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Highly Efficient Synthesis of Tri- and Tetrasubstituted Conjugated Enynes from Brønsted Acid Catalyzed Alkoxylation of 1-Cyclopropylprop-2-yn-1-ols with Alcohols

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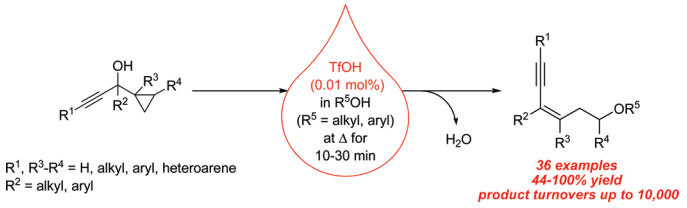

A highly efficient triflic acid catalyzed ring opening of a wide variety of 1-cyclopropyl-2-propyn-1-ols with alcohols as an efficient synthetic route to conjugated enynes is reported herein. The reaction was operationally straightforward and accomplished in good to excellent yields (44−100%), high product turnovers (up to 10,000), and with complete regioselectivity under mild conditions with a low catalyst loading of 0.01 mol %. The mechanism is suggested to involve protonation of the alcohol substrate by the TfOH catalyst, followed by ionization of the starting material. This causes ring opening of the cyclopropane moiety and trapping by the alcohol nucleophile to give the conjugated enyne product. The synthetic utility of the present method was also exemplified by the efficient large-scale conversion in gram quantities of one example studied in this work to the corresponding conjugated enyne product in excellent yield and turnover number.

Introduction

Conjugated enynes are important targets in organic synthesis because of their demonstrated versatility as intermediates in numerous strategies to compounds of current biological and materials interest. For this reason, simple methods that can install this unsaturated hydrocarbon moiety are highly desirable.[1] This is all the more so if it can be achieved without the competitive formation of undesired regio- and stereoisomers, examples of which have remain sparse.[1−4] We[3] and others[4] recently reported one such approach that gave conjugated enynes as single regioisomers from Au-, Ru_2-, or Yb-catalyzed ring opening of 1-cyclopropyl-2-propyn-1-ols with *N*- and *O*-centered nucleophiles. Although shown to be efficient, producing H_2O as potentially the only byproduct, the potential of this method for scale-up applications has been lessened by the need for high catalyst loadings. Added to this is the cost of the catalyst in reactions mediated by gold and ruthenium and a substrate scope limited to ones containing functional groups that cannot take part in strong metal coordination. In this regard, we envisioned that developing a Brønsted acid catalyzed version of this regioselective enyne forming reaction could hold promise as the basis to re-addressing these shortcomings. An inexpensive and commercially available reagent class that has a high tolerance to air and moisture, Brønsted acids have been reported to be versatile in mediating a wide

(1) For recent reviews, see: (a) Shirtcliff, L. D.; McClintock, S. P.; Haley, M. M. *Chem. Soc. Rev.* **2008**, *37*, 343. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (d) Zeni, G.; Braga, A. L.; Stefani, H. A. *Acc. Chem. Res.* **2003**, *36*, 731.

(2) For recent examples, see: (a) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. *J. Am. Chem. Soc.* **2006**, *128*, 5592. (b) Zhang, L.-M.; Wang, S.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Pahadi, N. K.; Camacho, D. H.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 1152. (d) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130.

(3) (a) Rao, W.; Zhang, X.; Sze, E. M. L.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 1740. (b) Rao, W.; Chan, P. W. H. *Chem.—Eur. J.* **2008**, *14*, 10486.

(4) (a) Yamauchi, Y.; Onodera, G.; Sakata, K.; Yuki, M.; Miyake, Y.; Uemura, S.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 5175. (b) Xiao, H.-Q.; Shu, X.-Z.; Ji, K.-G.; Qi, C.-Z.; Liang, Y.-M. *New J. Chem.* **2007**, *31*, 2041.

