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Gold-Catalyzed Bicyclic and [3+2]-Annulations of Internal Propargyl Alcohols with Nitrones and Imines To Yield to Two Distinct Heterocycles

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Abstract. A gold-catalyzed synthesis of 1,3-dihydrooxazolo[3,4-*a*]indoles from 1-oxo-3-yn-4-ols and nitrones is described; this new bicyclic annulation presents the first examples that internal alkynes can react with nitrones to undergo an oxoarylation route. DFT calculations indicate a [3,3]-sigmatropic shift of initial alkenylgold intermediates to elude the intermediacy of gold carbenes. We also developed new [3+2]-annulations of the same 1-oxo-3-yn-4-ols with imines, yielding oxazolidin-4-ylidene derivatives efficiently. The tethered alcohols of these 1-oxo-3-ynes allow trapping of their metastable 2-azadienium intermediates to enable a novel annulation. Our mechanistic analysis indicates that the two products, despite their structural relevance, are produced from two independent systems.

Keywords: Oxo-yne; Nitrones; Imines; Oxoarylation; Indoles; Oxazolidines

Introduction

Gold catalysis has emerged as a powerful tool to access useful heterocyclic compounds through the N,O-functionalization of alkynes with nitrones, nitrosoarenes and other nitroxy (N-O) compounds.[1] Molecules containing nitroxy functionalities have widespread occurrence in many bioactive molecules and alkaloids.[2] In the context of nitrone oxidants, their catalytic reactions with alkynes using Au(I) and Pt(II) catalysts generally follow two routes, involving either (i) formation of gold carbenes[3] or (ii) 3,3-sigmatropic shifts of initial alkenylgold intermediates.[4] Route (ii) is also known for those alkyne oxidations using sulfur oxides as the oxidants.[5] Eqs. 1-2 show two prominent systems for oxoarylation reactions using Pt(II) and Au(I) catalysts respectively; herein, initial alkenylmetal intermediates **In-1** and **In-2** undergo a 3,3-sigmatropic rearrangement to avoid Pt(II) and Au(I) carbene intermediates.[4] This [3,3]-rearrangement mechanism is confirmed with our DFT calculations.[4c] Such a 3,3-sigmatropic shift occurs exclusively with terminal alkynes, so as to minimize steric interactions in the phenyl attack at the Au-CH= carbon, as shown by species **In-1** and **In-2**. In alkyne oxidations with nitrones, we are aware of no internal alkyne that can undergo a 3,3-sigmatropic shift to afford oxoarylation products.

This work reports new gold-catalyzed annulations[6] of 4-hydroxy-1-oxo-but-2-ynes with nitrones to deliver 1,3-dihydrooxazolo[3,4-*a*]indoles (Eq 3), and hence provides the first examples that internal alkynes can afford oxoarylation products via a 3,3-sigmatropic rearrangement. Our DFT calculations support this hypothesis although steric interactions are involved. Apart from nitrones, we demonstrate new annulations of the same 4-hydroxy-1-oxo-but-2-ynes with imines to afford [3+2]-annulation products **5** (Eq 4). Although compounds **3** and **5** are related to each other structurally, our

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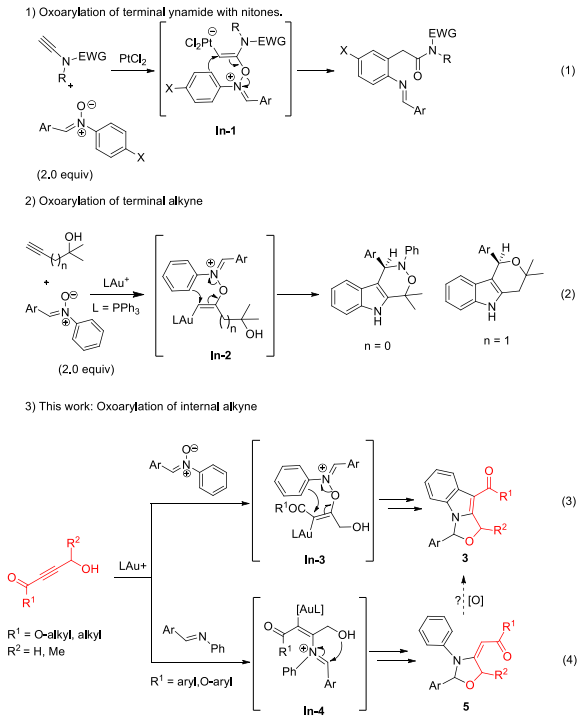
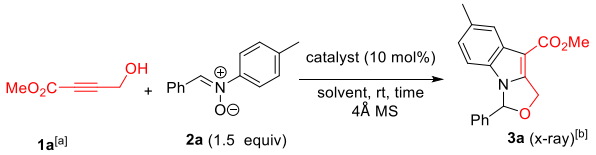


control experiments reveal two independent pathways for their formation.

