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Accessing Alternative Reaction Pathways of the Intermolecular Condensation between Homo-Propargyl Alcohols and Terminal Alkynes through Divergent Gold Catalysis

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Abstract

An intermolecular condensation of alkynols and terminal alkynes is reported. Using IPrAuNTf$_2$, an efficient Au-catalyzed cyclization-alkynylation strategy furnishes (2-arylalkynyl) cyclic ethers in moderate to excellent yields (up to 94%). This strategy is extended to the synthesis of functionalized 2,3-dihydrooxepines via the sequential Au-catalyzed ring expansion of the cyclic ether substrates.

Gold(I) catalysis has developed rapidly in recent years and the resulting methodologies have proved useful for the facile installation of molecular complexity.[1] Gold's intrinsic π-acid mode of activation has rendered it synthetically valuable in promoting reactions involving substrates bearing unsaturated C-C moieties (alkyne, allene, and alkene; Scheme 1A). Consequently, the design of selective catalytic systems is often problematic when multiple reactive functional groups are present.[2] Furthermore, additional challenges in attaining selectivity arise if these catalytic systems are a composite of intra- and inter- molecular reactions.[3]

Over the past several years, our group has demonstrated the application of 1,2,3-triazole gold(I) (TA-Au) catalysts in promoting these challenging transformations.[4] One relevant example is the intermolecular condensation between homo-propargyl alcohols and terminal aliphatic alkynes to afford 2,3-dihydrooxepines (Scheme 1B).[5] Within this reaction pathway, a vinyl ether intermediate is selectively formed via the intermolecular gold-catalyzed hydroalkoxylation of the terminal alkyne. Moreover, in exploring the reactivity of vinyl ethers with terminal alkynes under triazole gold-catalytic conditions, we later developed an intermolecular alkynylation of vinyl ethers.[6]

Despite these recent advances, certain concerns regarding the mechanisms of the reactions have not been completely addressed. First, the enyne cycloisomerization reaction between homo-propargyl alcohol **1** and terminal alkyne **2** was tolerated only by aliphatic alkynes (Scheme 1B). This result was unexpected considering that gold π-acid activation of aryl-substituted terminal alkynes is extensively documented.[7] A messy reaction mixture was obtained when aryl-substituted terminal alkynes such as phenylacetylene were used. Second, for the alkynylation of vinyl ether **4**, aliphatic alkynes such as 1-hexyne resulted in slightly

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lower yields in comparison with aromatic alkynes (Scheme 1C). Based on these observations, changing the substrate of either reaction has the potential to dramatically alter the reaction pathway, and this phenomenon warrants further investigation.

Our strategy in exploring this unique catalytic system was focused on: 1) extending the reaction scope of the 2,3-dihydrooxepine synthesis to include aryl-substituted terminal alkynes and, 2) exploring the possibility of a cascade process for the alkynylation of vinyl ether **B** (Scheme 2).[8–9]

As shown in Table 1, the reaction of **1a** with aromatic alkyne **2b** under our previously reported conditions resulted in a messy reaction, with no formation of dihydrooxepine **3a** (entry 2). To explore the plausibility of a cascade process, we screened various gold catalysts (see ESI†). Interestingly, when 5% RuPhosAuNTf$_2$ was used as the catalyst, alkyne **6b** was observed, albeit in low yield (31%, entry 3). Since the formation of **6b** requires gold π-acid activation of the internal alkyne of **1a**, we increased the reaction temperature with the objective of promoting the intramolecular cyclization of **1a** over intermolecular hydroalkoxylation. Gratifyingly, the reaction yield was improved to 61% (entry 4). Finally, ligand screening revealed IPrAuNTf$_2$ as the optimal catalyst, affording the desired product **6b** in excellent yield (5% loading, 91% yield, entry 5; 4% loading, 87% yield, entry 6). Having identified the optimal conditions, we turned our attention to exploring the reaction scope (Table 2).

A variety of phenylacetylene derivatives were subjected to the optimized reaction conditions and subsequently afforded the desired products in good yield (**6b–6l**). Other aromatic alkynes such as ferrocenyl (**6m**, structure confirmed by X-ray), thiophenyl (**6n**), and pyrenyl (**6o**) derivatives could also be utilized in the reaction. Additionally, alkynes bearing adamantyl (**6p**), indole (**6s**), and benzofuran (**6t**) moieties were tolerated without significant decomposition of the product. The amino acid derivative **6q** and estrone derivative **6r** were also prepared, demonstrating the tolerance of the reaction conditions to a variety of functional groups. Conversely, non-aromatic terminal alkynes such as cyclopentyl acetylene, 1-hexyne, and TMS acetylene, did not form the desired alkynylation product.