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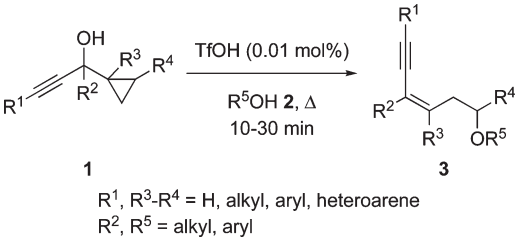
variety of organic transformations in excellent yields and with high selectivity.[5] In recent years, this has hitherto included stereoselective Brønsted acid mediated C−X (X = C, N, O, S) bond formation strategies that make use of alcohol pro-electrophiles such as allylic, benzylic, and propargylic alcohols.[6] To our knowledge, however, an efficient Brønsted acid catalyzed protocol for the regioselective synthesis of conjugated enynes from 1-cyclopropyl-2-propyn-1-ols has not been extensively explored.[7] As part of a program examining the utility of alcohols as pro-electrophiles in organic synthesis,[3,8] we report herein TfOH-catalyzed ring opening of 1-cyclopropyl-2-propyn-1-ols with alcohols (Scheme 1).[9] The conjugated enyne products were afforded in excellent yields, high product turnovers, and regioselectivities comparable to those reported for the closely related metal-promoted approaches to this synthetically useful building block.

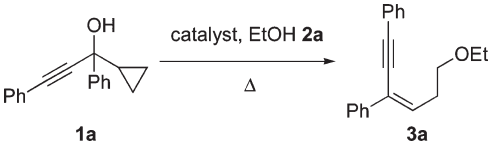
SCHEME 1. Regioselective TfOH-Catalyzed Synthesis of Conjugated Enyne from 1-Cyclopropyl-2-propyn-1-ols



Results and Discussion

All 1-cyclopropyl-2-propyn-1-ols studied in this work were prepared from reaction of the corresponding cyclopropyl ketone and substituted alkyne pretreated with LDA or ethynylmagnesium bromide in place of the alkyne and LDA, or alkynone with cyclopropylmagnesium bromide following literature procedures.[10] With 1-cyclopropyl-1,3-diphenylprop-2-yn-1-ol **1a** and EtOH **2a** as the probe substrates, a survey of different reaction conditions initially revealed alkoxylation of **1a** with a 2 mL stock solution of **2a** containing 5 mol % of TfOH at reflux for 15 min gave the best result (Table 1, entry 1). Under these conditions, (*Z*)-(6-ethoxyhex-3-en-1-yne-1,3-diyl)dibenzene **3a** was obtained as the sole product in quantitative yield. The *cis*-stereochemistry of the conjugated enyne product was confirmed by comparison with X-ray crystallographic analysis and NOE spectroscopic data of closely related adducts (vide infra) and reported literature values.[3,4] Our studies subsequently showed that a gradual decrease in the catalyst loading of TfOH from 5 to 1 to 0.1 to 0.01 mol % was found to result in no apparent loss in catalytic activity, and in each of these reactions the same product yield was attained (entries 3−5). On the other hand, further

TABLE 1. Optimization of Reaction Conditions[a]



entry	catalyst	catalyst loading (mol %)	solvent	yield (%)	product turnover
1	TfOH	5		100	20
2[b]	TfOH	5		81	16
3	TfOH	1		100	100
4	TfOH	0.1		100	1 000
5	TfOH	0.01		100	10 000
6	TfOH	0.005		49	9 800
7	TfOH	0.001		−[c]	−
8[d]	TfOH	0.01	PhMe	75	7 500
9[d]	TfOH	0.01	$(CH_2Cl)_2$	70	7 000
10[d]	TfOH	0.01	THF	65	6 500
11	Tf_2NH	0.01		20	2 000
12[e]	*p*-TsOH	5		55	11
13[f]	TFA	5		40	8
14[f]	HCl	5		10	2

[a]All reactions were performed at reflux for 15 min with 0.2 mmol of **1a** in 2 mL of **2a**. [b]Reaction conducted at room temperature for 24 h. [c]No reaction based on TLC and ^{1}H NMR analysis of the crude mixture. [d]Reaction conducted with 5 equiv of **2a**. [e]Reaction conducted for 24 h. [f]Reaction conducted for 2 h.

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(6) For reviews on the use of alcohols as pro-electrophiles, see: (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (c) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (d) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (e) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647. For selected examples on Brønsted acid catalyzed reactions with alcohol pro-electrophiles, see: (e) Bras, J. L.; Muzart, J. *Tetrahedron* **2007**, *63*, 7942. (f) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642. (g) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 2027. (h) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 727. (i) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311. (j) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841. (k) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605. (l) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383. (m) Young, J.-J.; Jung, L.-J.; Cheng, K.-M. *Tetrahedron Lett.* **2000**, *41*, 3415.