Results and Discussion

As Table 1 shows, we examined the reactions of methyl 4-hydroxy-1-oxo-but-2-ynoate **1a** with nitrones **2a** (1.5 equiv) using various gold catalysts; such reactions were performed in DCM with 10 mol% catalyst loading. In the case of P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$, 7-methyl-3-phenyl-1,3-dihydrooxazolo[3,4-*a*]indole **3a** was obtained in 41% yield (entry 1). The yield of compound **3a** was improved to 61% with PPh$_3$AuCl/AgNTf$_2$ (entry 2), and further improved to 69% with IPrAuCl/AgNTf$_2$ (entry 3). When we employed electron-deficient (PhO)$_3$PAuCl/AgNTf$_2$, the yield of compound **3a** decreased significantly to 38% (entry 4). Variations of silver salts as in IPrAuCl/AgX, (X = OTf and SbF$_6$) failed to increase the catalytic efficiency with 52-55% yields of compound **3a** (entries 5-6). For IPrAuCl/AgNTf$_2$ (10 mol%) in other solvents, the yields of desired product **3a** follow: DCE (60%) and toluene (57%). AgNTf$_2$ alone in DCM is entirely inactive for this transformation and when we tried a lower loading of IPrAuCl/AgNTf$_2$ (5 mol%), the desired product **3a** was obtained in only 53% yield (entry 10). We also tested the reaction with IPrAuCl and other counter anions NaBARF, AgBF$_4$, and AgBF$_6$, but then the yield of **3a** dropped to 28%, 15%, and 30% (entries 11-13). The structure of compound **3a** was elucidated by X-ray diffraction,[7] which revealed a bicyclic annulation between nitrone **2a** and internal alkyne **1a**, resulting in formation of this molecular framework after the loss of water.

Table 1. Catalyst Screening and Optimization of Conditions



Entry	Catalyst	Solvent	*t* (h)	Yield of **3a** (%)[b]
1	LAuCl/AgNTf$_2$	DCM	20	41
2	PPh$_3$AuCl/AgNTf$_2$	DCM	18	61
3	IPrAuCl/AgNTf$_2$	DCM	16	69
4	(OPh)$_3$PAuCl/AgNTf$_2$	DCM	24	38
5	IPrAuCl/AgOTf	DCM	18	52
6	IPrAuCl/AgSbF$_6$	DCM	18	55
7	IPrAuCl/AgNTf$_2$	DCE	20	60
8	IPrAuCl/AgNTf$_2$	toluene	24	57
9	AgNTf$_2$	DCM	24	-
10	IPrAuCl/AgNTf$_2$[c]	DCM	16	53
11	IPrAuCl/NaBARF	DCM	24	28
12	IPrAuCl/AgBF$_4$	DCM	24	15
13	IPrAuCl/AgBF$_6$	DCM	24	30

[a] [**1**] = 0.21 M. [b] Product yields are obtained after purification by column chromatography (silica gel), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, L = P(*t*-Bu)$_2$(*o*-biphenyl), [c] Catalyst (5 mol%).

We assessed the generality of these bicyclic annulations using various 4-hydroxy-1-oxo-but-2-ynes (**1**) and nitrone (**2**); the results are summarized in Table 2. Under the optimized conditions, bicyclic dihydrooxazolo[3,4-*a*]indole derivatives (**3**) were produced exclusively. Entries 1-3 show the reactions of methyl 4-hydroxy-1-oxo-but-2-ynoate **1a** with nitrones **2b-2d** bearing *p*-substituted anilines (X= OMe, Cl, H), yielding desired products **3b-3d** at 83-89%. For nitrones **2e-2g** (X= Me, Cl, Br) bearing *o*-substituted anilines, their corresponding products **3e-3g** were generated with 58-75 % yields (entries 4-6). We tested the reactions on additional nitrones bearing *p*-substituted imines **2h-2l** (Y = *t*-Bu, OMe, Cl, Br, F), further generating the expected bicyclic products **3h-3l** in 65-83% yields (entries 7-11), with electron-rich substituents (Y = *t*-Bu, OMe) being more productive. For *o*-, *m*-bromo-substituted imines as in nitrone **2m** and **2n**, their corresponding products **3m** and **3n** were obtained with 63% and 65% yields (entries 12-13). We performed the reaction also on thiophene-derived nitrone **2o** that produced compound **3o** with 80% yield (entries 14).