To fully investigate the scope of this alkynylation reaction, different alkynols were also assessed. Substitution at the *para* (**6aa–6ae**), *meta* (**6af–6ah**), and *ortho* (**6ai**) position of the benzene ring on the homopropargyl alcohol afforded good yields. Additionally, the naphthyl derivative **6aj** could be furnished in good yield (81%). To probe the *endo/exo* selectivity of the cyclization step, we used a series of extended-chain internal alkynols bearing aliphatic or phenyl substitution. Aliphatic substitution selectively yielded the *exo* product (**6ak**), while phenyl substitution resulted in a 10:3 mixture of *exo:endo* isomers (**6al**). Terminal alkynes were tolerated under the reaction conditions, yielding the 5-*exo* (**6am**), 6-*exo* (**6an**), and 7-*exo* (**6ao**) products. In contrast, the terminal alkyne substrate for 8-*exo* cyclization gave trace formation of the desired product. To determine the diastereoselectivity of the alkynylation reaction, we utilized enantiomerically pure alkynols. However, when an α-methyl

†Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data of new compounds. CCDC 1521359, 1521360, and 1521361. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

homopropargyl alcohol is used (**6aq**, dr = 3:2) or an α,β-di-substituted homopropargyl alcohol (**6ap**, dr = 1:1), low diastereoselectivity was exhibited. Next, we diverted our focus to the development of a strategy for the synthesis of the corresponding 2,3-dihydrooxepine **3b**.

During optimization of the reaction conditions (Table 1), we observed that if 2 equivalents of terminal alkyne **2b** were used, the yield of the desired product **6b** was reduced. Monitoring the reaction using ^{1}H-NMR revealed the formation of dihydrooxepine **3b** as the major by-product (see ESI†). Reducing the amount of phenylacetylene to 1.1 equivalents resulted in the formation of **3b** as the major product in 74% yield. Notably, **3b** was unstable upon chromatographic isolation. Therefore, the dienophile tetracyanoethylene was used to trap the product via a Diels Alder cycloaddition[10] and the adduct **7b** was obtained in 71% isolated yield over two steps. The structure of **7b** was unambiguously characterized by X-ray crystallography (see ESI†). With these new optimized conditions for the synthesis of 2,3-dihydrooxepines, various aromatic alkynes were subjected to the reaction and moderate yields of the derivatives were obtained (Table 2).

Accordingly, to explore the progression of this process, we monitored the kinetics of the reaction with ^{1}H-NMR. Interestingly, within approximately 15 minutes, homo-propargyl alcohol **1a** was completely converted to the corresponding ketone **1a'** via gold-catalyzed hydrolysis.[11] Thus, **1a'** serves as a viable intermediate in the formation of **6b**. After the full conversion of **1a'** to **6b**, a slow conversion of **6b** occurs with concomitant formation of **3b**. Monitoring the analogous reaction in the presence of 3 equivalents of phenylacetylene indicated low yield of **3b** (<30%) after 48 hours (Figure 1).

Therefore, this kinetic profile and the intermediary nature of **6b** suggest that, unlike the analogous reaction involving aliphatic terminal alkynes, oxepine **3b** was formed via rearrangement of alkyne **6b**.[12] To confirm this hypothesis, **6b** was isolated and subjected to the reaction conditions (5% $IPrAuNTf_2$, 40 °C). Within 6 hours, full conversion of **6b** was attained, with oxepine **3b** formed in 63% yield (Figure 2A). Notably, treating **6b** with a catalytic amount of $HNTf_2$ (5%) led to decomposition of the substrate with no observation of oxepine (Figure 2A). These results confirmed that this ring-expansion rearrangement is a gold-catalyzed process.

An additional mechanistic concern is the reactivity difference between aliphatic and aryl-substituted terminal alkynes. As shown in Figure 2B, treating either alkyne **1a** (Figure 2C) or ketone **1a'** (Figure 2D) with an equimolar ratio of aliphatic and aromatic alkyne afforded alkyne **6b** as the major product, with no aliphatic oxepine or alkynylation observed. This data suggests that gold-acetylides formed from either aliphatic or aryl-substituted terminal alkynes exhibit divergent reactivity within the catalytic system based on alkyne substitution. Therefore, the intramolecular cyclization of homo-propargyl alcohol **1a** efficiently out-competes the intermolecular hydroxylation of the terminal alkyne, selectively forming the alkynylation product **6b**.

This result contrasts with our previously reported system in which intermolecular hydroalkoxylation was preferred. Furthermore, by utilizing the N-heterocyclic carbene gold

catalyst $IPrAuNTf_2$,[13] the internal alkyne functionality of compound **6** can be activated to form oxepine **3** through a ring-expansion rearrangement (a detailed mechanistic study is currently under investigation). Consequently, aryl-substituted terminal alkynes are successfully implemented into a highly efficient gold-catalyzed synthesis of 2,3-dihydrooxepines for the first time.