(7) Liang and co-workers reported one example of *p*-TsOH-catalyzed alkoxylation of a 1-cyclopropyl-2-propyn-1-ol with MeOH that gave the corresponding conjugated enyne product in 58% yield; see ref 4b.

(8) (a) Zhang, X.; Rao, W.; Sally; Chan, P. W. H. *Org. Biomol. Chem.* **2009**, DOI: 10.1039/B908447A. (b) Kothandaraman, P.; Rao, W.; Zhang, X.; Chan, P. W. H. *Tetrahedron* **2009**, *65*, 1833. (c) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426. (d) Zhang, X.; Rao, W.; Chan, P. W. H. *Synlett* **2008**, *special issue*, 2204. (e) Wu, W.; Rao, W.; Er, Y. Q.; Loh, K. J.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620; *Tetrahedron Lett.* 2008, *49*, 4981. (f) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122; *Tetrahedron Lett.* 2008, *49*, 5112.

(9) For selected examples of other reactions mediated by TfOH, see: (a) Juma, B.; Adeel, M.; Villinger, A.; Reinke, H.; Spannenberg, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1073. (b) Singh, R.; Parai, M. K.; Panda, G. *Org. Biomol. Chem.* **2009**, *7*, 1858. (c) Li, A.; DeSchepper, D. J.; Klumpp, D. A. *Tetrahedron Lett.* **2009**, *50*, 1924. (d) Zhu, Z.-B.; Shi, M. *J. Org. Chem.* **2009**, *74*, 2481. (e) Kalbarczyk, K. P.; Diver, S. T. *J. Org. Chem.* **2009**, *74*, 2193. (f) Lu, J.-M.; Zhu, Z.-B.; Shi, M. *Chem.—Eur. J.* **2009**, *15*, 963. (g) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (h) Li, X.; Ye, S.; He, C.; Yu, Z.-X. *Eur. J. Org. Chem.* **2008**, 4296. (i) Li, W.; Shi, M. *J. Org. Chem.* **2008**, *73*, 4151. (j) Abid, M.; Teixeira, L.; Török, B. *Org. Lett.* **2008**, *10*, 933. (k) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (l) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (m) Coulombel, L.; Duñach, E. *Green Chem.* **2004**, *6*, 499. (n) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

(10) Please refer to Supporting Information, refs 3 and 4, and see: (a) Enholm, E. J.; Jia, Z. J. *J. Org. Chem.* **1997**, *62*, 9159. (b) Toda, F.; Imai, N. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2673.

investigations showed that reducing the catalyst loading 2-fold to 0.005 mol % gave **3a** in a lower yield of 49% (entry 6). Moreover, no product formation could be detected by TLC or ^{1}H NMR analysis of the crude mixture when 0.001 mol % of TfOH was employed, even on extending the reaction time to 20 h (entry 7). Similarly, a lower product yield of 81% was obtained on repeating the reaction with 5 mol % of TfOH at room temperature for 24 h (entry 2). In addition, comparable product yields of 65−75% were afforded when the reaction was repeated with 5 equiv of **2a** in solvents such as toluene, 1,2-dichloroethane, and THF (entries 8−10). Performing the reaction with other inexpensive and commercially available Brønsted acid catalysts was also found to be less effective (entries 11−14). In these latter reactions, the use of 0.01 mol % of Tf_2NH or 5 mol % of *p*-TsOH, TFA, and HCl gave **3a** in markedly lower yields of 10−55% along with a side product that could not be identified by ^{1}H NMR analysis or low resolution mass spectrometry. On the basis of the above results, reaction of **1a** with **2a** in the presence of 0.01 mol % of TfOH at reflux for 15 min was deemed to provide the optimal conditions (entry 5).[11] Under these conditions, a product turnover of 10,000 was also obtained, which to our knowledge is the highest thus far achieved for this reaction. Using these optimized conditions, we were pleased to find that a quantitative product yield of 2.01 g and the same turnover could be reproduced when the reaction was repeated on a large scale with 1.8 g (7.3 mmol) of **1a**.