We next assessed the scope of applicable 4-hydroxy-1-oxo-but-2-ynes. For various alkyl 2-ynoates (**1b-1e**, R^1 = ethyl, isopropyl, isobutyl and benzyl), their bicyclic annulations with standard nitrone **2a** rendered expected compounds **3p-3s** in 40-80% yields (entries 15-18), with electron-rich esters being less efficient. This observation indicates that

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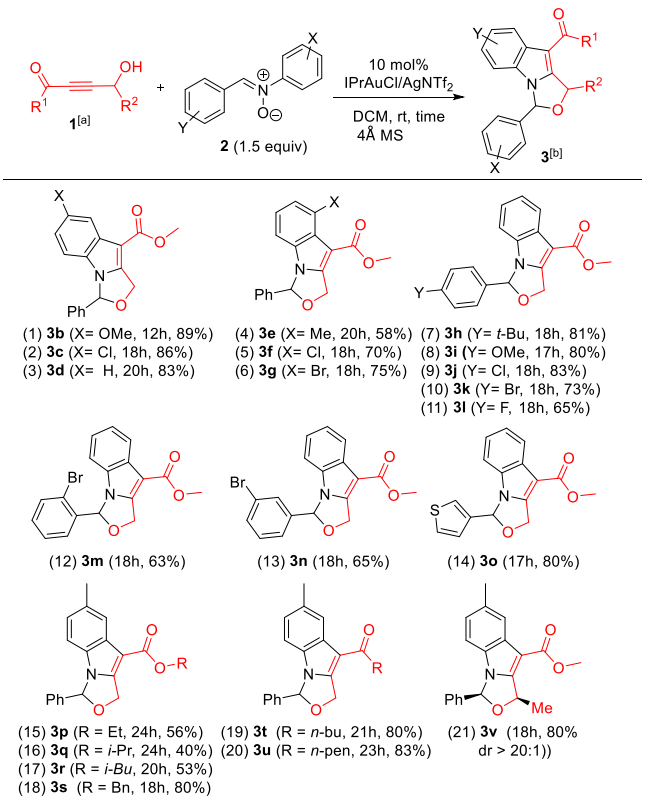
Table 2: Gold catalyzed bicyclic annulations



[a][**1**] = 0.21 M. [b] Product yields are obtained after purification by column chromatography (silica gel).

coordination of esters to a gold catalyst decreases the efficiency of these bicyclic annulations. We expanded the scope to alkyl alkynones **1f**, **1g** (R^1 = *n*-butyl, *n*-pentyl) that became applicable substrates, producing the desired **3t**-**3u** with yields 80-83% (entries 19-20). Accordingly, less basic alkynoates and alkynones are more suitable for these bicyclic annulations. Finally, we prepared methyl 4-methyl-4-hydroxybut-2-ynoate **1h** that gave compound **3v** (*dr* > 20:1) with 80% yield as one single diastereomer (entry 21). Its ^{1}H NOE spectrum reveals a *cis*-configuration of the oxazolidine ring.

In such nitrone annulations, we prepared 1-phenyl-4-hydroxy-2-butyn-1-one **1i** that afforded a different product **5a** via a reductive [3+2]-annulation (Eq 5); species **5a** can be visualized to result from a reductive cleavage of the indole ring of our bicyclic indoles **3**. We accordingly tested the reaction again using an imine **4a** to replace nitrone **2a**; this new process greatly improved the yield of **5a** up to 83% (Eq 6).

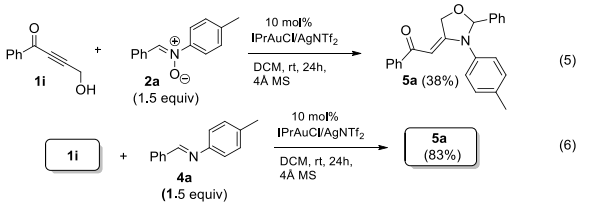
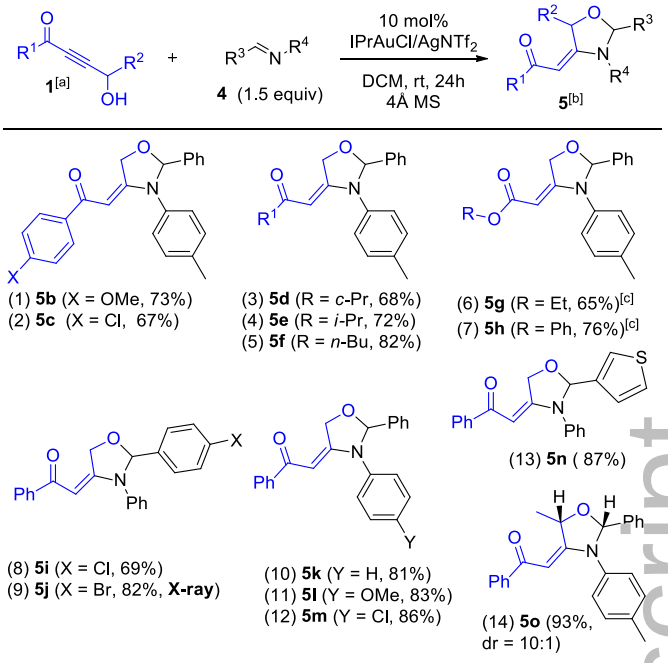