Herein, we report the gold-catalyzed intermolecular condensation of alkynols and aromatic terminal alkynes. It was discovered that the initial alkynylated substrates undergo a subsequent gold-catalyzed ring expansion to afford the corresponding 2,3-dihydrooxepines. This reaction represents a complementary synthesis to our previously reported enyne cycloisomerization. Additionally, the transformation is an illustration of reaction divergence that is tuned by altering the structure of the substrate. As a result of the mild reaction conditions, expedient functional group modification, and mechanistic insight gained, this study holds significant value in the advancement of gold-catalysis for the synthesis of complex molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. For a collection of recent reviews, see: Pflasterer S, Hashmi ASK. Chem. Soc. Rev. 2016; 45:1331–1367. [PubMed: 26673389] Dorel R, Echavarren AM. Chem. Rev. 2015; 115:9028. [PubMed: 25844920] Rudolph M, Hashmi ASK. Chem. Soc. Rev. 2012; 41:2448. [PubMed: 22182942] Krause N, Winter C. Chem. Rev. 2011; 111:1994. [PubMed: 21314182] Fürstner A. Chem. Soc. Rev. 2009; 38:3208. [PubMed: 19847352]
2. (a) Chen G-Q, Fang W, Wei Y, Tang X-Y, Shi M. Chem. Sci. 2016; 7:4318.(b) Fang W, Tang X-Y, Shi M. RSC Adv. 2016; 6:4047.(c) Tomás-Mendivil E, Toullec PY, Díez J, Conejero S, Michelet V, Cadierno V. Org. Lett. 2012; 14:2520. [PubMed: 22545702] (d) Alcaide B, Almendros P, Cembellín S, del Campo TM, Fernández I. Chem. Commun. 2013; 49:1282.(e) Meiss R, Kumar K, Waldmann H. Chem. Eur. J. 2015; 21:13526. [PubMed: 26356499] (f) Miró J, Sánchez-Roselló M, González J, del Pozo C, Fustero S. Chem. Eur. J. 2015; 21:5459. [PubMed: 25703591] (g) Rao WD, Koh MJ, Kothandaraman P, Chan PWH. J. Am. Chem. Soc. 2012; 134:10811. [PubMed: 22663059] (h) Brady PB, Carreira EM. Org. Lett. 2015; 17:3350. [PubMed: 26091188]
3. Wei Y, Shi M. ACS Catal. 2016; 6:2515.
4. (a) Motika SE, Wang Q, Akhmedov NG, Wojtas L, Shi X. Angew. Chem., Int. Ed. 2016; 55:11582. (b) Yang Y, Qin A, Zhao K, Wang D, Shi X. Adv. Synth. Catal. 2016; 358:1433.(c) Wang Q, Motika SE, Akhmedov NG, Petersen JL, Shi X. Angew. Chem., Int. Ed. 2014; 53:5418.(d) Duan H, Sengupta S, Petersen JL, Akhmedov NG, Shi X. J. Am. Chem. Soc. 2009; 131:12100. [PubMed: 19655739]
5. (a) Hosseyni S, Wojtas L, Li M, Shi X. J. Am. Chem. Soc. 2016; 138:3994. [PubMed: 26959521] (b) Snieckus V, Frota LC. Synfacts. 2016; 12:573.
6. Hosseyni, S., Smith, CA., Shi, X. Org. Lett. ASAP; 2016.
7. (a) Wang W, Hammond GB, Xu B. J. Am. Chem. Soc. 2012; 134:5697. [PubMed: 22376128] (b) Gorin DJ, Toste FD. Nature. 2007; 446:395. [PubMed: 17377576]

8. For selected examples of metal-catalyzed oxonium alkynylation, see: Yao X-Q, Li C-J. Org. Lett. 2006; 8:1953. [PubMed: 16623593] Obradors C, Echavarren AM. Chem. Eur. J. 2013; 19:3547. [PubMed: 23424154] Michalska M, Songis O, Taillier C, Bew SP, Dalla V. Adv. Synth. Catal. 2014; 356:2040. Ueda H, Yamaguchi M, Kameya H, Sugimoto K, Tokuyama H. Org. Lett. 2014; 16:4948. [PubMed: 25203164] Ueda H, Yamaguchi M, Tokuyama H. Chem. Pharm. Bull. 2016; 64:824. [PubMed: 27373638]

9. For selected examples of metal-catalyzed iminium alkynylation, see: Koradin C, Polborn K, Knochel P. Angew. Chem., Int. Ed. 2002; 41:2535. Knöpfel TF, Zarotti P, Ichikawa T, Carreira EM. J. Am. Chem. Soc. 2005; 127:9682. [PubMed: 15998061] Han J, Xu B, Hammond GB. J. Am. Chem. Soc. 2010; 132:916. [PubMed: 20041710]

10. (a) Yan J, Tay GL, Neo C, Lee BR, Chan PWH. Org. Lett. 2015; 17:4176. [PubMed: 26291118] (b) Borrero NV, DeRatt LG, Barbosa LF, Abboud KA, Aponick A. Org. Lett. 2015; 17:1754. [PubMed: 25797466] (c) Gonzalez AZ, Toste DF. Org. Lett. 2010; 12:200. [PubMed: 19961192]