To determine the generality of the present procedure, we next turned our attentions to the reactions of a variety of 1-cyclopropyl-2-propyn-1-ols with **2a** (Table 2). This revealed that the reactions of substituted 1-cyclopropyl-2-propyn-1-ols containing pendant electron-withdrawing or electron-donating groups with **2a** gave the corresponding conjugated enyne products **3b**−**e** and **3j**−**k** in yields of 88−98% and with turnovers up to 9,800 (entries 1−4, 9 and 10). Similarly, the analogous reactions involving starting alcohols containing a combination of electron-withdrawing and electron-donating groups with **2a** afforded the corresponding enyne products in comparable yields of 90−92% and with turnovers up to 9,200 (entries 5 and 6). More notably, 1-cyclopropyl-2-propyn-1-ols bearing a pyridine or nitrile moiety were found to proceed well under the present conditions and furnish the corresponding conjugated enyne adducts **3h**−**k** in excellent yields and product turnovers (entries 7−10). This compares well with our previous works, which reported that a closely related pyridine-containing alcohol substrate was resistant to the ring-opening process with *p*-$TsNH_2$ using ytterbium catalysis.[3a] Likewise, substituted 1-cyclopropyl-2-propyn-1-ols **1l**−**n** and **1z** with a sterically bulky naphthalene group were found to afford **3l**−**n** and **3z** in excellent yields and product turnovers (entries 11−13 and 25). A similar outcome was found for reactions of 1-cyclopropyl-2-propyn-1-ols containing alkyl groups or both an alkyl and aryl substituent or a terminal alkyne moiety. In these reactions, the corresponding enyne adducts **3o**−**v** were furnished in yields of 75−96% and with up to 9,600 turnovers (entries 14−21). Reactions of starting alcohols with an alkene or alkyne moiety on the carbinol carbon as in **1w** and **1x** were also found to give the corresponding enyne adducts **3w** and **3x** in excellent yields and product turnovers (entries 22 and 23). Similarly, an inspection of entries 24 and 25 in Table 2 showed tetrasubstituted conjugated enynes **3y** and **3z** could be obtained in yields of 95% and 92% and with turnover numbers of 9,500 and 9,200, respectively, for the alkoxylation of 1-cyclopropyl-2-propyn-1-ols bearing a quaternary carbon center. Additionally, the present procedure worked well for starting alcohols with a pendant furan or thiophene functionality, providing the corresponding enyne adducts **3α**−**χ** in excellent yields and product turnovers (entries 26−28). This is noteworthy as such aromatic ring structures are commonly found in a myriad of bioactive natural and pharmaceutical compounds.[12] As anticipated, reaction of the secondary 1-cyclopropyl-2-propyn-1-ol **1δ** under the standard conditions was the only case that was found to give the ethereal substitution product **5** as the sole adduct in 91% yield (entry 29). A similar outcome in product chemoselectivity leading to preferential formation of the substitution adduct from reaction of a secondary 1-cyclopropyl-2-propyn-1-ol with aniline has also been reported for the analogous Ru_2-catalyzed approach.[4a]

In this work, the reaction of **1a** with a variety of different alcohol nucleophiles was also examined (Table 3). Under the standard conditions, reaction of **1a** with benzyl alcohol **2b** gave the corresponding conjugated enyne adduct **3δ** in 80% yield and with a turnover number of 8,000 (entry 1). Similarly, reaction of **1a** with alcohols bearing a terminal alkene moiety gave **3ε** and **3φ** in 75% and 82% yield and with turnovers of 7,500 and 8,200, respectively (entries 2 and 3). In our hands, comparable product yields and turnovers were also obtained in instances where it was initially envisaged that reactions with nucleophiles containing a sterically demanding group on the α-carbon such as an *i*-Pent, *t*-Bu, and cyclohexyl group as in **2e**−**g** would detrimentally influence the reactivity of the present procedure (entries 4−6).

