

Tandem Ruthenium-Catalyzed Redox Isomerization—O-Conjugate Addition: An Atom-Economic Synthesis of Cyclic Ethers

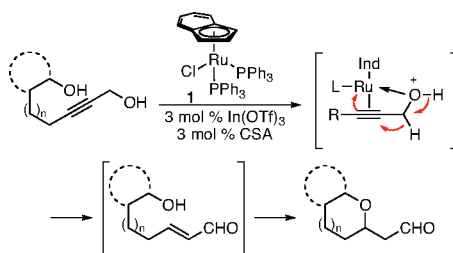
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ABSTRACT



An atom-economical method for the convenient synthesis of tetrahydropyrans and tetrahydrofurans is reported. Enones and enals derived from the [IndRu(PPh₃)₂Cl]-catalyzed redox isomerization of primary and secondary propargyl alcohols undergo a subsequent intramolecular conjugate addition to provide cyclic ethers in excellent yields.

A primary focus in our laboratory is the invention and use of atom-economical reactions for the rapid construction of molecular complexity from relatively simple starting materials. Toward this end, we have frequently employed alkynes as the key building blocks from which an array of functionalities can be accessed.¹ Alkynes are particularly well-suited to this strategy because of the exceptional ease and chemoselectivity with which they can be installed, particularly when they are substituted with propargyl alcohols, and the diversity of functional groups (including 1,3- and 1,4-dienes, enones, enals,

dienones, dienals, vinyl halides, and vinyl silanes) to which they can be converted.² When used as synthetic equivalents of more reactive moieties, their robust nature obviates the need for protecting groups.

(2) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995.

(3) Examples of tetrahydropyran- and tetrahydrofuran-containing natural products include Bryostatin, Salinomycin, Latrunculin A, Spongistatin 1, Swinholide A, Hemibrevitoxin B, Glabrescol, Pamamycin 607, and Sclerophytin A.

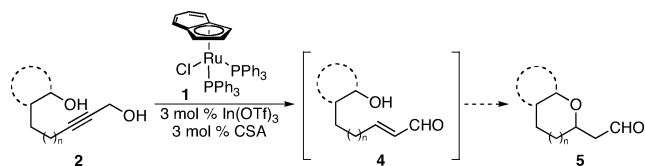
(4) For reviews containing leading references on the development of methods for the synthesis of tetrahydropyrans, tetrahydrofurans, and oxepanes, see: (a) Piccialli, V. *Synthesis* **2007**, 17, 2585. (b) Elliot, M. C. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 2301. (c) Boivin, T. L. *Tetrahedron* **1987**, 43, 3309. Recent advances: (d) Zhu, H.; Wickenden, J. G.; Campbell, N. E.; Leung, J. C. T.; Johnson, K. M.; Sammis, G. M. *Org. Lett.* **2009**, 11, 2019. (e) Fu, G. C.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2009**, 48, 2225. (f) Dzudza, A.; Marks, T. *Org. Lett.* **2009**, 11, 1523. (g) Gonzalez-Rodriguez, C.; Escalante, L.; Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2009**, 11, 1531. (h) Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2008**, 49, 7153. (i) Kimishima, A.; Nakata, T. *Tetrahedron Lett.* **2008**, 49, 6563. (j) Jamison, T. F.; Vilotijevic, I. *Science* **2007**, 317, 1189. (k) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, 46, 6874. (l) Yadav, J. S.; Rajasekhar, K.; Murty, M. S. *Synlett* **2005**, 12, 1945. (m) Trost, B. M.; Yang, H.; Wuitschik, G. *Org. Lett.* **2005**, 7, 4761.

(1) Reviews containing leading references in this area: (a) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, 44, 6630. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, 35, 695. (c) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, 101, 2067. Recent advances: (d) Trost, B. M.; Bertogg, A. *Org. Lett.* **2009**, 11, 511. (e) Trost, B. M.; Ashfeld, B. L. *Org. Lett.* **2008**, 10, 1893. (f) Trost, B. M.; Ferreira, E. M.; Gutierrez, A. C. *J. Am. Chem. Soc.* **2008**, 130, 16176. (g) Trost, B. M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* **2008**, 130, 17258. (h) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, 128, 6745. (i) Trost, B. M.; McClory, A. *Org. Lett.* **2006**, 8, 3627. (j) Trost, B. M.; Huang, X. *Chem. Asian J.* **2006**, 1, 469.

