Ambient Schmittel Cyclization Promoted by Chemoselective Triazole-Gold Catalyst

Qiaoyi Wang, Siddhita Aparaj, Novruz G. Akhmedov, Jeffrey L. Petersen, and Xiaodong Shi*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

Xiaodong.Shi@mail.wvu.edu

Received January 27, 2012



The Schmittel cyclization was achieved at room temperature through triazole–gold (TA–Au) catalyzed propargyl vinyl ether rearrangement. Other tested $[L-Au]^+$ catalysts gave complex reaction mixtures under identical conditions with no desired products observed. Importantly, because of the employment of mild conditions, sterically hindered groups (such as *t*-Bu) on allene termini were no longer required, which allowed successful synthesis of previously challenging substrates.

Over the past several decades, the thermal cycloaromatizations of enediyne (Bergman and Pascal)¹ and enyne–allene (Myers-Saito and Schmittel)² have attracted considerable attention due to their fundamentally intriguing mechanisms and the crucial biological applications.³

10.1021/ol300227a © 2012 American Chemical Society Published on Web 02/22/2012 Experimental and computational mechanistic investigations suggested that these transformations proceed via diradical intermediates.⁴ Two different cyclization paths have been disclosed for the enyne-allene systems (Scheme 1): C2-C7 and C2-C6 cyclizations.

ORGANIC LETTERS

2012 Vol. 14, No. 5

1334-1337

For the enyne–allene system, the formation of aromaticity provides the driving force for the Myers-Saito (C2–C7) cyclization. The Schmittel (C2–C6) path is also energetically favored due to the carbon hybridization conversion from sp to sp^2 . However, the C2–C7 cyclization is generally preferred and appropriate substitutions on alkyne termini are usually required for altering the regioselectivity to C2–C6 cyclization.⁵ Nevertheless, the ability to construct 5-membered ring makes the Schmittel cyclization an interesting strategy for complex poly aromatic structure construction.

One particular intriguing transformation was the cascade cyclization of aromatic substituted allenes, which was

^{(1) (}a) Jones, R. R.; Bergman, R. G. J. Am. Chem. Soc. **1972**, 94, 660– 661. (b) Bergman, R. G. Acc. Chem. Res. **1973**, 6, 25–31. (c) Greer, E. M.; Lavinda, O. J. Org. Chem. **2010**, 75, 8650–8653. (d) Vavilala, C.; Byrne, N.; Kraml, C. M.; Ho, D. M.; Pascal, R. A., Jr. J. Am. Chem. Soc. **2008**, 130, 13549–13551.

^{(2) (}a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. J. Am. Chem. Soc.
1989, 111, 8057. (b) Myers, A. G.; Dragovich, P. S. J. Am. Chem. Soc.
1989, 111, 9130. (c) Nechab, M.; Campolo, D.; Maury, J.; Perfetti, P.;
Vanthuyne, N.; Siri, D.; Bertrand, M. P. J. Am. Chem. Soc. 2010, 132, 14742–14744. (d) Schmittel, M.; Strittmatter, M.; Kiau, S. Tetrahedron Lett. 1995, 36, 4975–4978. (e) Schmittel, M.; Strittmatter, M.; Kiau, S. Angew. Chem., Int. Ed. Engl. 1996, 35, 1843–1845. (f) Vavilala, C.; Bats, J. W.; Schmittel, M. Synthesis 2010, 13, 2213–2222.

^{(3) (}a) Nicolaou, K. C.; Dai, W. M. Angew. Chem., Int. Ed. Engl.
(3) (a) Nicolaou, K. C.; Dai, W. M. Angew. Chem., Int. Ed. Engl.
(1991, 30, 1387–1416. (b) Choi, T. A.; Czerwonka, R.; Fröhner, W.;
(1991, 30, 1387–1416. (c) Choi, T. A.; Czerwonka, R.; Fröhner, W.;
(1991, 30, 1387–1416. (c) Choi, T. A.; Czerwonka, R.; Fröhner, W.;
(1991, 30, 1387–1416. (c) Choi, T. A.;
(2006, 1, 812–815. (c) Thevissen, K.; Marchand, A.; Chaltin,
(2006, 1, 812–815. (c) Thevissen, K.; Marchand, A.; Chaltin,
(2007), P.; Meert, E. M. K.; Cammue, B. P. A Curr. Med. Chem. 2009, 16, 2205–2211.

