought to realize the reaction using the 1,6-enyne **1a** (Table 1). The primary task was to reduce the production of 3-isobutenyl-1*H*-indene (**4**), which results from a competitive cycloisomerization.[12] In a standard operation, the nitrone **2a** (ca. 0.38 M) was first stirred with the catalyst (5 mol %) in DCE (25 °C) for five minutes, and then **1a** in DCE (equal volume) was slowly added to this solution, using a syringe pump, over a 1 hour period.[13] The conversion was complete at the end of the addition. As shown in entries 1 and 2, we obtained only **4** in 46 and 43 % yield using $AgSbF_6$ and $AgNTf_2$, respectively. Cationic gold complexes, $[PPh_3AuCl]$/AgX (X = SbF_6, NTf_2), gave the nitrone cycloadduct **3a** as a single diastereomer in moderate yield (35–39 %) together with **4** in 15–20 % yield (entries 3 and 4). Pleasingly, the use of [P(*o*-biphenyl)(*t*Bu)$_2$AuCl]/AgX (X = SbF_6, NTf_2) gave the desired **3a** in 95 and 86 % yield (entries 5 and 6). [IPrAuCl]/AgX (X = SbF_6, NTf_2) gave **3a** in 75–72 % yield in addition to a small amount of **4** (15–18 %; entries 7 and 8). For

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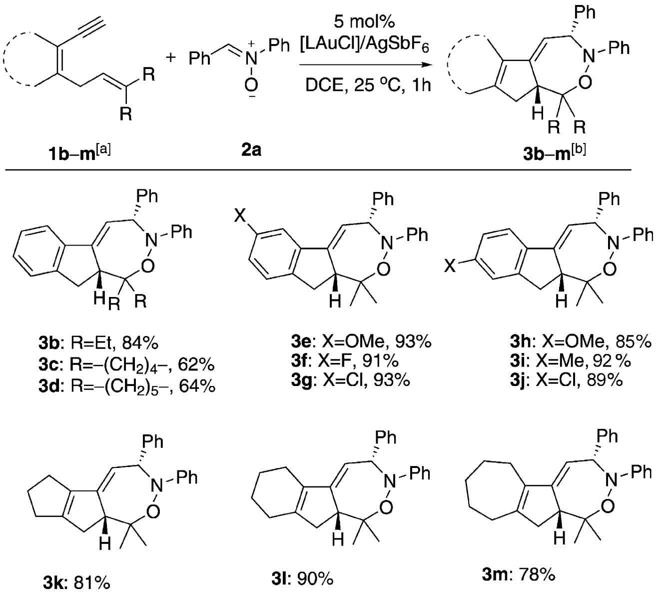
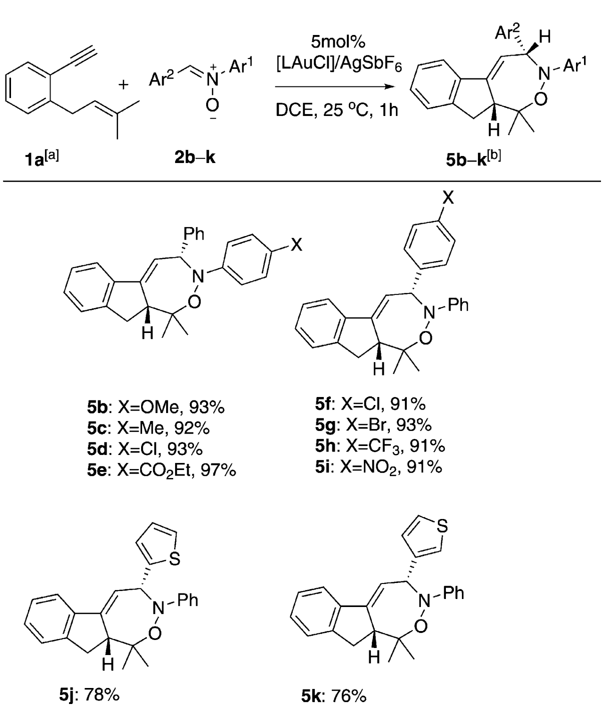
[(*o*-biphenyl)P(*t*Bu)$_2$AuSbF$_6$], the yields of **3a** depended on solvents: CH$_2$Cl$_2$ (87%), 1,4-dioxane (82%), and toluene (71%). Structural characterization of **3a** relied on an X-ray diffraction study[14] (see the Supporting Information).

