Gold Catalysis

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Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade**

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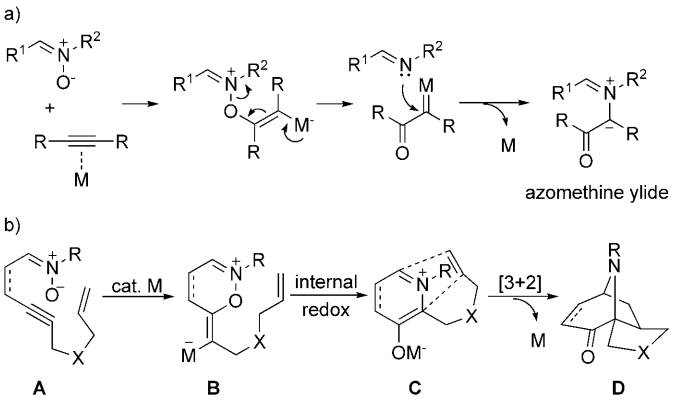
Dedicated to Professor Junghun Suh on the occasion of his 60th birthday

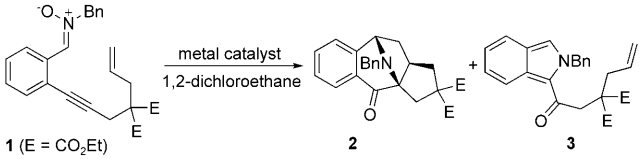
1,3-Dipolar cycloaddition of ylidic species, such as azomethine ylides with π bonds, is a powerful method for the construction of complex N heterocycles.[1] Its utility has been proven in numerous natural product syntheses, providing expedient routes to complex polycyclic skeletons.[2] Among various approaches for the generation of azomethine ylide, metal-catalyzed decomposition of α-diazo carbonyl compounds,[3] and subsequent carbene addition and cycloaddition has been one of the most popular and effective approaches.[4] However, diazo derivatives (or their precursors) can be explosive, which limits their use in large-scale applications. In addition, their syntheses from carbonyl compounds involve stoichiometric amounts of a base and the generation of waste from the diazo-transfer agents. To solve this problem, we envisioned using a nitrone as an oxidant for the alkyne under electrophilic metal catalysis; that is, addition of the nitrone to a metal-activated alkyne with subsequent N–O cleavage by back bonding would lead to an α-carbonyl carbenoid by an internal redox (IR) reaction.[5,6] Addition of an imine would then generate an azomethine ylide equivalent in both a safe and atom-economical fashion (Scheme 1a).[7,8] Furthermore, the inter-/intramolecular dipolar cycloaddition (DC) cascade with a catalyst turnover would provide an expedient route to azabicyclo[3.2.1]octane systems (Scheme 1b) from a simple precursor.

To probe such reactivity, nitrone **1** was easily prepared from the condensation of *ortho*-1,6-enynyl benzaldehyde and *N*-benzyl hydroxyamine, and then treated with electrophilic metal salts (Table 1). When **1** was treated with 5 mol% of $PtCl_2$ in 1,2-dichloroethane (DCE) at 100°C, the expected azabicyclo[3.2.1]octane **2** was indeed obtained and isolated in a 73% yield as a single diastereomer (Table 1, entry 1).[9] Its tetracyclic structure was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[10] Among the metals we tested, various Pt^{II}, Ag^{I}, and Au^{III} salts were found to be effective for the IR-DC cascade reaction (Table 1, entries 1–4 and 8), whereas cationic Au^{I} complexes gave inferior results (Table 1, entries 5 and 6).[11] When bulky [tBu$_2$(o-biphenyl)-Au]OTf was used, a side product, whose NMR spectra are consistent with isoindole **3**, was isolated in 66% yield (Table 1, entry 7; also see Eq. (2) and Scheme 2).[13] Among the catalysts surveyed, $AuCl_3$ (5 mol%) gave the best results,



Scheme 1. a) Generation of an azomethine ylide by a metal-catalyzed internal redox reaction. b) Internal redox/dipolar cycloaddition (IR-DC) cascade.

Table 1: Catalyst screening by using **1** as the substrate.