Table 3: Synthesis of oxazolidine with imines



[a][**1**] = 0.15 M. [b] Product yields are obtained after purification by column chromatography (silica gel) [c] Reaction temperature = 40 °C.

Structural characterization of compound **5a** relied on X-ray diffraction of its relative **5j** (*vide infra*).[7]

Table 3 depicts the substrate scope of these [3+2]-annulations using various 4-hydroxy-1-oxo but-2-ynes (**1**) and imines (**4**). Most internal alkynes herein were also effective for gold-catalyzed bicyclic annulations when nitrones served as the reaction partners. For 1-aryl-4-hydroxybut-2-yn-1-ones (R^1 = 4-MeOC_6H_4, 4-ClC_6H_4), their annulations with imine **4a** delivered oxazolidine species **5b** and **5c** with 73% and 67% yields (entries 1-2). Alkyl-substituted ketones (R^1 = cyclopropyl, isopropyl and *n*-butyl) also gave desired oxazolidines **5d**-**5f** with 68-82% yields (entries 3-5). We tested these imine annulations with various alkynyl esters (R^1 = OEt and OPh), producing compounds **5g** and **5h** in 65% and 76% yields respectively (entries 6-7). We next tried other imines bearing imino groups (X = Cl and Br); their corresponding products **5i** and **5j** were generated with 69% and 82% yields (entries 8-9). The molecular structure of compound **5j** was characterized with X-ray diffraction.[7] For imines bearing varied anilines (Y = H, OMe and Cl), their corresponding products **5k**-**5m** were obtained in satisfactory yields (81-86%, entries 10-12). 3-Thiophene-containing imine was also amenable to this [3+2]-annulation to deliver compound **5n** in 87% yield (entry 13). For 4-methyl-4-hydroxy-but-2-yn-1-ol (R^2 = Me), its annulation with imine **2a** produced *cis*-configured oxazolidine **5o** stereoselectively (*dr* = 10:1); the yield was up to 93% (entry 14).

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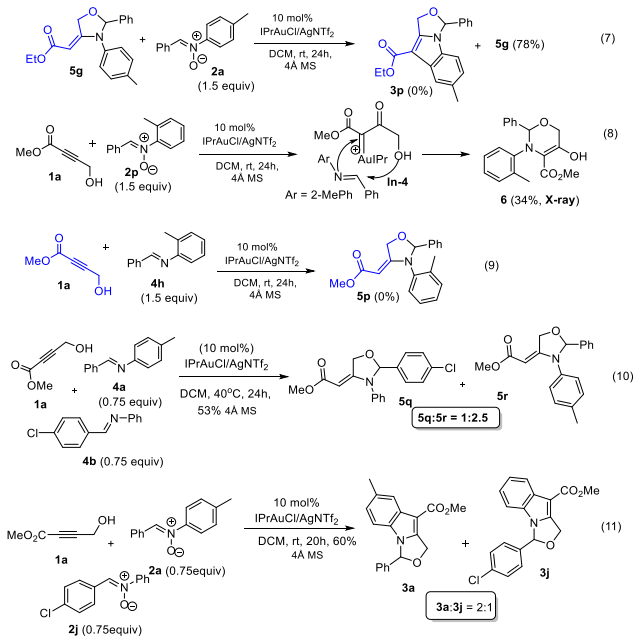