We examined the reactions of **2a** with various 1,6-enynes (**1b–m**) to assess the substrate scope, including benzenoid and nonbenzenoid bridges (Scheme 2). The cycloaddition reactions were performed in DCE (25°C) using [P(*o*-biphenyl)(*t*Bu)$_2$AuCl]/AgSbF$_6$ (5 mol%). This cycloaddition is applicable to substrates bearing various alkenes, such as 3-pentylidene, cyclopentylidene, and cyclohexylidene, thus giving the desired cycloadducts **3b–d** in 62–84% yield. For the benzenoid substrates **1e–g** bearing a C4 substituent (X = OMe, F, Cl), the reactions proceeded smoothly to give the desired compounds **3e–g** with yields exceeding 91%. Excellent yields (85–92%) were obtained also for products **3h–j** bearing various C5 substituents (X = OMe, Me, Cl). The scope of this cycloaddition is substantially expanded with its applicability to nonbenzenoid substrates containing a cyclopentenyl, cyclohexenyl, and cycloheptenyl bridge, thus giving the corresponding products **3k–m** in 78–90% yield.



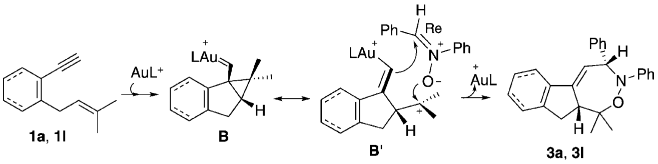
Scheme 2. [2+2+3] Nitrone cycloadditions on various 1,6-enynes. [a] [substrate] = 0.19 M. [b] All product yields are reported for compounds isolated after purification on silica gel. L = P(*t*Bu)$_2$(*o*-biphenyl), DCE = 1,2-dichloroethane.

Scheme 3 shows the applicability of the cycloaddition of the 1,6-enyne **1a** with various nitrones (**2b–k**). We obtained only the desired cycloadducts **5b–k** as single diastereomers with yields exceeding 76%. We tested the cycloadditions on nitrones **2b–e**, bearing both electron-deficient and electron-rich aniline moieties (Ar^1 = 4-XC$_6$H$_4$; X = OMe, Me, Cl, CO$_2$Et), and the corresponding cycloadducts **5b–e** were obtained in excellent yields (92–97%). These cycloadditions can also be extended to the nitrones **2f–i** bearing electron-deficient imines (Ar^2 = 4-XC$_6$H$_4$; X = Cl, Br, CF$_3$, NO$_2$), thus giving the corresponding cycloadducts **5f–i** with yields of greater than 91%. For the nitrones **2j** and **2k** bearing a 2- and 3-thienyl group, respectively, the corresponding cycloadducts **5j** and **5k** were obtained in 76–78% yield.



Scheme 3. Cycloadditions of enyne **1a** with various nitrones. [a] [substrate] = 0.19 M. [b] All product yields are reported for compounds isolated after purification on silica gel. L = P(*t*Bu)$_2$(*o*-biphenyl).

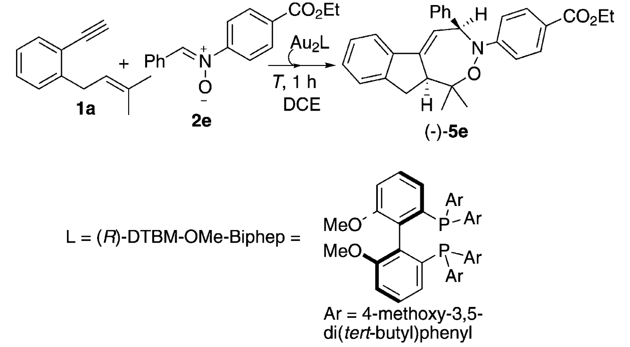
Scheme 4 shows a plausible mechanism to rationalize the stereochemistry of the resulting cycloadducts **3a** and **3l** using the 1,6-enynes **1a** and **1l**, respectively, and nitrone **2a**. The substrates **1a** and **1l** are less flexible in conformation and facilitate the initial cyclization. In the presence of a gold catalyst, we postulate that an initially formed cyclopropylgold carbenoid[4–5] has a strong alkenylgold carbocation character (**B′**),[15] which is attacked by nitrone **2a** in a concerted pathway, thus giving either the cycloadduct **3a** or **3l** with excellent diastereoselectivity.