11. Nguyen TXM, Son-Meniel B, Jullian J-C, Figadere B. Lett. Org. Chem. 6:630.

12. For recent examples of gold-catalyzed ring expansions, see: Zhu L-L, Li X-X, Zhou W, Li X, Chen Z. J. Org. Chem. 2011; 76:8814. [PubMed: 21919452] Bolte B, Gagosz F. J. Am. Chem. Soc. 2011; 133:7696. [PubMed: 21513342] Kim K-D, Yeom H-S, Shin S, Shin S. Tetrahedron. 2012; 68:5241. Yuan W, Dong X, Wei Y, Shi M. Chem. Eur. J. 2012; 18:10501. [PubMed: 22807410] An J-H, Yun H, Shin S, Shin S. Adv. Synth. Catal. 2014; 356:3749. Zhao J, Liu J, Xie X, Li S, Liu Y. Org. Lett. 2015; 17:5926. [PubMed: 26596136] Chen M, Sun N, Xu W, Zhao J, Wang G, Liu Y. Chem. Eur. J. 2015; 21:18571. [PubMed: 26490371]

13. Díez-González S, Marion N, Nolan SP. Chem. Rev. 2009; 109:3612. [PubMed: 19588961]

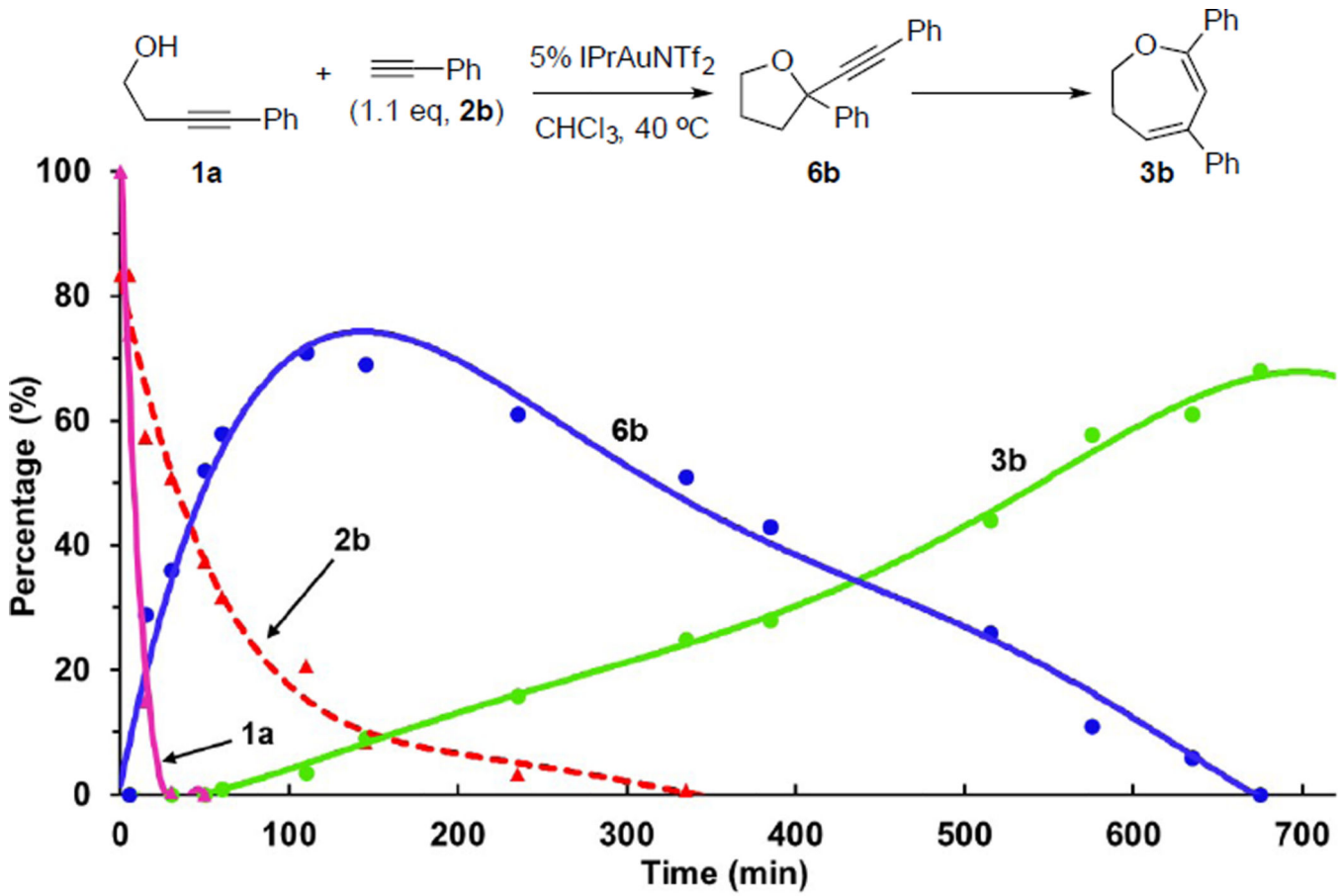


Figure 1.
Reaction kinetic profile

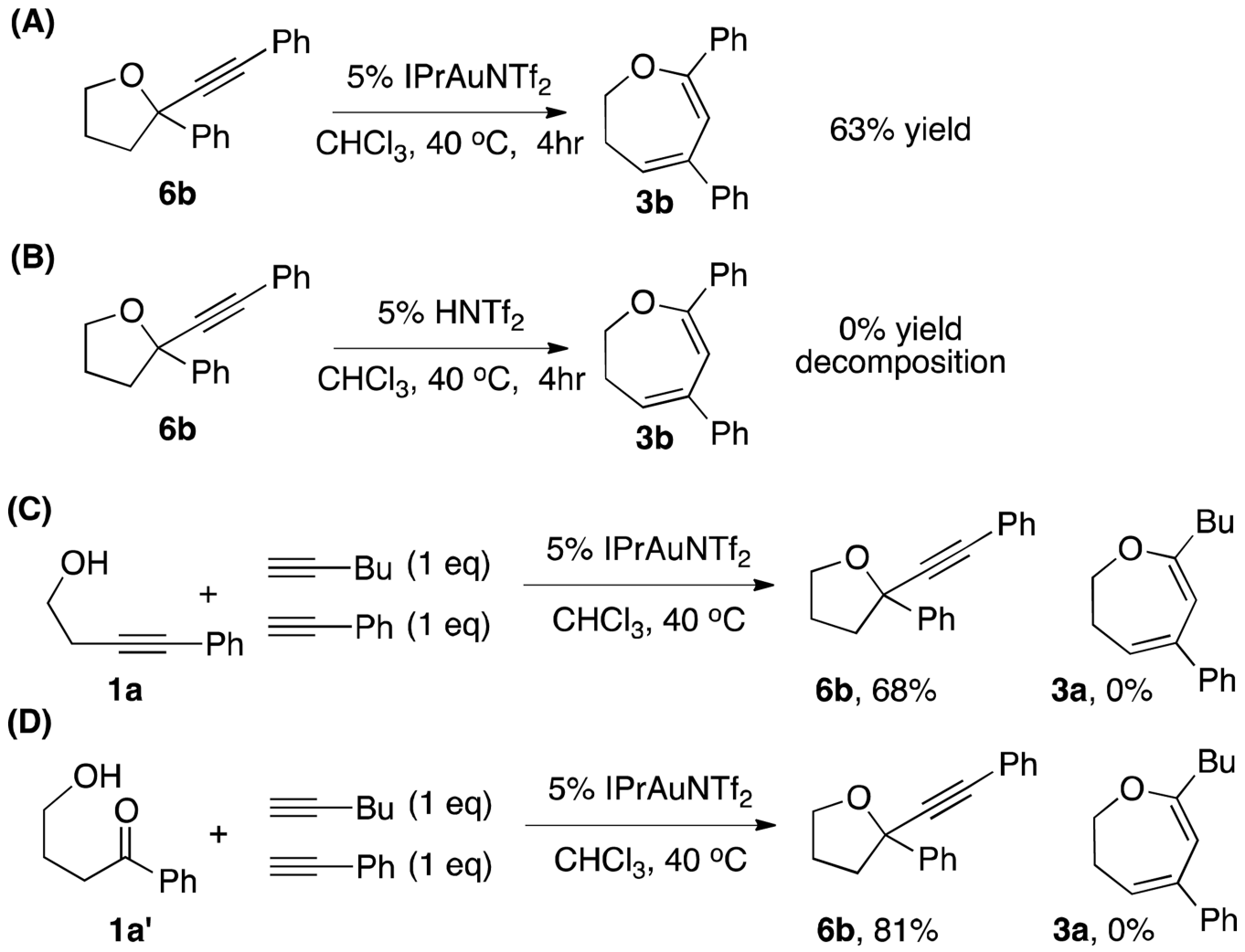
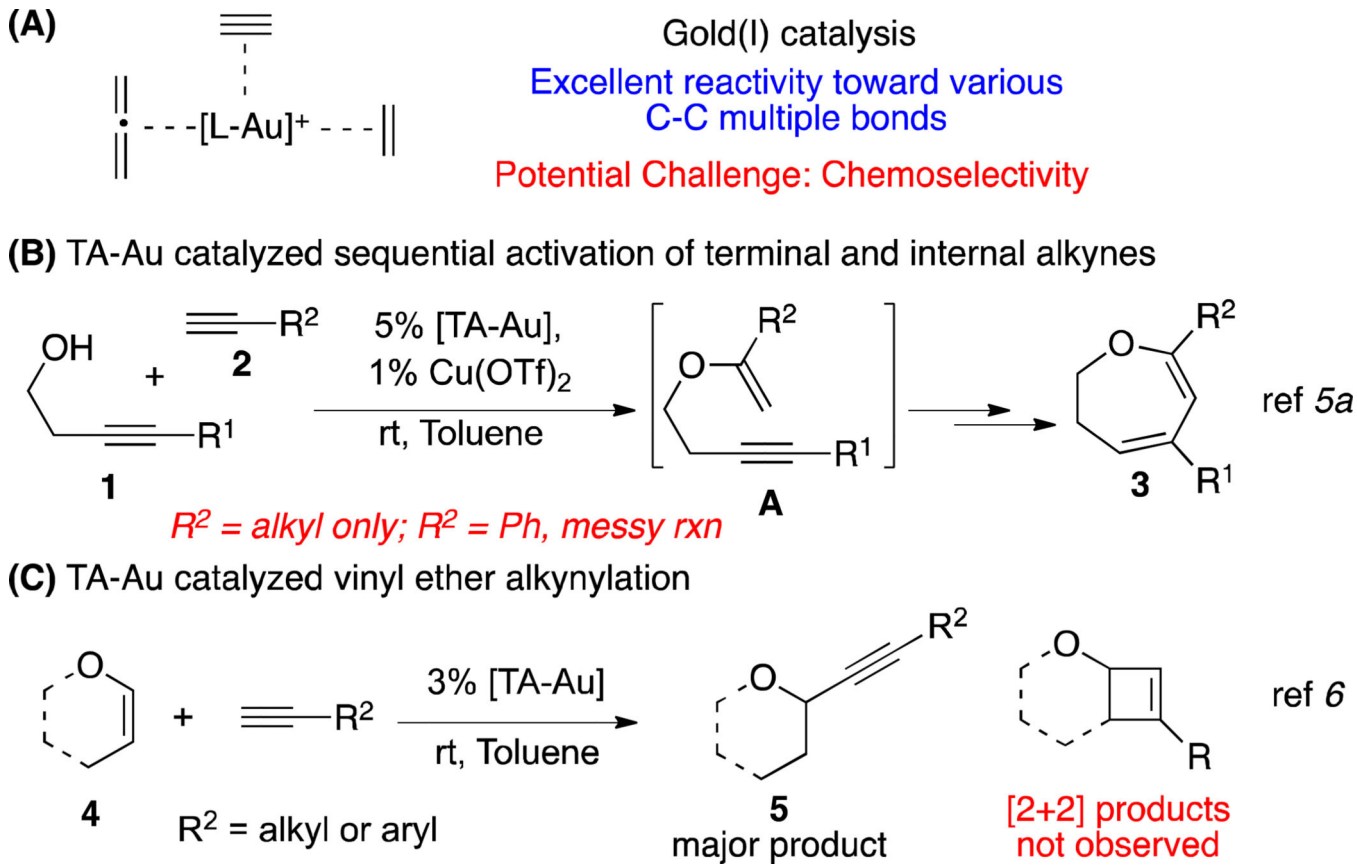
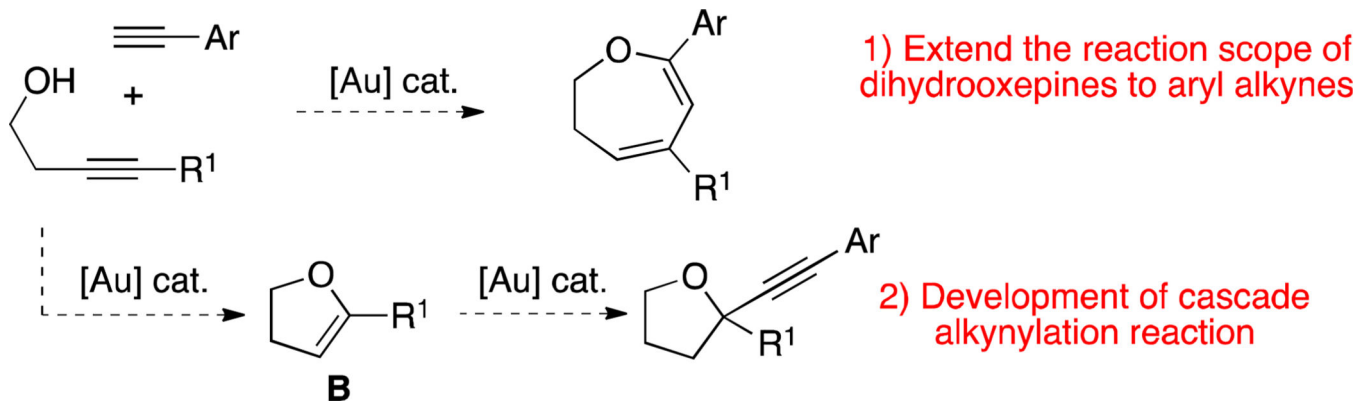