Oxazolidine **5g** might serve as an intermediate for compound **3p** in the course of the bicyclic annulation of ethyl 4-hydroxybut-2-ynoate **1b** with nitrone **2a**. This hypothesis proved invalid because compound **5g** was not convertible to its oxidized form **3p** in the presence of nitrones and gold catalyst (Eq 7). To confirm their irrelevance, we performed two reactions as depicted in Eqs 8-9. With nitrone **2p**, its reaction with methyl 4-hydroxy-1-oxo-but-2-yne **1a** delivered compound **6** in 34% yield; its molecular structure was characterized with X-ray diffraction (Eq 8).[7,8] In contrast, the annulation of alkynoate **1a** with imine failed to deliver [3+2]-annulation product **5p** (Eq 9). The two annulations of methyl 4-hydroxy-1-oxo-but-2-yne **1a** with nitrone **2p** or imine **4h** hence proceeded through two independent paths. We performed cross experiments on the two annulations. In Eq 10, the reaction of species **1a** with two imines **4a** and **4b** yielded only two annulation products **5q** and **5r** according to ^{1}H NMR spectral analysis. Similarly, we observed no additional product in the annulations of species **1a** with two nitrones **2a** and **2j** in the bicyclic annulations (Eq 11). Accordingly, both imine and nitrone remains intact through these gold-catalyzed annulations.

We performed density functional theory (DFT) calculations[9] to elucidate the mechanism of the nitrone oxidations. The Gibbs free energy surface of the proposed mechanism is depicted in Figure 1. In the nitrone oxidations, we find that the target molecule **3d** was produced from an attack of a nitrone on gold-π-alkyne species **A**, resulting in the formation of alkenylgold intermediates **B** (Figure 1 (a)). This process releases ΔG = -38.1 kJ/mol with kinetic barrier $\Delta G‡$ = 23.0 kJ/mol. We were unable to locate the transition state to yield gold carbene intermediates. Instead, a [3,3]-sigmatropic shift of species **B** proved to be feasible even though a steric interaction was encountered; the kinetic barrier is 78.6 kJ/mol with a release of energy of 79.1 kJ/mol. Accordingly, an internal alkyne is also accessible to an oxoarylation product via a non-carbene route. We examined the optimized geometry of TSbc that has a long N-O bond of 1.70 Å, whereas the distance between the two reacting carbons is estimated to be 4.25 Å. This information indicates that a [3,3]-rearrangement actually occurs through an initial lengthening of the nitroxy N-O bond to enable an aryl attack at the alkenylgold carbon. Once the oxoarylation intermediate **C** is formed, its aromatization can occur via a 1,2-proton migration to induce a loss of the gold fragment; the barrier is 89.5 kJ/mol to form species **D** (Figure 1 (b)). A final bicyclic cyclization is achievable with a prior coordination of the carbonyl of species **E** with the gold catalyst, further forming iminium species **F**; the activation barrier is only 26.8 kJ/mol. The last two steps **F**→**G** and **G**→**H** are procedures of known organic reactions; their feasibilities are also described with our DFT calculations to involve a maximum barrier of 94.6 kJ/mol.

Conclusion

This work reports two distinct gold-catalyzed annulations for 4-hydroxy-1-oxobut-2-ynes. A new bicyclic annulation [10] is achieved with nitrone as the oxidant to yield 1,3-dihydrooxazolo[3,4-*a*]indoles efficiently. Our DFT calculations reveal a [3,3]-sigmatropic rearrangement of the initial alkenylgold intermediates. When the same 4-hydroxybut-2-ynoates are treated with imines and a gold catalyst, oxazolidin-4-ylidene derivatives are produced in high yields. [11] Although the structural skeletons of the two annulation products seem to be related, our control experiments revealed two independent pathways for their formation.

Experimental Section

Typical procedure for synthesis of methyl 7-methyl-3-phenyl-1,3-dihydrooxazolo[3,4-*a*]indole-9-carboxylate (3a)

A catalytic flask was charged with IPrAuCl (27.21 mg, 0.04 mmol), $AgNTf_2$ (17.0 mg, 0.04 mmol) and to this mixture was added dry DCM (1 mL). The mixture was stirred for 5 min at room temperature. To this solution was added a DCM (1 mL) solution of **1a** methyl 4-hydroxybut-2-ynoate (50 mg, 0.4382 mmol) and nitrone **2a** (138.85 mg, 0.65 mmol); the resulting solution was further stirred at room temperature for 16 h. The solution was filtered over a short Celite bed, and concentrated to form crude product **3a**. Flash silica chromatography [EA/hexane (10:90)] afforded the desired product **3a** (93.0 mg, 0.30 mmol, 69%) as white solid; ^{1}H NMR (600 MHz, CDCl3): δ 7.91 (d, *J* = 1.2 Hz, 1H), 7.44 ~ 7.38 (m, 3H), 7.36 ~ 7.34 (m, 2H), 6.86 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.65 (m, 2H), 5.52 (dd, *J* = 14.4, 2.4 Hz, 1H), 5.34 (dd, *J* = 14.4, 1.8 Hz, 1H), 3.90 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ 165.1, 147.3, 135.9, 132.0, 131.7, 130.4, 129.2, 129.0, 127.2, 123.9, 121.5, 110.0, 97.9, 91.2, 68.1, 51.0, 21.5; ESIMS calcd. For $C_{19}H_{17}NO_3$ [M+Na]: 330.1106; [M+Na] found: 330.1107.