Scheme 4. A proposed mechanism for the diastereoselective [2+2+3] cycloaddition.

Our results for the enantioselective cycloaddition of the 1,6-enyne **1a** with nitrone **2e** are shown in Table 2. Among the commonly used C2-bisphosphine ligands, (*R*)-DTBM-MeO-Biphep gave the best performance for enantioselectivity (see the Supporting Information). The use of [LAu$_2$Cl$_2$]/2AgSbF$_6$ (L = (*R*)-DTBM-MeO-Biphep, 5 mol%) gave the desired compound (−)-**5e** in 71% yield with 70% *ee*

Table 2: Enantioselective cycloaddition with nitrone.



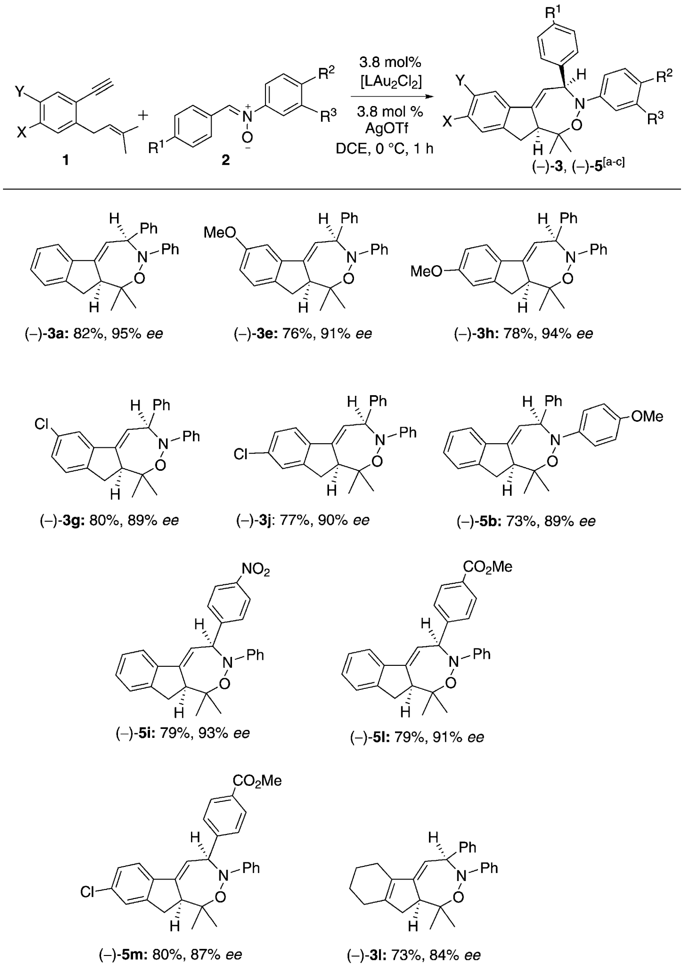
Entry	Catalyst (mol %)[a,b]	T [°C]	**9e** Yield [%]	*ee* [%][c]
1	[LAu$_2$Cl$_2$] (5)/AgSbF$_6$ (10)	25	71	(−)-70
2	[LAu$_2$Cl$_2$](5)/AgOTf (10)	25	73	(−)-75
3	[LAu$_2$Cl$_2$] (5)/AgOTf (10)	0	71	(−)-76
4	[LAu$_2$Cl$_2$] (5)/AgOTf (5)	0	76	(−)-84
5	[LAu$_2$Cl$_2$] (3.8)/AgOTf (3.8)	0	74	(−)-92

[a] [substrate] = 0.19 M. [b] All product yields are reported for compounds isolated after purification on silica gel. [c] The *ee* values were determined by HPLC using a Chiralpak OD-H column.