Functionalized tetrahydropyrans (THPs) and tetrahydrofurans (THFs) are ubiquitous motifs in biologically significant natural products and medicinal agents.³ Due to the structural diversity of these units in targets of interest, numerous methods have been developed for their synthesis.⁴

Previously we have shown that catalyst **1**, along with cocatalysts indium(III) triflate and camphorsulfonic acid (CSA), can effect the redox isomerization of propargyl alcohols to enals and enones.⁵ We envisioned that heterocycles such as THPs and THFs could be constructed from propargyl alcohols such as **2** utilizing a redox isomerization–conjugate addition sequence (Scheme 1). The proposed

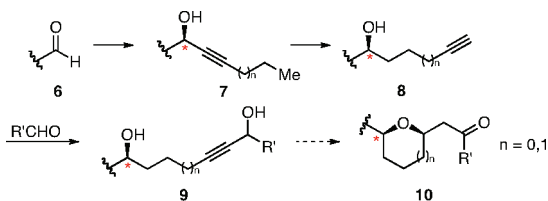
Scheme 1. Tandem Redox Isomerization–Conjugate Addition to Generate Cyclic Aldehydes



sequence involves the isomerization of a propargyl alcohol containing a pendant alcohol (**2**) to furnish the corresponding enal (**4**), capable of spontaneous cyclization to cyclic ether **5**.⁶

If successful, this method would provide quick access to cyclic ethers, allowing for their introduction via simple addition chemistry. Several groups,⁷ including ours,⁸ have developed enantioselective methods for constructing chiral propargyl alcohols. With chiral propargyl moiety **7** in hand, isomerization of the internal alkyne to the terminal alkyne using the base-promoted “acetylene zipper” reaction⁹ followed by deprotonation and addition of terminal alkyne **8** into an aldehyde (R'CHO) would provide the requisite precursor **9** for the formation of cyclic ether **10** (Scheme 2).

Scheme 2. Facile Access to Cyclic Ethers



We anticipated that this method would form THPs with high diastereoselectivity, given the thermodynamic preference for cis- over trans-substitution in 2,6-disubstituted THPs, and form THFs with reduced diastereoselectivity.^{2,10,11}

(5) (a) Trost, B. M.; Livingston, R. B. *J. Am. Chem. Soc.* **1995**, *117*, 9586. (b) Trost, B. M.; Livingston, R. B. *J. Am. Chem. Soc.* **2008**, *130*, 11970.

(6) While preparing the current manuscript, this was demonstrated by our group with nitrogen nucleophiles: Trost, B. M.; Maulide, N.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 16502.

Indeed, when propargyl alcohol **11**, which bears a pendant hydroxy group, was submitted to the redox isomerization conditions, THP **12** was obtained along with the uncyclized, isomerized product **13** in a 21:65 ratio (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions

entry	mol % 1	cocatalyst	acid	time (h)	convn (%) ^a	yield ^b
1	5	40% InCl ₃	10% Et ₃ NHFPF ₆	1.25	100	21% 12 , 65% 13
2	5	40% InCl ₃	10% Et ₃ NHFPF ₆	4	100	70% 12
3 ^c	5	40% InCl ₃	10% Et ₃ NHFPF ₆	1.5	100	78% 12
4 ^d	5	40% InCl ₃	10% Et ₃ NHFPF ₆	1.5	100	—
5	5	40% InCl ₃	10% Et ₃ NHFPF ₆ , 20% CSA	1.5	100	—
6	5	20% InCl ₃	10% Et ₃ NHFPF ₆ , 20% CSA	1.5	93	—
7	5	—	10% Et ₃ NHFPF ₆ , 50% CSA	3	86	—
8	5	—	10% Et ₃ NHFPF ₆ , 100% CSA	3	94	—
9	2	5% In(OTf) ₃	10% CSA	0.25	87	—
10	3	5% In(OTf) ₃	5% CSA	0.25	98	—
11	3	5% In(OTf) ₃	10% CSA	0.25	92	—
12	3	5% In(OTf) ₃	5% CSA	1	100	75% 12
13	3	3% In(OTf) ₃	20% CSA	1.5	100	80% 12
14	10	10% AgOTf	40% TsOH	6	100	—
15	5	5% AgOTf	20% TsOH	6	35	—

^a Conversion refers to the consumption of **11**; determined by GC and NMR. ^b Isolated yield. ^c Addition of 40% TsOH and continued reflux (15 min) after completion of isomerization. ^d Addition of 40% CSA and continued reflux (15 min) after completion of isomerization.