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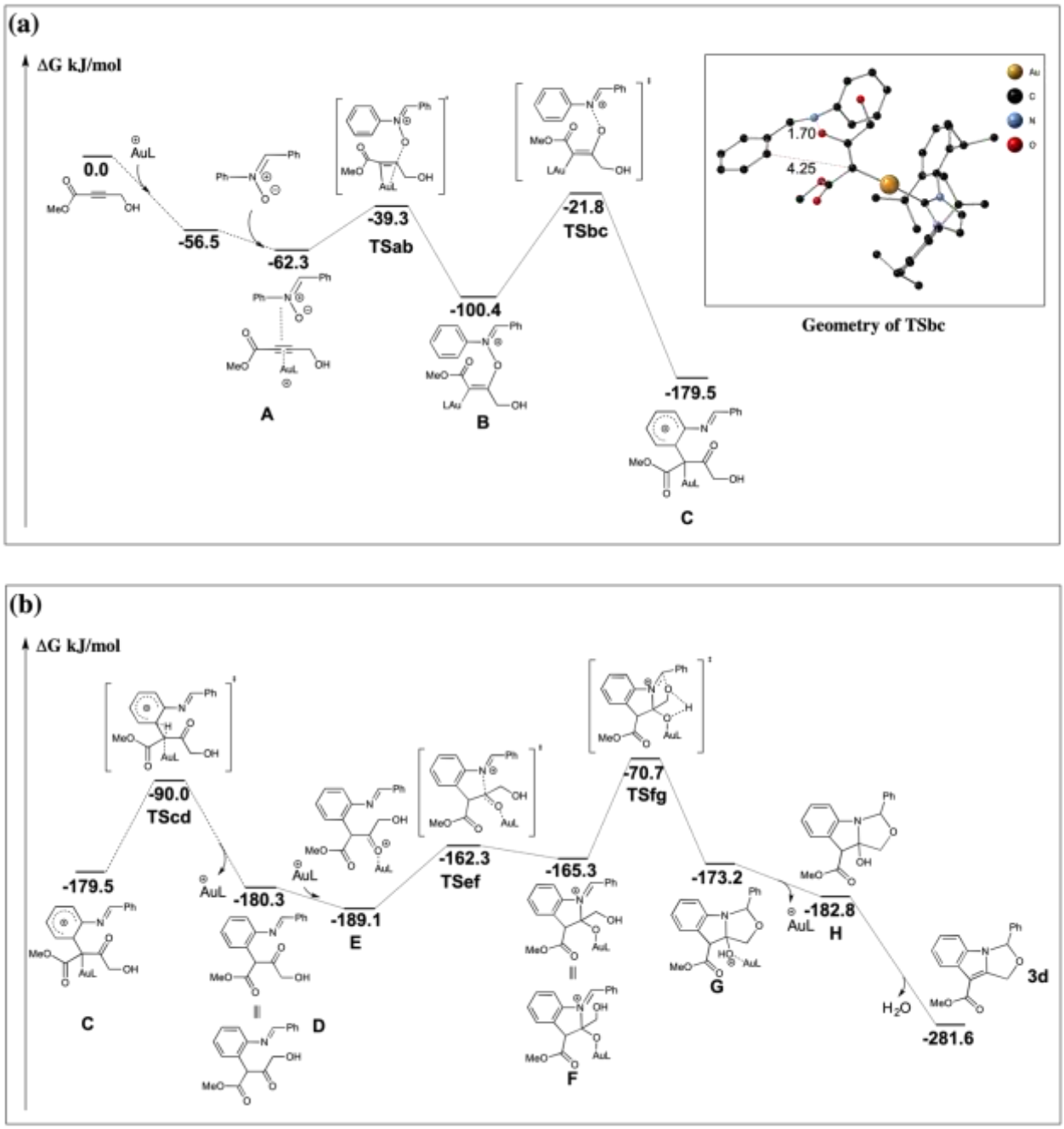

Figure 1. Gibbs free energy surface from DFT calculations. DCM is used as the solvent, and L represents IPr. The inset in part (a) is the three-dimensional representation of the optimized structure of TSbc.