Entry[a]	Cat. (mol%)	t [h]	T [°C]	Yield **2** [%][b]	Yield **3** [%]
1	$PtCl_2$ (5)	1	100	73[c]	13
2	$PtBr_2$ (5)	1	100	70	13
3	$AuCl_3$ (5)	2	RT	81	<5
4	$AuCl_3$ (1)	1	70	61[c,g]	0
5	[Au(IMes)]SbF_6 (5)	20	100	44	6
6	[Au(PPh_3)]OTf (5)	12	70	n.r.[d]	–
7	[Au(L)]OTf (5)[e]	4	50	trace	66[c]
8	$AgSbF_6$ (5)	1	70	45	0[f]
9	$AuCl_3$ (2)	1	70	88(82[c,g])	0

[a] [**1**] = 0.1 M in 1,2-dichloroethane. [b] Yield based on NMR spectra of the crude reaction mixture unless otherwise noted. [c] Yield of isolated product. [d] No reaction. [e] L = tBu$_2$P(2-biphenyl). [f] 43% **1** remained. [g] In CH_3NO_2. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene.

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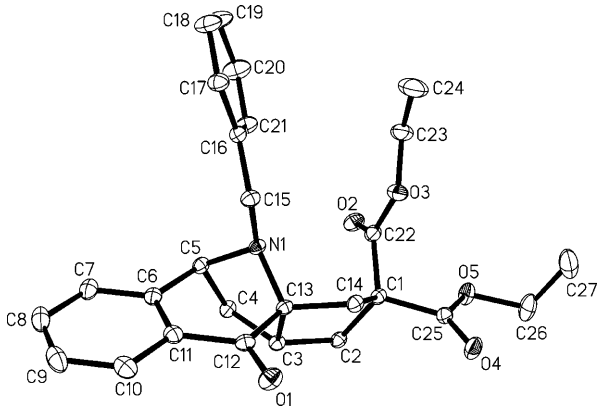
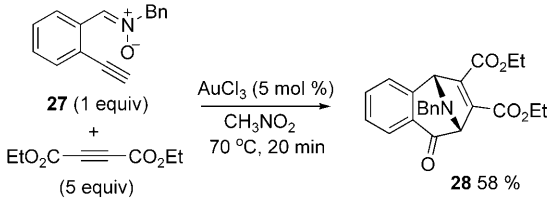


Figure 1. Molecular structure of compound **2** (ORTEP view). Selected bond lengths [Å] and angles [°]: O1–C12 1.2187(15), N1–C5 1.4726(15), N1–C13 1.4771(14); N1-C5-C6 111.14(10), N1-C5-C4 99.97(9), C6-C5-C4 112.52(10).

providing **2** (81%) in 2 hours at room temperature (Table 1, entry 3). Significant catalytic activity was observed even when the catalyst loading was lowered to 1 mol%, although higher temperature was required (Table 1, entry 4). Additional screening of the solvent led to $AuCl_3$ (2 mol%) in CH_3NO_2 (70°C) as our optimized conditions (Table 1, entry 9), and then we examined the generality of this reaction.[11]

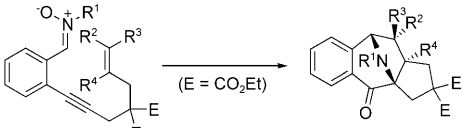
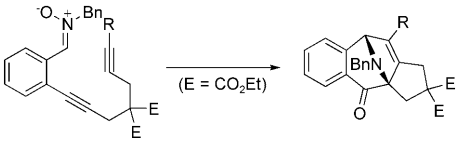
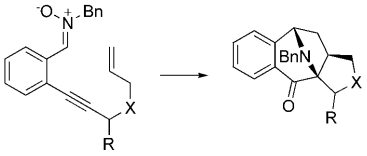
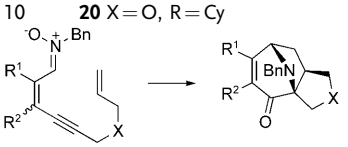
Various substituents on the enyne skeleton were well-tolerated, efficiently providing the desired azabicyclo-[3.2.1]octanes (Table 2). For example, variously substituted olefins (Table 2, entries 1–4), as well as enoates (Table 2, entry 5) on the alkene were suitable. *N*-methyl nitrone **12**, 1,6-diynyl **14** and **16**, as well as substrates having an NTs (Ts = *p*-toluenesulfonyl) or $C(CH_2OBn)_2$ tether (e.g. **18** and **21**) gave satisfactory yields of the desired azabicycles (Table 2, entries 6–11). However, the allyl propargyl ether **20** was not a suitable substrate under the reaction conditions. Importantly, the skeletal variation allows departure from the *o*-alkynyl benzaldehyde motif; substrates **21**, **23**, and **25**, having an alkene tether between the nitrone and the enyne, also underwent an efficient IR-DC cascade with reasonable yields (Table 2, entries 11–13). Notably, for the reaction of **21** (*E*/*Z*=1:1 mixture), only the *Z* isomer participated in the reaction (Table 2, entry 11).