^{(4) (}a) Alabugin, I. V.; Gilmore, K.; Patil, S.; Manoharan, M.; Kovalenko, S. V.; Clark, R. J.; Ghiviriga, I. J. Am. Chem. Soc. 2008, 130, 11535–11545. (b) Sakai, S.; Nishitani, M. J. Phys. Chem. A 2010, 114, 11807–11813. (c) Prall, M.; Wittkopp, A.; Schreiner, P. R. J. Phys. Chem. A 2001, 105, 9265–9274. (d) Sakai, S.; Nishitani, M. J. Phys. Chem. A 2010, 114, 11807–11813. (e) Chen, H. T.; Chen, H. L.; Ho, J. J. J. Phys. Org. Chem. 2010, 23, 134–140.

^{(5) (}a) Gillmann, T.; Isen, T. H.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257–1259. (b) Garcia, J. G.; Ramos, B.; Pratt, L. M.; Rodriguez, A. *Tetrahedron Lett.* **1995**, *36*, 7391–7394.

⁽⁶⁾ Schmittel, M.; Mahajan, A. A.; Bucher, G. J. Am. Chem. Soc. 2005, 127, 5324–5325.

⁽⁷⁾ Zhang, Y.; Petersen, J. L.; Wang, K. K. *Tetrahedron* **2008**, *64*, 1285–1293.

Scheme 1. The Myers-Saito and the Schmittel Cyclizations



recently independently reported by Schmittel⁶ and Wang⁷ (Scheme 2).

Scheme 2. Enyne-Allene Cascade Cyclization



Because the thermal cyclizations require high temperature, efforts have been aimed at conducting diradical cyclization under milder conditions. In 2005, Schmittel reported the photochemical envne-allene C2-C6 cyclization⁶ (Scheme 2A). Cyclization products 1a and 1b were obtained in modest yields (15%) with poor selectivity (1:1). It was expected that the diradical conformers A and B were under equilibrium (A as the energetically favored conformer with minimized steric repulsion). To obtain the sequential cyclization product 1a, Wang and co-workers reported an alternative thermal strategy⁷ (Scheme 2B), which used a bulky tert-butyl group to push the diradical equilibrium toward B conformer. Compound 1c was then successfully obtained with improved yields. Later, Wang and co-workers demonstrated the synthetic utility of this method for the preparation of heteroaromatic and polyaromatic structures.⁸

While the C2–C6 cyclization was mechanistically interesting and synthetically inspiring, there were limitations. First, the reaction conditions required high temperature and the overall efficiency was low. Second, the sterically hindered group was required to drive the equilibrium to conformer **B** for effective aromatic cyclization, thereby limiting the reaction scope. Herein, we report the triazolegold (TA-Au, 3 mol %) catalyzed propargyl vinyl ether cascade rearrangement and cyclization to form the desired benzannulated indenes at room temperature. The key aspects for this work are: (a) the use of TA-Au catalysts offered excellent chemoselectivity for selective formation of allene intermediates with no further activation; (b) the ability to form the highly reactive envne-allene intermediates under mild conditions, allowing effective diradical cyclization without the assistance from bulky substituted group. As a result, the previously challenging non-tertbutyl substituted envne-allenes Schmittel cyclization (Scheme 3) was successfully achieved for the first time.

Scheme 3. The Challenging Non-tert-butyl Substrates



As shown in Scheme 3, the identical thermal conditions did not work for phenyl-substituted alkyne 2a and 2b even though they were derivatives of compounds shown in Scheme 2B. This was caused either by the difficulty in 1,3-H-shift for the synthesis of allene (2a) or by the rapid decomposition of the diradical. Considering that the proper conformation of diradical intermediate C was required for the cyclization between phenyl and vinyl radical and the harsh conditions likely caused the decomposition prior to the conformation equilibrium. We postulated that the Schmittel cyclization of these challenging substrates might be achieved by conducting the reaction under milder conditions (such as room temperature) to avoid the diradical decomposition. The key is then to identify strategies that allow effective synthesis of envne-allene under mild conditions.