Figure 2.
Exploration of reaction mechanism



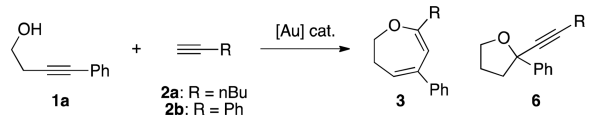
Scheme 1.
Gold-catalyzed C-C multiple bond activation



Scheme 2.
Proposed reaction pathways

Table 1

Optimization of reaction conditions[a,b]



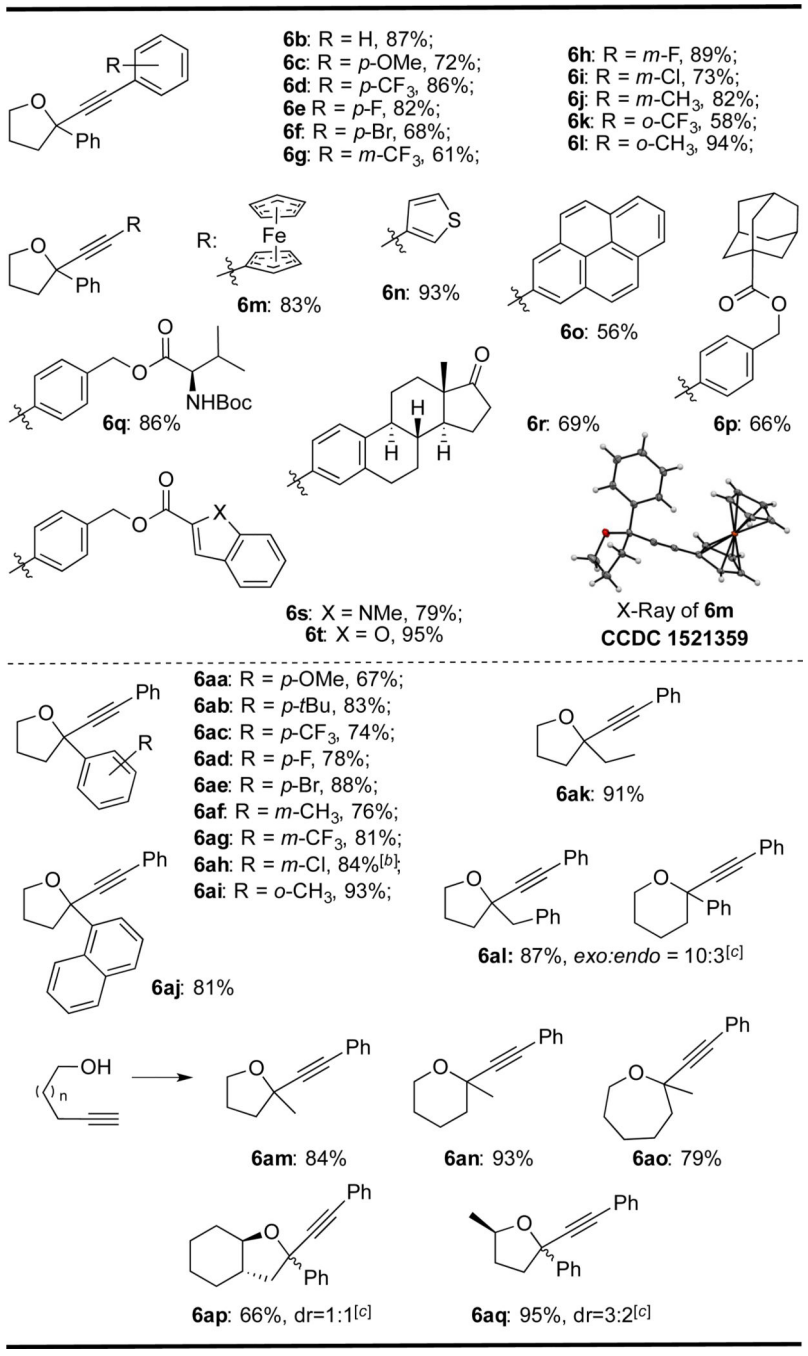
Entry	Conditions	2 (eq)	convn (%)	yield (%)	
				3	6
1	5% [XPhosAu(TA)]OTf, 1% $Cu(OTf)_2$, toluene, rt, 24h	2a (3)	100	84%	n.d.
2	Same conditions as entry 1, messy reaction	2b (3)	100	<5%	n.d.
3	5% $RuPhosAuNTf_2$, $CHCl_3$, rt, 12h	2b (3)	100	n.d.	47%
4	5% $RuPhosAuNTf_2$, $CHCl_3$, 40 °C, 4h	2b (3)	100	n.d.	61%
5	5% $IPrAuNTf_2$, $CHCl_3$, 40 °C, 4h	2b (3)	100	n.d.	91%
6	4% $IPrAuNTf_2$, $CHCl_3$, 40 °C, 4h	2b (3)	100	n.d.	87%
7	1% $IPrAuNTf_2$, $CHCl_3$, 40 °C, 4h	2b (3)	100	n.d.	34%
8	5% $IPrAuNTf_2$, $CHCl_3$, 40 °C, 4h	2b (2)	100	56%	36%
9	Other catalysts (5) including $AuCl_3$, HOTf, $pTsOH•H_2O$, $In(OTf)_3$, $Pd(OAc)_2$, CuBr, $Cu(OTf)_2$, $ZnBr_2$, AgOTf	2b (3)	<30%	n.d.	<5%

