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Trifluoromethanesulfonic Acid Catalyzed Isomerization of Kinetic Enol Derivatives to the Thermodynamically Favored Isomers

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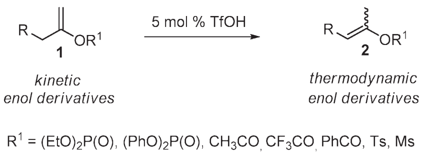
ABSTRACT



Trifluoromethanesulfonic acid catalyzed isomerization of kinetic enol derivatives to the thermodynamically favored isomers was developed. Under the present conditions, kinetic enol phosphates, enol acetates and benzoates, and enol sulfonates were smoothly isomerized to produce the corresponding thermodynamically favored isomers in good to excellent yields.

Considerable attention has been focused on the selective synthesis of enol derivatives due to their usefulness in various synthetic transformations.[1] An early, and still frequently used, route to enol derivatives is the trapping of ketone or aldehyde enolates generated in situ under either kinetic- or equilibrium-controlled conditions.[2] The major issue in these transformations is selectivity (kinetic *vs*. thermodynamic). In particular, the more substituted thermodynamic enol derivatives from unsymmetrical ketones normally predominate under thermodynamic conditions but do not form exclusively, which is a serious problem in the regioselective alkylation of unsymmetrical ketones.[3] Moreover, hydrolysis of labile enol derivatives to carbonyl compounds provokes another problem. Thus,

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[1] (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98*, 2868. (b) Rasmuseen, J. K. *Synthesis* **1977**, 91. (c) Colvin, E. W. *Chem. Soc. Rev*. **1978**, *7*, 15. (d) Brownbridge, P. *Synthesis* **1983**, 1. (e) Brownbridge, P. *Synthesis* **1983**, 85. (f) Cazeau, P.; Dubondin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075–2089. (g) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev*. **1997**, *97*, 2063. (h) Wu, J.; Yang, Z. *J. Org. Chem*. **2001**, *66*, 7875. (i) Galbo, F. L.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem*. **2003**, *68*, 6360. (j) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett*. **2005**, *46*, 4261. (k) Hansen, A. L.; Ebran, J.-P.; Gogsig, T. M.; Skrydstrup, T. *Chem. Commun*. **2006**, 4137. (l) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 3349. (m) Ebran, J.-P.; Hansen, A. L.; Gogsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc*. **2007**, *129*, 6931. (n) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett*. **2007**, *9*, 1659. (o) Gauthier, D.; Beckendorf, S.; Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem*. **2009**, *74*, 3536. (p) Steel, P. G.; Wood, T. M. *Synthesis* **2009**, 3897.

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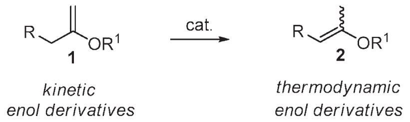
the preparation of thermodynamic enol derivatives with high selectivity is of synthetic importance and a longstanding problem to be solved.[4] In recent years, Brønsted acids have been reported to be versatile in catalyzing a wide variety of organic transformations.[5] Herein, we report trifluoromethanesulfonic acid catalyzed isomerization of kinetic enol derivatives to the much less accessible thermodynamically favored isomers (Scheme 1).[6]

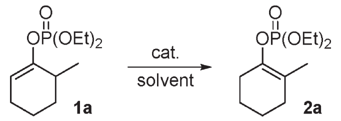
Scheme 1. Isomerization of Kinetic Enol Derivatives to the Thermodynamically Favored Isomers