At this juncture, we would like to highlight the chemo- and regioselective nature of the present reaction. Our studies found that the (*Z*)-isomer was obtained as the sole product for all of the reactions described in Table 2 where the tertiary starting alcohol contained a pendant internal alkyne moiety. Similarly, the (*E*)-product was furnished exclusively from reactions with substrates containing a terminal alkyne. For reactions affording the tetrasubstituted conjugated enynes **3y** and **3z**, the *E*:*Z* product selectivities obtained were found to be comparable to the *cis*:*trans* ratios of the respective racemic starting alcohols based on ^{1}H NMR measurements. Reaction of **1x** was the only other example that was found to give the corresponding conjugated enyne **3x** as an inseparable mixture of *E*/*Z* isomers in a ratio of 5: 1 (entry 23 in Table 2). The presence of a bulky substituent on the acetylene moiety of the substrate such as a naphthalene ring as in **1l**−**n** and **1z** was also found to have no influence on the regioselective outcome of the reaction. In addition, no side products were obtained under our experimental conditions based on ^{1}H NMR analysis of the crude mixtures in all except one case, which is consistent with our earlier

(11) The reaction of **1a** with **2a** in the presence of 0.01 mol % of TfOH at reflux for 15 min was repeated 3 times to ensure the accuracy and reproducibility of the reported yield of **3a**.

(12) (a) Fraxedas, J. *Molecular Organic Materials: From Molecules to Crystalline Solids*; Cambridge University Press: Cambridge, 2006. (b) Kleeman, A.; Engel, J. *Pharmaceutical Sustances: Synthesis, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001. (c) Humphrey, M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

TABLE 2. TfOH-Catalyzed Alkoxylation of 1a−δ with 2a[a]

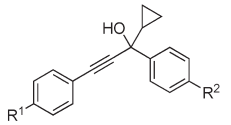
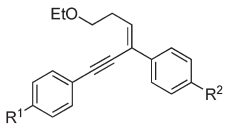
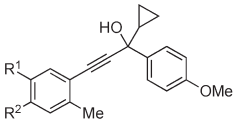
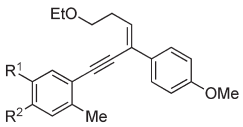
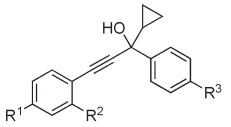
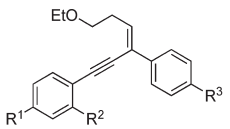
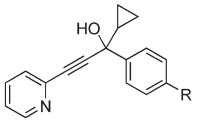
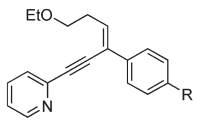
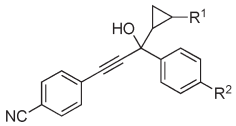
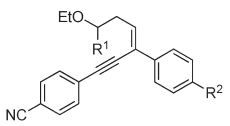
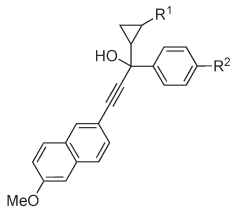
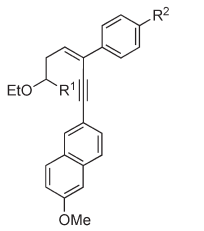
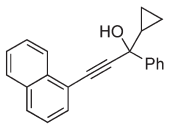
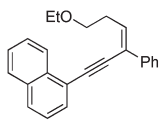
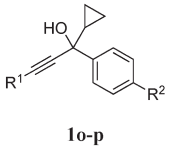
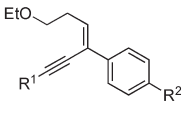
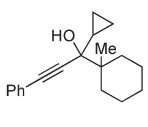
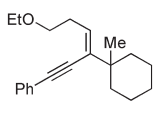
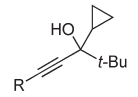
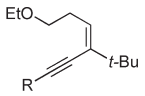
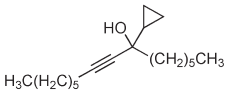
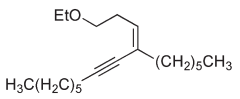
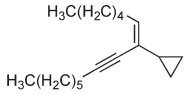
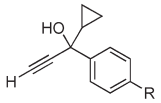
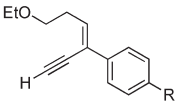
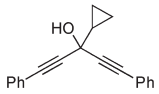
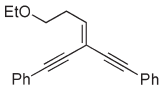
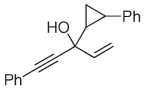
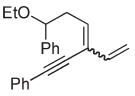
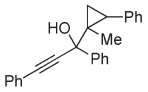
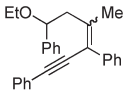
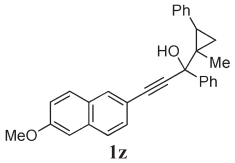
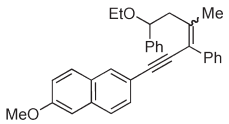
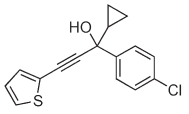
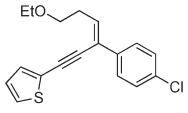
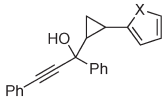
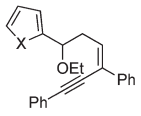
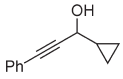
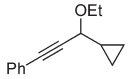
entry	alcohol	product	yield (%)	turnovers
1	 **1b-c**	 **3b**, R^1 = H, R^2 = F	92	9,200
2		**3c**, R^1 = H, R^2 = Cl	95	9,500
3	 **1d-e**	 **3d**, R^1 = H, R^2 = OMe	90	9,000
4		**3e**, R^1 = R^2 = Me	88	8,800
5[b]	 **1f-g**	 **3f**, R^1 = CF_3, R^2 = H, R^3 = OMe	90	9,000
6		**3g**, R^1 = OMe, R^2 = Me, R^3 = F	92	9,200
7[c]	 **1h-i**	 **3h**, R = F	91	9,100
8[c]		**3i**, R = OMe	91	9,100
9[d]	 **1j-k**	 **3j**, R^1 = H, R^2 = F	98	9,800
10[d]		**3k**, R^1 = Ph, R^2 = H	91	9,100
11	 **1l-m**	 **3l**, R^1 = H, R^2 = OMe	93	9,300
12		**3m**, R^1 = Ph, R^2 = H	90	9,000
13	 **1n**	 **3n**	97	9,700
14	 **1o-p**	 **3o**, R^1 = $(CH_2)_5CH_3$, R^2 = Cl	96	9,600
15		**3p**, R^1 = $(CH_2)_3CH_3$, R^2 = H	89	8,900
16	 **1q**	 **3q**	92	9,200