[a]General conditions: **1** (0.2 mmol), **2** (eq), and gold catalyst (mol %) in $CHCl_3$ (0.8 mL) under Ar;

[b]The yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 2

Reaction scope of alkynylation cascade[a,b,c]



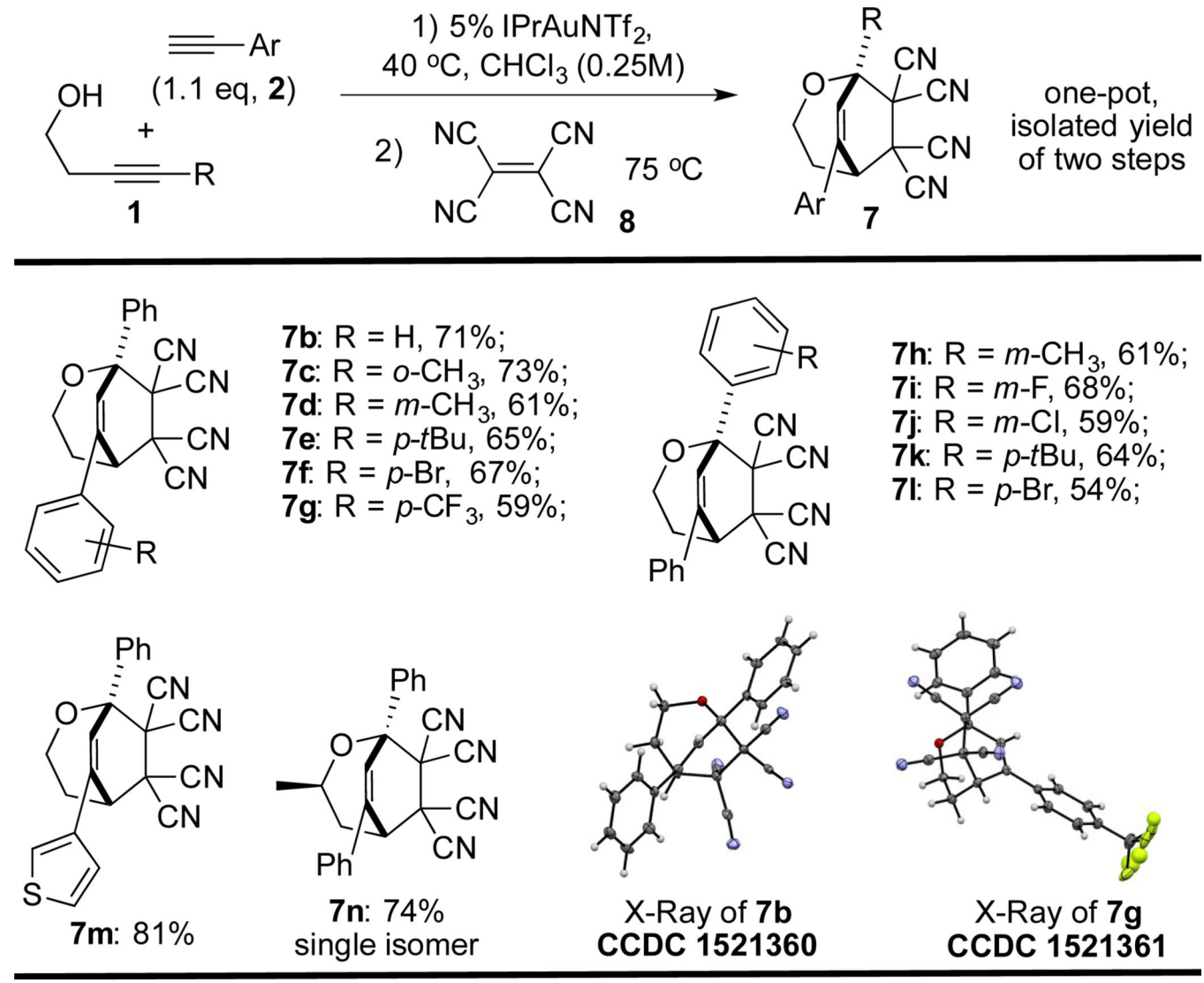
[a]General conditions: **1** (0.2 mmol), **2** (3 eq), $IPrAuNTf_2$ (3 mol %) in $CHCl_3$ (0.8 mL) under Ar at 40 °C. Yields of isolated products are given. Reference the ESI for detailed conditions.

[b]Reaction heated at 60 °C

[c]Ratio determined via ^{1}H-NMR.

Table 2

Reaction scope of oxepine adducts[a]



[a]General conditions: **1** (0.4 mmol), **2** (1.1 eq), and $IPrAuNTf_2$ (5 mol %) in dry $CHCl_3$ (1.6 mL) under Ar atmosphere at 40 °C. The crude was passed through silica, **8** (1.5 eq) was added, and the reaction was heated at 75 °C. Yields of isolated products are given.