R^1 = $(EtO)_2P(O)$, $(PhO)_2P(O)$, CH_3CO, CF_3CO, PhCO, PhCH=CHCO, Ph—≡—CO, Ts, Ms, Me, TBS

In order to examine the feasibility of isomerization of kinetic enol phosphates to the thermodynamically favored isomers, we began our study with a wide range of Brønsted acid catalysts and found that the present reaction was very sensitive to acid (Table 1). When the isomerization was carried out with kinetic enol phosphate **1a** derived from 2-methylcyclohexen-1-one using AcOH, TFA, and *p*-TsOH, the reaction did not proceed to give an observable amount of the thermodynamic enol phosphate **2a** (entries 1–5), whereas the reaction with TfOH and Tf_2NH afforded the thermodynamically favored **2a**. Treatment of **1a** with 5 mol % TfOH in CH_2Cl_2 at 60 °C for 15 h produced **2a** in 90% yield (**1a**:**2a** = 1:12, entry 7). Isomerization reaction in toluene did not occur at 40 °C (entry 6) but proceeded smoothly at 60 °C. Toluene gave the better selectivity (93%, **1a**:**2a** = 1:22, entry 8) than CH_2Cl_2 (entry 7). 10 mol % TfOH in toluene gave similar results to 5 mol % (entries 8 and 9). DCE afforded **2a** in 94% yield (**1a**:**2a** = 1:25, entry 10). Because chloroform gave the best result among the solvents tested, isomerization reactions were carried out with an NMR tube with a J Young valve using $CDCl_3$ as a solvent and *p*-xylene (1 equiv) as an internal standard. Subjecting **1a** with 5 mol % TfOH in $CDCl_3$ at 60 °C for 9 h gave **2a** in 96% yield (**1a**:**2a** = 1:26, entry 11). When the amount of TfOH catalyst was reduced, the conversion yield of **1a** and selectivity was decreased (entries 11–13). The catalytic activity of Tf_2NH was slightly lower than that of TfOH (91%, **1a**:**2a** = 1:19, entry 14).

Table 1. Optimization of Isomerization



entry	cat	solvent	temp (°C)	time (h)	yield (%)[a]
1	5 mol % AcOH	$CDCl_3$	60	24	0 (98)[b]
2	5 mol % TFA	$CDCl_3$	60	24	0 (96)[b]
3	5 mol % TFA	toluene	100	24	0 (96)[b]
4	5 mol % *p*-TsOH	$CDCl_3$	60	24	0 (98)[b]
5	5 mol % *p*-TsOH	toluene	100	24	0 (97)[b]
6	5 mol % TfOH	toluene	40	4	0 (93)[b]
7	5 mol % TfOH	CH_2Cl_2	60	15	90 (1:12)
8	5 mol % TfOH	toluene	60	14	93 (1:22)
9	10 mol % TfOH	toluene	60	12	91 (1:17)
10	5 mol % TfOH	DCE	60	9	94 (1:25)
11	**5 mol % TfOH**	**$CDCl_3$**	**60**	**9**	**96 (1:26)**
12	3 mol % TfOH	$CDCl_3$	60	18	95 (1:21)
13	1 mol % TfOH	$CDCl_3$	60	24	75 (1:3)
14	5 mol % Tf_2NH	$CDCl_3$	60	9	91 (1:19)

[a] Ratios in parentheses indicate ratio of **1a** to **2a**. NMR yield. *p*-Xylene (1 equiv) was used as an internal standard. NMR tube with J Young valve was used. [b] NMR yield of **1a**.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to the isomerization of a wide range of kinetic enol derivatives **1** to the thermodynamically favored isomers **2**, and the results are summarized in Table 2. The kinetic enol phosphate **1b** derived from trapping lithium enolate generated in situ from 2-methylcyclopenten-1-one and LDA with diethyl chlorophosphate was subjected to 5 mol % TfOH in $CDCl_3$ at 25 °C for 12 h, producing the thermodynamically favored isomer **2b** in 98% yield (entry 1). The present method worked equally well with enol diphenylphosphate (**1c**), leading to selective formation of thermodynamic enol phosphate **2c** in 97% yield (entry 2). Several acyclic kinetic enol phosphates were isomerized well under the standard conditions (entries 3–6). Kinetic enol phosphate **1d** obtained from cyclohexyl methyl ketone was isomerized to **2d** in 98% yield catalyzed by 5 mol % TfOH in $CDCl_3$ at 25 °C for 3 h (entry 3). Enol phosphate **1e** containing a 3,4-dimethylphenoxy group smoothly reacted with 5 mol % TfOH to provide the desired product **2e** in 97% yield (*dr* = 1:2, entry 4). A chloro group was tolerated under the present reaction conditions (entry 6), and a cyano group gave a somewhat lower yield (75%, *dr* = 1:4, **1f**:**2f** = 1:3.3)