Increasing the reaction time allowed complete cyclization to the THP (entry 2). It was also found that the degree of cyclization was pH-dependent and that the addition of strong acids allowed isolation of the cyclized product exclusively (entries 3–15). Under the indium(III) trichloride conditions, addition of *p*-toluenesulfonic acid (TsOH) and continued reflux after the isomerization was complete gave good yields of the corresponding THP (entry 3). Additional studies revealed that the procedure could be reduced to one step by including a stronger Brønsted acid during the isomerization (entries 5–13). The essential role of the indium cocatalyst was revealed by adding high-to-stoichiometric amounts of CSA without the indium cocatalyst; in these cases, the

(7) For reviews, see: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (b) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. Recent advances: (c) Xu, Z.; Mao, J.; Zhang, Y. *Org. Biomol. Chem.* **2008**, *6*, 1288. (d) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901. (e) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457. (f) Hsieh, S.-H.; Gau, H.-M. *Synlett* **2006**, *12*, 1871.

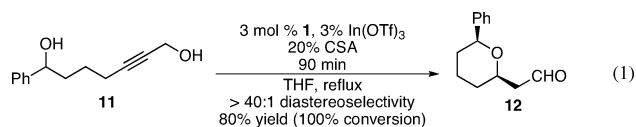
(8) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8.

(9) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171.

(10) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*, 3rd ed.; Plenum Press: New York, 1990; Chapter 3.

(11) Similar diastereoselectivities have been observed by ourselves and others in the formation of saturated heterocycles under thermodynamic conditions: Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819.

reaction failed to reach quantitative conversion (entries 7 and 8). Further examination of cocatalysts revealed that indium(III) triflate could be used in significantly lower amounts (entries 9–13) than indium(III) trichloride (entries 3–6) to achieve higher conversion with shorter reaction times. Replacing indium triflate with silver triflate slowed down the reaction significantly and typically led to inferior results (entries 14 and 15). Ultimately, the indium(III) triflate conditions proved capable of effecting the tandem isomerization and cyclization in good yields with low loadings of all components (entry 13). Thus, with 3% indium(III) triflate and 20% CSA, **12** could be obtained as the sole product. As anticipated, the product THP was formed with complete selectivity for the *cis* diastereomer (eq 1).¹²



Employing these optimized conditions, we were able to construct a variety of functionalized tetrahydropyrans (Table 2). As demonstrated by **12** and **14b**, aldehyde acceptors are transformed in good yields to the corresponding THPs (entries 1 and 2). In addition to enals, enones are competent

Table 2. Scope of Redox Isomerization–Conjugate Addition in the Formation of Tetrahydropyrans^a

entry	propargyl alcohol	product	isolated yield
1			80%
2			50%
3			71%
4 ^b			85%
5			86%
6			53%

^a All reactions run as in eq 1 for a period of 2 h unless otherwise stated.

^b Reaction run for 4 h with 40% CSA.

conjugate acceptors, furnishing THPs with pendant ketone moieties in high yields (entries 3–6). Keto-ether **15b** was formed from **15a** in 71% yield (entry 3). Bicyclic products such as **14b** and **16b** were obtained in moderate to high yields (50% and 85%, entries 2 and 4) and excellent dr (>40:1). Ynols containing pendant alkynes were also tolerated, providing cyclized products in high yields (entries 5 and 6). We were pleased to find the electrophilic ynoate moiety present in **18a** and **18b** was maintained; products derived from conjugate addition to the pendant alkyne were not observed.

To investigate the formation of tetrahydrofurans using this method, **19a** was prepared and subjected to the optimized reaction conditions; as expected, THF **19b** was formed in 77% yield (Table 3, entry 1). Sterically unencumbered esters

Table 3. Scope of Redox Isomerization–Conjugate Addition in the Formation of Tetrahydrofurans^a

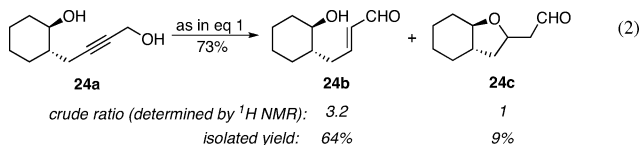
entry	propargyl alcohol	product	isolated yield
1			77%
2			77%
3			72%
4			75%
5			72%

^a All reactions run as in eq 1.