We then attempted to extend this chemistry to an intermolecular dipolar cycloaddition. To our delight, when alkyne/nitrone **27** was reacted with 5 equivalents of diethyl acetylenedicarboxylate (DEAD) in the presence of $AuCl_3$, dipolar cycloaddition of the azomethine ylide gave product **28** in 58% yield; notably, none of the competing nitrone cycloaddition product was observed [Eq. (1)]. Intriguingly, in the absence of DEAD, substrate **27** did not react at all to



(1)

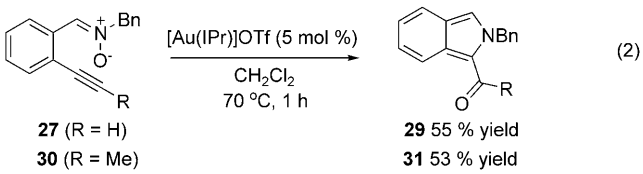
Table 2: Scope of IR-DC cascade reaction.

Entry[a]	Substrate[b]	Conditions	Product, yield [%][c]
			
1	**1** R^1 = Bn, R^2, R^3, R^4 = H	70°C, 1 h	**2**, 82
2	**4** R^1 = Bn, R^2, R^3 = H, R^4 = Me	70°C, 1.5 h	**5**, 59
3	**6** R^1 = Bn, R^2/R^3 = Me/H and H/Me (*E*/*Z*=3:1), R^4 = H	70°C, 0.5 h	**7**, 80[d]
4	**8** R^1 = Bn, R^2, R^3 = Me, R^4 = H	70°C, 0.5 h[e]	**9**, 67
5	**10** R^1 = Bn, R^2 = CO_2Me, R^3, R^4 = H	70°C, 0.5 h	**11**, 83
6	**12** R^1 = Me, R^2, R^3, R^4 = H	70°C, 2.5 h	**13**, 75
			
7	**14** R = Me	70°C, 1 h[e]	**15**, 76
8	**16** R = Ph	70°C, 0.5 h[e]	**17**, 77
			
9	**18** X = NTs, R = H	70°C, 1 h	**19**, 85
10	**20** X = O, R = Cy	70°C, 1 h	dec.[f]
			
11	**21** R^1,R^2 = H (*E*/*Z*=1:1), X = $C(CH_2OBn)_2$	70°C, 2 h	**22**, 89[g]
12	**23** R^1 = H, R^2 = *n*Bu, X = $C(CO_2Et)_2$ (*Z* isomer)	70°C, 0.5 h	**24**, 55
13	**25** R^1, R_2 = $(CH_2)_4$, X = $C(CO_2Et)_2$	70°C, 1 h	**26**, 58

[a] 2 mol% of $AuCl_3$ unless otherwise noted. [b] [Substrate] = 0.1 M in CH_3NO_2. [c] Yield of products isolated after chromatography; all products were obtained as single respective diastereomers, except entry 3. [d] Product **7** in 3:1 d.r. in favor of the structure shown. [e] 4 mol% of $AuCl_3$ was used. [f] Decomposed. [g] Based on the recovered starting *E* isomer (47%). Cy = cyclohexyl.

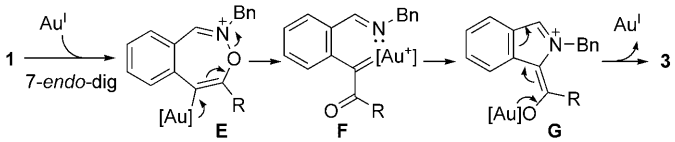
afford a free azomethine ylide under $AuCl_3$ catalysis; it remained intact under otherwise identical conditions.[12] However, treating **27** with [Au(IPr)]OTf (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; 5 mol%) in CH_2Cl_2 in the absence of DEAD, led instead to the isolation of isoindole/aldehyde **29** in 55% yield [Eq. (2)]. Under similar conditions **30** was transformed into known compound **31**, confirming our assignment of the isoindole structure.[13]

The generality and efficiency of the above IR-DC cascade reaction strongly supports the intermediacy of an azomethine ylide (**C**, Scheme 1b). The formation of isoindole **3** (as well as



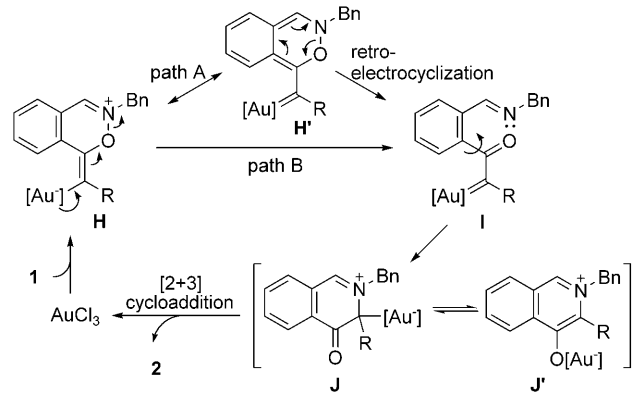
(2)

29 and **31**) could also be rationalized as a result of an internal redox sequence shown in Scheme 2. In this case, the initial 7-*endo*-dig attack of the O atom of the nitrone on the alkyne and subsequent N–O cleavage will lead to α-oxo Au-carbenoid **F**. Subsequent addition of the imine to this carbenoid leads to **G**, from which the catalyst is regenerated to provide **3**.