Typical procedure for synthesis of (*E*)-1-phenyl-2-(2-phenyl-3-(*p*-tolyl)oxazolidin-4-ylidene)ethanone (5a)

A catalytic tube was charged with IPrAuCl (19.38 mg, 0.03 mmol), $AgNTf_2$ (12.10 mg, 0.03 mmol) and to this mixture was added dry DCM (1 mL); the mixture was stirred for 5 min at room temperature. To this solution was added a DCM (1 mL) solution of **1i** 4-hydroxy-1-phenylbut-2-yn-1-one (50 mg, 0.31 mmol) and imine **4a** (91.43 mg, 0.46 mmol), and the resulting mixture was further stirred at room temperature for 24 h. The solution was filtered over a short Celite bed and concentrated in vacuo to afford crude product **5a**. Flash silica chromatography [EA/hexane (10:90)] yielded the desired product **5a** (92 mg, 0.25 mmol, 83%) as brown liquid. (92.2 mg, 83%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.41 ~ 7.30 (m, 8H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.18 (s, 1H), 5.89 (s, 1H), 5.79 (d, *J* = 16 Hz, 1H), 5.51 (d, *J* = 16 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 188.9, 161.3, 140.1, 137.8, 137.1, 134.3, 131.0, 130.4, 129.8, 128.5, 128.1, 127.5, 127.3, 126.4, 96.6, 87.1, 74.3, 21.1; ESI-MS calcd. For $C_{24}H_{21}NO_2$ [M+Na]: 378.1470; [M+Na] found: 378.1464.

Acknowledgements

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References

[1] For reviews on N,O-functionalizations of alkynes, see: a) H. S.Yeom, S. Shin, *Acc. Chem. Res*, **2014**, 47, 966-977; b) D. B. Huple, S. Ghorpade, R. S. Liu, *Adv. Synth. Catal.* **2016**, *358*, 1348-1367; c) A. S. K. Hashmi, *Chem. Rev*. **2007**, *107*, 3180-3211.

[2] See selected reviews: a) F. Hu, M. Szostak, *Adv. Synth. Catal*. **2015**, *357*, 2583-2614; b) P. Vitale, A. Scilimati, *Curr. Org. Chem*. **2013**, *17*, 1986-2000; c) A. L. Sukhorukov, S. L. Lorfe, *Chem. Rev*. **2011**, *111*, 5004-5041; d) P. Grunanger, P. Vita-Finzi, J. E. Dowling, in: *Chemistry of Heterocyclic Compounds*, Part 2, Vol. 49, (Ed.: E. C. Taylor. P. Wipf), Wiley, New York USA, 1999, pp 1-888; e) P. Pevarello, R. Amici, M. G. Brasca, M. Villa, M. Virasi, in*: Targets in Heterocyclic Systems* **1999**, *3*, 301-339.

[3] a) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad, R. S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15372-15375; b) Y. C. Hsu, S. A. Hsieh, P. H. Li, R. S. Liu**,** *Chem. Commun.* **2018**, *54*, 2114-2117; c) R. L. Sahani, M. D. Patil, S. B. Wagh, R. S. Liu, *Angew. Chem., Int. Ed.* **2018**, *57*, 14878-14882; d) H. Wei, M. Bao, K. Dong, L. Qiu, B. Wu, W. Hu, X. Xu, *Angew. Chem., Int. Ed.* **2018**, *57*, 17200-17204; e) H. S. Yeom, Y. Lee, J. E. Lee, S. Shin, *Org. Biomol. Chem*. **2009**, *7*, 4744-4752; f) D. Quin, J. Zhang, *Chem. Eur. J*. **2013**, *19*, 6984-6988; g) H. Yeom, J. Lee, S. Shin, *Angew. Chem. Int. Ed.* **2008**, *47*, 7040-7043.

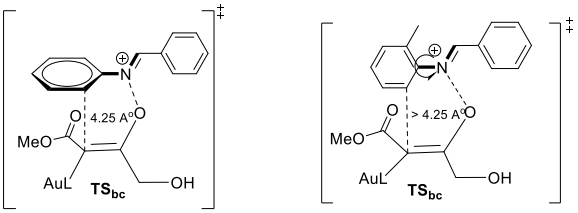
[4] a) R. L. Sahani, R. S. Liu, *ACS Catal.* **2019**, *9*, 5890-5896; b) S. Bhunia, J. C. Chang, R. S. Liu, *Org. Lett*, **2012**, 14, 21, 5522-5525; c) A. V. Sasane, A. S. K. Raj, T. H. Chao, M. J. Chen, R. S. Liu. *Chem. Eur. J*. (10.1002/chem.202003840)

[5] a) A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledos, M. S. Mercedes, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906; b) C. W. Li, K. Pati, G. Y. Lin, S. M. A Sohel, H. H. Hung, R. S. Liu, *Angew. Chem., Int. Ed.* **2010**, *49*, 9891; c) Y. Wang, L. Ye, L. Zhang, *Chem. Commun*. **2011**, *47*, 7815.