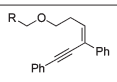
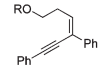
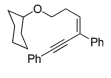
TABLE 2. Continued

entry	alcohol	product	yield (%)	turnovers
17	 **1r-s**	 **3r**, R = Ph	98	9,800
18		**3s**, R = $(CH_2)_5CH_3$	88	8,800
19	 **1t**	 **3t** +  **4**	44 (42)[e]	4,400
20	 **1u-v**	 **3u**, R = Cl	85	8,500
21		**3v**, R = H	75	7,500
22	 **1w**	 **3w**	96	9,600
23	 **1x**	 **3x**	92[f]	9,200
24[g]	 **1y**	 **3y**	95[h]	9,500
25[i]	 **1z**	 **3z**	92[j]	9,200
26	 **1α**	 **3α**	89	8,900
27	 **1β-χ**	 **3β**, X = O	87	8,700
28[k]		**3χ**, X = S	88	8,800
29	 **1δ**	 **5**	91	-

[a]All reactions were performed at reflux for 15 min with 0.2 mmol of **1** in 2 mL of a stock solution of **2a** containing 0.01 mol % of TfOH. [b]Reaction conducted for 25 min. [c]Reaction conducted for 30 min. [d]Reaction conducted for 20 min. [e]Yield in parentheses denotes that isolated for the cyclopropyl enyne side product **4**. [f]Product obtained as an inseparable 5:1 mixture of *E*/*Z* isomers. [g]Starting alcohol used as a mixture of diastereomers in a ratio=3:2. [h]Product obtained as an inseparable 3:2 mixture of *E*/*Z* isomers. [i]Starting alcohol used as a mixture of diastereomers in a ratio=3:1. [j]Product obtained as an inseparable 3:2 mixture of *E*/*Z* isomers. [k]Reaction conducted for 10 min.

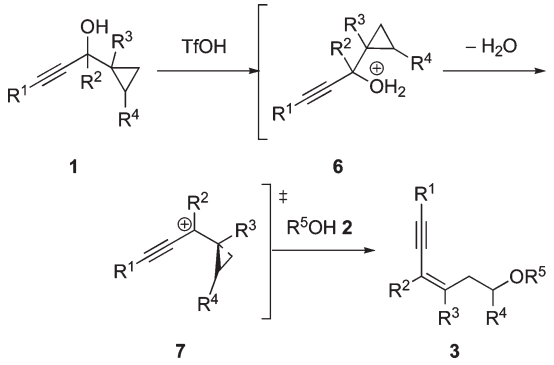
findings for the reaction of **1a** with **2a**. Under our conditions, reaction of **1t** was the only instance that was found to afford **3t** in 44% yield and along with **4** as a side product in 42% yield (entry 19 in Table 2). The *cis* stereochemistry in **3j** was determined by X-ray crystallographic analysis[13] (see Figure S70 in Supporting Information) and NOE measurements, and the *trans* regiochemistry in **3u** was confirmed by NOE analysis.