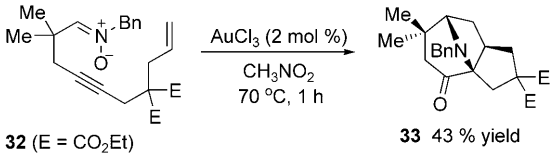
Scheme 2. Proposed mechanism for the formation of isoindole **3**.

Interestingly, the use of a bulky and relatively electron-rich Au^{I} catalyst produced **3** selectively (Table 1, entry 7 and Eq. (2)), for reasons that are not clear at this stage. On the other hand, an Au^{III} complex completely diverts the reaction



Scheme 3. Proposed mechanism for the IR-DC cascade reaction.

pathway to 6-*exo*-dig process as delineated in Scheme 3. Detailed mechanistic analysis of the N–O bond cleavage (**H**/**H′**→**I**) in this redox cascade led to the identification of two plausible pathways: 1) The 6-*exo*-dig attack of the nitrone on the Au-activated alkyne would generate **H**, which has a possible resonance structure depicted as **H′**. A retro-electrocyclization would then lead to α-carbonyl Au-carbenoid **I** (path A) and subsequent carbene addition to **J** (or its O-bound tautomer **J′**). 2) Alternatively, the same species (**I**) could be generated without undergoing dearomatization (path B). To differentiate between these possibilities, substrate **32** having a saturated bridge between the enyne and the nitrone was prepared and treated with $AuCl_3$ [Eq. (3)]. In this case, desired **33** was isolated in 43% yield, proving that the conjugation between the nitrone and the alkyne is not



(3)

required for the internal redox; this led us to favor path B as a possible IR mechanism for the formation of azomethine ylide **J**/**J′**.[14]

Additionally, we reasoned that the subsequent dipolar cycloaddition probably occurs at the stage of the Au-bound **J**/**J′** based on some observations: failure of **27** to undergo a redox reaction in the absence of DEAD under $AuCl_3$ catalysis to form a free stabilized azomethine ylide suggests that the catalyst turnover occurs only after the cycloaddition of Au-bound azomethine ylide **J**/**J′**. In addition, the current dipolar cycloaddition occurs at lower temperatures relative to those of related azomethine ylides (even at RT, Table 1, entry 3),[2] presumably because of the favorably modulated frontier molecular orbital (FMO) of the dipole for a facile cycloaddition.

In summary, we have described herein a novel gold-catalyzed generation of an azomethine ylide, featuring an internal redox reaction between a tethered nitrone and an alkyne under electrophilic metal catalysis. The azomethine ylide that is formed undergoes an efficient cycloaddition cascade in a highly diastereoselective manner. The benefit of atom economy (100%) as well as environmental safety is apparent from this approach. Efforts are currently directed toward an asymmetric version of this IR-DC cascade.

Experimental Section

Representative procedure for an IR-DC cascade reaction: $AuCl_3$ (0.5 mg, 0.0018 mmol, 2 mol%; for a lower catalyst loading, 0.02 M stock solutions in respective solvents were used) was added to a solution of alkyne/nitrone **1** (40 mg, 0.089 mmol) in nitromethane (0.8 mL). The resulting mixture was heated to 70 °C for an hour. (At this point the mixture turned blue-green and the TLC indicated complete conversion. However, there was no appreciable amount of precipitate or metallic gold.) The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/hexanes = 1:2) to afford 32.8 mg (82%) of **2** as pale yellow crystals.

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[10] See the Supporting Information (SI) for details. CCDC 680836 (**2**) contains 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.

[11] See Table S1 in the Supporting Information for full details of catalyst screening.

[12] As suggested by the reviewers, the reaction was also run with 1.0 equiv of $AuCl_3$ in an attempt to detect the azomethine ylide intermediate. In this case, however, immediate decomposition of the starting material (< 1 min at RT as observed by TLC) and very messy NMR spectra resulted. Addition of dipolarophile (DEAD) to this mixture did not produce any observable amount of **28**.

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