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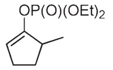
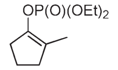
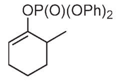
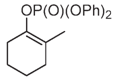
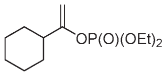
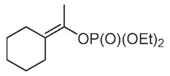
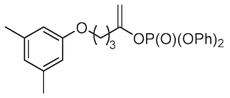
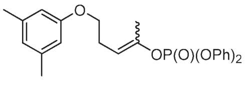
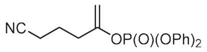
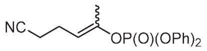
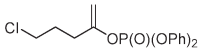
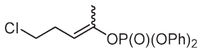
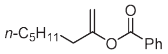
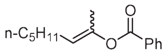
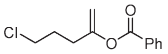
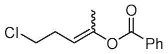
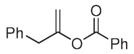
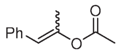
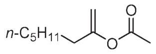
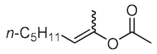
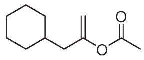
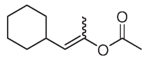
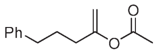
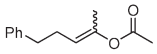
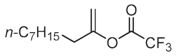
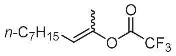
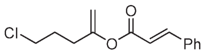
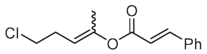
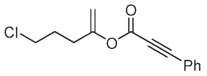
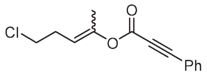
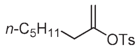
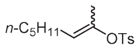
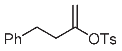
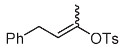
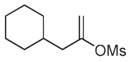
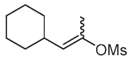
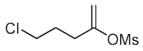
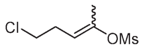
(6) For selected examples of other reactions mediated by TfOH, see: (a) Singh, R.; Parai, M. K.; Panda, G. *Org. Biomol. Chem.* **2009**, *7*, 1858. (b) Li, A.; DeSchepper, D. J.; Klumpp, D. A. *Tetrahedron Lett.* **2009**, *50*, 1924. (c) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (d) Li, X.; Ye, S.; He, C.; Yu, Z.-X. *Eur. J. Org. Chem.* **2008**, 4296. (e) Abid, M.; Teixeira, L.; Török, B. *Org. Lett.* **2008**, *10*, 933. (f) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (g) Coulombel, L.; Duñach, E. *Green Chem.* **2004**, *6*, 499. (h) Lu, J.-M.; Zhu, Z.-B.; Shi, M. *Chem.—Eur. J.* **2009**, *15*, 963. (i) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

Table 2. TfOH-Catalyzed Isomerization of Kinetic Enol Derivatives to the Thermodynamically Favored Isomers[a]

entry	kinetic enol derivatives		time (h)	thermodynamic enol derivatives		yield (%)[b]	ratio[c]
1		**1b**	12		**2b**	98	1:63
2[d]		**1c**	18		**2c**	97	1:29
3		**1d**	3		**2d**	98	1:56
4		**1e**	5		**2e**	97 (1:2)	1:38
5[d]		**1f**	24		**2f**	75 (1:4)	1:3.3
6		**1g**	3		**2g**	97 (1:2)[e]	1:37
7		**1h**	0.08		**2h**	92 (1:3.3)	1:93
8[f]		**1i**	0.5		**2i**	86 (1:4)	1:69
9		**1j**	0.25		**2j**	100 (1:3)	0:100
10[f]		**1k**	1		**2k**	83 (1:3.3)	1:33:6[g]
11[f]		**1l**	1.5		**2l**	80 (1:3)	1:48
12[f]		**1m**	0.5		**2m**	75 (1:3.8)	1:50:15[g]
13		**1n**	0.5		**2n**	95 (1:2.9)	1:58
14[h]		**1o**	24		**2o**	89 (1:3.5)	1:8
15[h]		**1p**	24		**2p**	90 (1:3.4)	1:12
16		**1q**[i]	0.5		**2q**	99 (1:10)	1:100
17		**1r**[j]	0.08		**2r**	96 (1:5.4)	1:26
18		**1s**[k]	0.25		**2s**	97 (1:1.2)	1:42
19		**1t**	0.25		**2t**	87 (1:5)	1:13

[a] Reactions were carried out at room temperature unless otherwise noted. [b] NMR yield. *p*-Xylene (1 equiv) was used as an internal standard. NMR tube with J Young valve was used. Diastereomeric ratio. [c] Ratios of **1** and **2** after reaction. [d] Reactions were carried out at 60 °C. [e] *E*/*Z* ratio. [f] 1 mol % TfOH was used. [g] Ratios of **1**, **2**, and ketone after reaction. [h] Reactions were carried out at 80 °C. [i] Mixture (1:1) of kinetic and thermodynamic enol tosylate was used. [j] Mixture (2:1) of kinetic and thermodynamic enol tosylate was used. [k] Mixture (3.7:1) of kinetic and thermodynamic enol mesylate was used.