In the past several years, our group has been working on the application of 1,2,3-triazoles as ligands in adjusting transition metal catalyst reactivity.⁹ Several new 1,2,3triazole coordinated metal catalysts/reagents have been

 ^{(8) (}a) Wen, B.; Petersen, J. L.; Wang, K. K. Chem. Commun. 2010,
 46, 1938–1940. (b) Cui, H.; Akhmedov, N. G.; Petersen, J. L.; Wang,
 K. K. J. Org. Chem. 2010, 75, 2050–2056.

^{(9) (}a) Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Shi, X. *Adv. Syn. Catal.* **2011**, *353*, 2584–2588. (b) Wang, D.; Zhang, Y.; Cai, R.; Shi, X.; Beilstein J. Org. Chem. **2011**, *7*, 1014–1020. (c) Wang, D.; Gautam, L. N. S.; Bollinger, C.; Harris, A.; Li, M.; Shi, X. Org. Lett. **2011**, *13*, 2618–2621. (d) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N.; Shi, X. J. Am. Chem. Soc. **2009**, *131*, 12100–12102. (e) Duan, H.; Yan, W.; Sengupta, S.; Shi, X. Bioorg. Med. Chem. Lett. **2009**, 3899–3902.

recently discovered.¹⁰ One particularly interesting triazole complex was the triazole–gold catalyst (TA–Au), which exhibited unique reactivity toward alkyne activations.^{9e} For example, our group recently reported the asymmetric synthesis of substituted allenes through propargyl ether rearrangement at room temperature with TA–Au catalyst. Unlike other conventional $[L-Au]^+$ catalysts, the TA–Au offered excellent chemoselectivity, selectively activating alkynes over allenes.^{9b,c}

This new catalyst provided the opportunity to investigate our hypothesis, achieving selective C2–C6 Schmittel cyclization of the challenging 1,3-disubstituted allenes (nobulky substituted group on phenyl terminal) under milder conditions. To test our hypothesis, propargyl vinyl ether **4a** and propargyl ester **4a'** were prepared and treated with various gold catalysts as shown in Figure 1.



Figure 1. The Schmittel cyclization at room temperature.

Both propargyl vinyl ether and propargyl ester could undergo 1,3-migration through gold catalyzed alkyne activation.^{9b,c} The concern was whether TA-Au could selectively activate the propargyl alkyne other than the other triple bond and allene intermediate. The screening of catalysts revealed that common $[L-Au]^+$ catalysts, including [PPh₃Au]⁺, [iPrAu]⁺, and [XPhosAu]⁺, gave complex reaction mixtures with no desired products observed, due to the poor chemoselectivity. Using TA-Au catalyst, the desired aldehyde 5a was successfully obtained (which was subsequently reduced to alcohol 6a for easy isolation with 35% isolated yields over two steps). Notably, the reaction with TA-Au catalyst was "clean" and the only cyclization product observed was 6a. The major side reaction was the polymerization. No C2-C7 or other cyclization products were identified. The overall yield, though modest, was significantly higher than both photoinitiation (15%) and thermal condition (0%). Treatment of propargyl ester 4a' with gold catalysts gave no reactions, which was likely caused by the unfavored propargyl ester 3,3-migration.

The structure of 6a was confirmed by the X-ray diffrac-



Figure 2. X-ray structure of 7a.

tion of the corresponding tosyl derivatives **7a** as shown in Figure 2. Overall, this result supported our hypothesis that (A) enyne–allene cyclization was energetically favored and could occur at room temperature, and (B) TA–Au catalyst could selectively activate the propargyl ether, generating the allene intermediates that allowed the subsequent aromatization. To the best of our knowledge, this is the first example of an enyne–allene C2–C6 cyclization at room temperature without the aid from bulky substituents.