(entry 1). [LAu$_2$Cl$_2$]/2 AgOTf at a 5 mol% loading improved the enantioselectivity of compound (−)-**5e** to 75% *ee* (entry 2). The reaction in a cold DCE solution (0 °C) had little influence on its *ee* value (entry 3). However, a change of the Ag/Au ratio to 1:1 for [LAu$_2$Cl$_2$]/AgOTf increased the *ee* value to 84% at 0 °C; here, one Au−Cl bond in gold catalyst remains intact (entry 4). We managed eventually to obtain (−)-**5e** with 92% *ee* and 74% yield at a low loading catalyst loading (Au/Ag = 1:1, 3.8 mol%, entry 5). We assigned the absolute configuration of (−)-**5e** according to an X-ray diffraction study on its analogue (−)-**5m** (see the Supporting Information).

With [LAu$_2$Cl$_2$]/AgOTf (3.8 mol%, L = (R)-DTBM-MeO-Biphep), we conducted enantioselective cycloadditions on additional 1,6-enynes and nitrones (Scheme 5). The initial results show the enantioselectivity of the prototype product (−)-**3a** for which the *ee* value was up to 95%. We tested this chiral gold catalyst on the benzenoid substrates **1e, 1g, 1h**, and **1j**, and their corresponding products (−)-**3e**, (−)-**3g**, (−)-**3h**, and (−)-**3j** were obtained with high *ee* values (89–94%). We studied the reaction of nitrones bearing an electron-rich aniline moiety and the resulting product (−)-**5b** was obtained in 73% yield and 89% *ee*. The same reactions on several nitrones bearing an electron-deficient imine produced the cycloadducts (−)-**5i**, (−)-**5l**, and (−)-**5m** with satisfactory *ee* values (87–93%). For the nonbenzenoid substrate **1l**, the resulting cycloadduct (−)-**3l** was obtained in 84% *ee*. X-xay diffraction of compound (−)-**5m** was performed to clarify its absolute configuration.

Before this work, there was no report on the [2+2+3] cycloadditions of nitrones. The use of a 1,6-enyne as a 1,4-dipole equivalent remains a challenging task. We have developed a new diastereoselective cyclization/[2+2+3] cycloaddition cascade between 1,6-enynes and nitrones. The reactions are applicable not only to a broad range of nitrones, but also 1,6-enynes of benzenoid and nonbenzenoid systems. We also report the success on the enantioselective synthesis of cycloadducts using [LAu$_2$Cl$_2$]/AgOTf (L = (R)-DTBM-MeO-Biphep). Most nitrone cycloadducts were obtained with high enantiopurity.



Scheme 5. Gold-catalyzed enantioselective cycloadditions. [a] [substrate] = 0.19 M. [b] All product yields are reported for compounds isolated after purification on silica gel. [c] The *ee* values were determined by HPLC using a Chiralpak OD-H or AD-H column. L = (R)-DTBM-OMe-Biphep.

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[13] This addition method is crucial for the desired [4+3] cycloaddition. We obtained the cycloisomerization product **4** predominantly (ca. 85%) when a mixture of **1a** and **2a** was stirred together with $[\mathrm{P}(o\text{-biphenyl})(t\mathrm{Bu})_2\mathrm{AuCl}]/\mathrm{AgSbF}_6$ in 1,2-dichloroethane.

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Communications

Synthetic Methods

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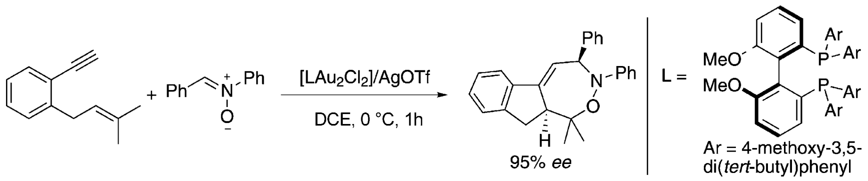
R.-S. Liu* ______________ ■■■■–■■■■

Intermolecular Gold-Catalyzed Diastereo- and Enantioselective [2+2+3] Cycloadditions of 1,6-Enynes with Nitrones



Going for gold: The title reaction has been developed and demonstrates a wide substrate scope with respect to the 1,6-enynes and nitrones (see scheme; DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl). The results for the enantioselective versions are also presented.