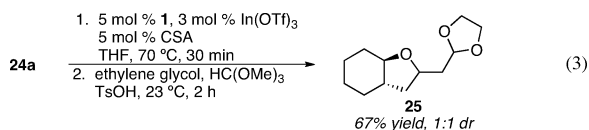
were also compatible; ester-ynol **20a** formed THF **20b** in 77% yield (entry 2). To examine the inherent diastereoselectivity in the formation of tetrahydrofurans, **21a** was synthesized and tested. While **21b** was formed in an excellent 72% yield, cyclization occurred without the diastereocontrol observed for the THPs (entry 3). This can be ascribed to the reduced energy difference between the *cis*- and *trans*-2,5-disubstituted THF system, as compared to the analogous *cis*- and *trans*-2,6-disubstituted THP system.

We were pleased to find that substrates such as **22a**, a 1,6-enyne, and **23a**, a 1,6-diyne, were tolerated (entries 4

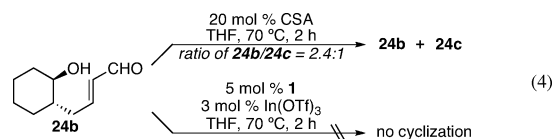
and 5). This is particularly impressive as the two points of unsaturation in the substrate are positioned so that they might tightly bind to the cationic ruthenium catalyst in a bidentate fashion and prevent catalyst turnover. When **24a** was exposed to the redox isomerization conditions, a mixture of linear and cyclized products was obtained, albeit in 73% overall yield (eq 2). We had surmised that the strained 6,5-ring system might be difficult to form, and it was therefore not surprising that the linear product **24b** was favored over THF **24c**, in contrast to the 6,6-trans-fused system (Table 2, entry 2). While the ^1H NMR spectrum of the crude reaction



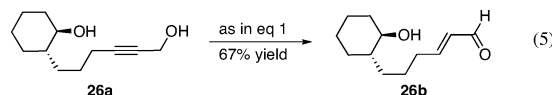
the ratio of cyclized to linear products to be 1:3.2, respectively, only 9% of the cyclized product was isolated, along with 64% of **24b**. Doubling the reaction time increased the ratio to 1:1.5 (cyclized/linear), concomitant with the formation of several decomposition products. The reluctance of **24b** to undergo the conjugate addition could be overcome by use of a two-step, one-pot protocol. Upon completion of the redox isomerization (30 min), addition of ethylene glycol, trimethyl orthoformate, and TsOH followed by continued stirring at room temperature afforded acetal **25** in 67% isolated yield (eq 3).



In an effort to determine the degree of catalyst participation in the conjugate addition, linear product **24b** was exposed to **1** and indium(III) triflate in the absence of CSA. After 2 h, none of the cyclized product was observed (eq 4). In contrast, treating **24b** with catalytic CSA in the absence of both **1** and indium(III) triflate resulted in conversion of 29% of **24b** to **24c**. Thus, it is unlikely that the ruthenium catalyst is involved in the cyclization event.



Unfortunately, efforts to form oxepanes via the isomerization–conjugate addition sequence did not generate the desired cyclic products. Extended reaction times and higher acid loadings did not effect the cyclization; only the linear, isomerized product **26b** was isolated from diol **26a** in 67% yield (eq 5).



The tandem redox isomerization–O–conjugate addition allows for the facile construction of THFs and THPs from readily accessible starting materials. The reaction is simple, robust, and exceptionally mild, a quality demonstrated by its tolerance of a wide variety of functional groups. Low catalyst loadings and short reaction times further enhance the utility of this transformation. Additionally, the cyclic ethers derived from this sequence contain a pendant carbonyl that can be used for further elaboration. Currently our efforts are focused on improving the diastereoselectivity of the reaction to form disubstituted THFs and investigations of synthetic applications.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Diastereomer determined by diagnostic value of coupling constants (J).