Table 1. Screening of the Reaction Conditions^a

4a	1) 3 % TA – Au, DCM			
	2) NaBH ₄ , MeOH	—→ 5a		

entry	$concn\left(M\right)$	$temp(^{\circ}C)$	time	conv (%)	yield $(\%)^b$
1	0.075	rt	$15 \min$	>99	37
2	0.075	$^{-10}$	24 h	0	ND
3	0.075	0	6 h	>99	44
4	0.1	0	6 h	>99	48
5	0.2	0	4 h	>99	32
5	0.01	0	48 h	>99	20
6	0.005	0	48 h	>99	12

^{*a*} General reaction condition: **4a** (0.2 mmol), catalyst (3 mol %) in solvent (2 mL), the reactions were monitored by TLC, 0 °C to rt. ^{*b*} Conversion and yields were determined by NMR with 1,3,5-trimethoxybenzene as internal standard.

Screening of solvents revealed dichloromethane as the optimal solvent (see details in Supporting Information). Considering that polymerization was the major side reaction, different concentrations and reaction temperatures were evaluated (Table 1). The TA-Au catalyst lost reactivity at -10 °C. Lowering the reaction temperature to 0 °C improved the overall reaction yield to 48%.

Some representative aromatic substituents at the allene termini were prepared to evaluate the reaction substrate scope. The results are summarized in Figure 3.

^{(10) (}a) Ladouceur, S.; Fortin, D.; Zysman-Colman, E. *Inorg. Chem.* **2011**, *50*, 11514–11526. (b) Inomata, S.; Hiroki, Hi.; Terashima, T.; Ogata, K.; Fukuzawa, S. *Tetrahedron* **2011**, *67*, 7263. (c) Uppal, B. S.; Booth, R. K.; Ali, N.; Lockwood, C.; Rice, C. R.; Elliott, P. I. P. *Dalton Trans.* **2011**, *40*, 7610–7616.



Figure 3. Substrate scope.

As indicated in Figure 3, the C2–C6 cyclization could occur for both electron donating and electron withdrawing substituents on the aromatic rings. Electron withdrawing groups gave significantly improved yields by reducing the undesired diradical polymerization.¹¹ Conjugation did not show significant influence to the cyclization, which was consistent with the proposed mechanism that involved a highly reactive diradical intermediate. To further evaluate the reaction mechanism, propargyl vinyl ether with "reversed" substitution pattern (8a) and TMS-substituted al-kyne (8b) were prepared and reacted with TA–Au catalyst.

As shown in Figure 4A, propargyl ether **8a** 1,3-rearragnement would produce the trisubstituted allene. Under the photocyclization condition shown in Scheme 2A, the diradical intermediates proceeded through two different reaction paths, which should lead to the formation of **9a** and **9a'**. Interestingly, the TA-Au catalyzed conditions gave exclusively **9a** as the cyclization product. This might be explained by the mild reaction conditions that favored the aromatic cyclization instead of the elimination (formation of **9a'**), which highlighted the significantly improved selectivity of this method over thermal and photo conditions. Switching the alkyne termini substituents from Ph to TMS helped to successfully isolate the proposed allene intermediate **9b** (Figure 4B, decreasing



Figure 4. Mechanism investigations.

cyclization reaction rates), which provided another solid evidence for the proposed mechanism and the unique reactivity of TA-Au (activate alkyne over allene).

In conclusion, reported herein is a new catalytic version of the Schmittel cyclization. The TA–Au catalyst offered impressive chemoselectivity, activating the specific alkynes only, which allowed the sequential cyclization to occur at much milder conditions. Both the allene intermediate and the final products were unambiguously confirmed. As a result, an effective new strategy was uncovered under much milder conditions and enhanced substrate scope (substrates that could not be achieved with previously reported thermal or photo conditions). Therefore, this new method opens the possibility for mechanistic investigation and new diradical based drug discovery by this interesting enyne-allene cyclization process.

Acknowledgment. We thank the NSF (CHE-0844602), WVU-PSCoR for financial support.

Supporting Information Available. Experimental details, characterization data, spectrographic data and CIF file of compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

^{(11) (}a) Xiao, Y.; Hu, A. *Macromol. Rapid Commun.* **2011**, *32*, 1688–1698. (b) Ma, J.; Ma, X.; Deng, S.; Li, F.; Hu, A. J. Polym. Sci., Part A: Polym. Chem. **2011**, *49*, 1368–1375.

The authors declare no competing financial interest.