TABLE 3. TfOH-Catalyzed Alkoxylation of 1a with 2b−g[a]

entry	alcohol	product	yield (%)	turnovers
1	 **2b-d**	 **3δ**, R = Ph	80	8,000
2		**3ε**, R = $CH_2OCH_2CH{=}CH_2$	75	7,500
3		**3ϕ**, R = $CH{=}CH_2$	82	8,200
4[b]	 **2e-f**	 **3γ**, R = *i*-Pent	86	8,600
5[b]		**3η**, R = *t*-Bu	80	8,000
6	 **2g**	 **3ι**	76	7,600

[a]All reactions were performed at reflux for 20 min with 0.2 mmol of **1a** in 2 mL of a stock solution of **2** containing 0.01 mol % of TfOH. [b]Reaction conducted for 15 min.

SCHEME 2. Tentative Mechanism for TfOH-Catalyzed Alkoxylation of 1-Cyclopropyl-2-propyn-1-ols with Alcohols



Although highly speculative, we propose the mechanism of the present reaction to proceed in a manner similar to that reported for the closely related Yb-catalyzed amination of 1-cyclopropyl-2-propyn-1-ols with sulfonamides.[3a] As outlined in Scheme 2, this could involve activation of the alcohol substrate through protonation of the hydroxyl group by the Brønsted acid. This results in the formation of a protonated intermediate **6**, which can undergo elimination to give a putative carbocation species **7**. It is possible that subsequent cyclopropylcarbinol-homoallylic rearrangement of this newly formed cationic species and trapping with **2** would deliver the enyne **3**.[14] The *E*/*Z* product selectivities obtained when $R^3 = H$ could be due to **7** adopting the conformation shown in Scheme 2 with the least amount of unfavorable steric interactions between the substituents and cyclopropane ring.[15] However, for reactions when R^3 = Me that lead to the tetrasubstituted conjugated enyne adduct, such conformational changes may be less favored due to steric interactions between the substituents resulting from rotation of the $C^{\oplus}$−C(cyclopropyl) bond in **7**. For reactions where R^4 = Ph, we postulate that a possible reason for preferential S_N1' attack at the carbon center bearing the substitutent is so that formation of the more sterically hindered tri- or tetrasubstituted enyne adduct can be avoided.[15] The origin of the elimination and ethereal substitution products **4** and **5** could be due to the respective deprotonation and direct attack by **2a** of this resultant carbocation species before ring fragmentation could occur.

(13) CCDC 720922 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.

(14) The involvement of a cyclopropylmethyl carbocation formed in situ has also been proposed for the catalytic hydroamination of methylenecyclopropanes; see: (a) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Yamamoto, Y. *Heterocycles* **2005**, *66*, 333. (b) Chen, Y.; Shi, M. *J. Org. Chem.* **2004**, *69*, 426. (c) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019.

(15) For similar regioselectivties reported in other cyclopropylmethyl carbocation fragmentation processes, see: Honda, M.; Mita, T.; Nishizawa, T.; Sano, T.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2006**, *47*, 5751 and references therein.

Conclusion

In summary, we have presented a Brønsted acid catalyzed method for the nucleophilic ring opening of 1-cyclopropyl-2-propyn-1-ols with alcohols as an expedient route to conjugated enynes. The reaction was shown to be applicable to a wide variety of starting alcohols containing electronic and sterically demanding substrate combinations that complimented the metal-mediated versions of this reaction.[3,4] The efficiency of the present operationally straightforward method was exemplified by the excellent product yields and turnover numbers along with complete regioselectivities achieved with a low catalyst loading of 0.01 mol %. Moreover, the approach offers a potential scale-up strategy for the regioselective synthesis of conjugated enynes, which was demonstrated by the large-scale synthesis of one example in quantitative yield and with a high turnover number. This is notable as the present catalytic method makes use of inexpensive and easily accessible alcohol substrates in combination with the low cost and green credentials[5−7,8d−f,9] often associated with such metal-free catalytic systems.