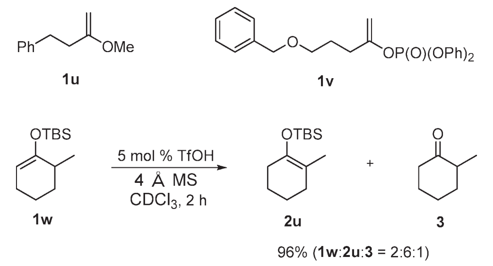
(entry 5). The geometric structure (*E*:*Z* = 1:2) of **2g** was determined from NOSEY measurement.

Isomerization of vinyl benzoates proceeded cleanly and rapidly at room temperature and was complete within 0.5 h. Exposure of chloro vinyl benzoate **1i** to 1 mol % TfOH afforded **2i** in 86% yield (*dr* = 1:4) for 30 min (entry 8). Treatment of kinetic enol benzoate **1j** with 5 mol % TfOH produced thermodynamic enol benzoate **2j** in quantitative yield (*dr* = 1:3) for 15 min due to the conjugation effect (entry 9). The vinyl acetate **1l** was easily isomerized to **2l** in 80% yield (*dr* = 1:3) with 1 mol % TfOH (entry 11). Kinetic enol acetates **1k** and **1m** worked well with 1 mol % TfOH, but the corresponding ketones were slightly contaminated through hydrolysis (entries 10 and 12). Reactive enol trifluoroacetate **1n** did not cause any problem, yielding the thermodynamically favored isomer **2n** in 95% yield (*dr* = 1:2.9, entry 13). When enol derivatives (**1o** and **1p**)[7] derived from cinnamic acid and phenyl propiolic acid were treated with 5 mol % TfOH, the reaction required longer reaction times (24 h) to yield the thermodynamically favored isomers **2o** and **2p** (entries 14 and 15).

Similarly, the isomerization of enol tosylates under the present conditions proceeded cleanly at room temperature. When a mixture (1:1) of kinetic and thermodynamic enol tosylate **1q** was treated with 5 mol % TfOH, the thermodynamically favored isomer **2q** was obtained in quantitative yield (entry 16). Therefore, the present method is very meaningful, when preparation of thermodynamic sulfonates is not selective (entries 16–18). Moreover, we were pleased to obtain the thermodynamically favored mesylate **2t** in 87% yield from kinetic enol derivative **1t** in the presence of 5 mol % TfOH at room temperature (entry 19).

However, this method reaches a limit with more electron-rich enol ethers. When kinetic methyl vinyl ether **1u** was treated with 5 mol % TfOH, methyl phenethyl ketone was produced through hydrolysis (Scheme 2). 1 mol % or 0.1 mol % TfOH led even to decomposition of **1u**. The enol phosphate **1v** decomposed under the present conditions. Subjecting **1w** to 5 mol % TfOH in the presence of a 4 Å molecular sieve gave thermodynamically favored isomer **2u** (64%) together with **1w** (21%) and 2-methylcyclohexen-1-one (**3**) (11%).

Scheme 2



In summary, we have developed trifluoromethanesulfonic acid catalyzed isomerization of kinetic enol derivatives to the thermodynamically favored isomers. Under the present conditions, kinetic enol phosphates, enol acetates and benzoates, and enol sulfonates were cleanly isomerized to produce the corresponding thermodynamically favored isomers in good to excellent yields. Various functional groups including cyano, chloro, dimethylphenoxy, alkenyl, and alkynyl were tolerated under the present reaction conditions.

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

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[7] (a) Chary, B. C.; Kim, S. *J. Org. Chem.* **2010**, *75*, 7928. (b) Goossen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706. (c) Cui, D. M.; Meng, Q.; Zheng, J. Z.; Zhang, C. *Chem. Commun.* **2009**, 1577. (d) Chae, S.; Gao, R. *Organometallics* **2009**, *28*, 6585. (e) Melis, K.; Opstal, T.; Verpoort, F. *Eur. J. Org. Chem.* **2002**, *22*, 3779.