[6] For gold-catalyzed annulation reactions, see selected reviews: a) A. S. K. Hashmi, G. J. Hutchings. *Angew. Chem. Int. Ed*. **2006**, *45*, 7896-7936; b) X. Zhao, M. Rudolph, A. S. K. Hashmi. *Chem. Commun*.. **2019**, *55*, 12127-12135; c) A. S. K. Hashmi. *Acc. Chem. Res*. **2014**, *47*, 864-876; d) A. M. Asiria, A. S. K. Hashmi. *Chem. Soc. Rev*. **2016**, *45*, 4471-4503; e) D. Pflasterer, A. S. K. Hashmi. *Chem. Soc. Rev***. 2016**, *45*, 1331-1367; f) N. T. Patil, Y. Yamamoto, *Chem. Rev*. **2008**, *108*, 3395-3442; g) S. Abu Sohel, R. S. Liu, *Chem. Soc. Rev*. **2009**, *38*, 2269-2281; h) M. E. Muratore, A. Homs, C. Obradors, A. M. Echavarren, *Chem. Asian. J*. **2014**, *9*, 3066-3082; i) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev*. **2008**, *108*, 3351-3378.

[7] CCDC-2013288 (**3a**), CCDC-2013287 (**5j**), and CCDC-2022885 (**6**) 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.

[8] Formation of compound **6** (Eq 8) was produced from gold-carbene intermediates because the *ortho*-methylphenyl substituent of nitrone impedes the phenyl attack. The optimized geometry of TSbc required a planar geometry between this phenyl and C=N-O plane so that the distance became minimized to 4.25 Å. The presence of an *ortho*-methyl group is expected to increase this distance because this planarity is not maintained because of steric hindrance. This effect is expected to generate gold carbenes.



[9] The geometry optimizations and zero-point vibrational energy (ZPVE) were calculated using the B3LYP-D3 functional combined with the LANL2DZ basis set for Au and the 6-31G** basis set for the other atoms (denoted as LACVP**). To obtain a more accurate electronic energy, single-point energy calculations based on the same functional, but using a larger basis set (LANL2TZ for Au and 6-311++G** for the others) were performed. Solvation energies were calculated using the CPCM implicit solvation model. The solvation calculations used the B3LYP/LACVP** level of theory and the gas-phase optimized structures. The Gaussian09 package was used for all DFT calculations.

[10] For gold-catalyzed bicyclic annulations involving two components; see selected examples: a) A. S. K. Raj, R. S. Liu., *Angew. Chem. Int. Ed*. **2019**, *58*, 10980-10984; b) A. S. K. Raj, K. C. Tan, L. Y. Chen, M. J. Cheng, R. S. Liu. *Chem. Sci*., **2019**, *10*, 6437-6442; c) C. C. Lin, T. M. Teng, A. Odedra, R. S. Liu. *J. Am. Chem. Soc*. **2007**, *129*, 3798-3799; d) H. Gao, X. Zhao, Y. Yu, J. Zhang. *Chem. Eur. J*. **2010**, *16*, 456-459; e) H. Gao, X. Wu, J Zhang. *Chem. Eur. J*. **2011**, *17*, 2838-2841; f) T. M. Teng, R. S. Liu. *J. Am. Chem. Soc.* **2010**, *132*, 9298-9300; g) T. M. Teng, A. Das, D. B. Huple, R. S. Liu. *J. Am. Chem. Soc*. **2010**, *132*, 12565-12567.

[11] For the [3+2]-imine annulations, the mechanism proceeds through an independent route, explicitly through an attack of imine at gold π-alkyne **A'** to yield species **B'** that was trapped with a tethered alcohol to form intermediate **C',** and ultimately observed product **5a.**

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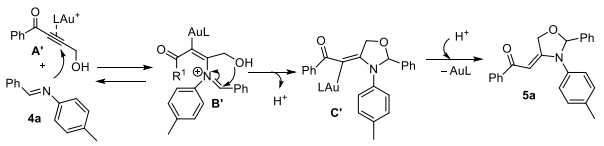

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FULL PAPER

Gold-catalyzed Bicyclic and [3+2]-Annulations of Internal Propargyl Alcohols with Nitrones and Imines to Yield to Two Distinct Heterocycles

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