Experimental Section

Experimental Procedure for TfOH-Catalyzed Preparation of Conjugated Enyne (3). To round-bottom flask containing **1** (0.2 mmol) was added TfOH (0. 01 mol %) in the form of 2 mL of a stock solution containing 0.88 μL of TfOH in 1 L of **2** under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at reflux and monitored to completion by TLC analysis. The crude mixture was quenched with water, extracted with EtOAc (3 × 10 mL), and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (eluent, *n*-hexane/EtOAc = 19: 1) furnished the title compound **3**.

***(Z)*-6-Ethoxy-1,3-diphenylhex-3-en-1-yne (3a).** Light brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71−7.68 (m, 2H), 7.57−7.53 (m, 2H), 7.40−7.30 (m, 6H), 6.55 (t, 1H, J = 7.3 Hz), 3.64 (t, 2H, J = 6.7 Hz), 3.57 (q, 2H, J = 7.0 Hz), 2.90 (q, 2H, J = 6.8 Hz), 1.25 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1, 134.7, 131.6, 128.39, 128.38, 128.3, 127.7, 126.1, 124.9, 123.4, 95.6, 86.6, 69.5, 66.2, 32.1, 15.3; IR (neat, cm^{-1}) 3419, 3018, 2399, 1645, 1215, 756, 669; HRMS (ESI) calcd for $C_{20}H_{21}O$ 277.1592, found 277.1605.

(6-Ethoxy-4-methyl-6-phenylhex-3-en-1-yne-1,3-diyl)dibenzene (3y). Colorless oil; mixture of *E*/*Z* isomers = 3: 2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.03 (m, 24H), 4.61 (t, 1H, J = 6.9 Hz, *E* or *Z* regioisomer), 4.29 (q, 1H, J = 5.8 Hz, *E* or *Z* regioisomer), 3.41−3.15 (m, 3H), 2.95−2.85 (m, 2H, *E* or *Z* regioisomer), 2.61−2.34 (m, 2H, *E* or *Z* regioisomer), 2.16 (s, 3H, *E* or *Z* regioisomer), 1.66 (s, 3H, *E* or *Z* regioisomer), 1.11 (t, 3H, J = 6.9 Hz, *E* or *Z* regioisomer), 1.06 (t, 3H, J = 7.0 Hz, *E* or *Z* regioisomer); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.6, 143.7, 142.6, 142.4, 139.3, 139.2, 131.3, 129.3, 129.1, 128.3, 128.27, 128.26, 128.22, 128.12, 128.10, 127.7, 127.5, 127.4, 126.9, 126.8, 126.6, 126.4, 124.0, 121.4, 120.9, 93.4, 93.0, 90.4, 90.2, 81.7, 80.6, 64.3, 64.2, 46.2, 43.2, 22.1, 21.5, 15.4, 15.3; IR (neat, cm^{-1}) 3419, 3019, 1595, 1215, 1097, 759, 701, 667; HRMS (ESI) calcd for $C_{27}H_{27}O$ 367.2062, found 367.2075.

(*Z*)-6-(Benzyloxy)-1,3-diphenylhex-3-en-1-yne (3δ). Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.74 (m, 2H), 7.62−7.58 (m, 2H), 7.46−7.32 (m, 12H), 6.61 (t, 1H, J = 7.3 Hz), 4.64 (s, 2H), 3.76 (t, 2H, J = 6.6 Hz), 3.01 (q, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 138.1, 134.6, 131.6, 128.49, 128.46, 128.4, 127.9, 127.8, 127.7, 127.6, 126.1, 125.1, 123.4, 95.7, 86.7, 72.9, 69.2, 32.1; IR (neat, cm^{-1}) 3427, 3018, 2399, 1637, 1423, 1215, 927, 756, 669; HRMS (ESI) calcd for $C_{25}H_{23}O$ 339.1749, found 339.1751.

Acknowledgment. This work is supported by a College of Science Start-Up Grant from Nanyang Technological University.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for starting alcohols **1** and conjugated enynes **3**, NOE spectra of **3j** and **3u**, CIF file of **3j**. This material is available free of charge via the Internet at http://pubs.acs.org.