ORGANIC LETTERS

2013
Vol. 15, No. 1
38–41

Cyclopropenone Catalyzed Substitution of Alcohols with Mesylate Ion

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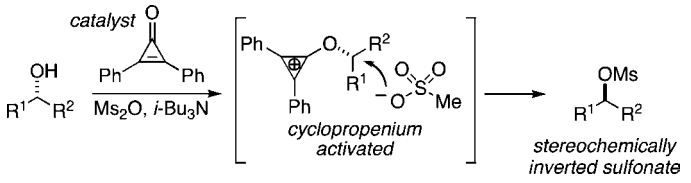
Received October 30, 2012

ABSTRACT



The cyclopropenone catalyzed nucleophilic substitution of alcohols by methanesulfonate ion with inversion of configuration is described. This work provides an alternative to the Mitsunobu reaction that avoids the use of azodicarboxylates and generation of hydrazine and phosphine oxide byproducts. This transformation is shown to be compatible with a range of functionality. A cyclopropenone scavenge strategy is demonstrated to aid purification.

Chemical transformations involving the nucleophilic substitution of alcohols are a crucial component of the synthetic toolbox. One of the most widely used approaches is the Mitsunobu reaction,[1] a process in which a diazodicarboxylate and triphenylphosphine conspire to effect the nucleophilic substitution of hydroxyl groups, typically with inversion of stereochemistry. Due to the importance of this type of transformation, the Mitsunobu reaction has become a key technology for the preparation of complex molecules.[1d] Unfortunately, a number of major drawbacks plague the Mitsunobu reaction, including the toxic and explosive nature of diazodicarboxylates and the problematic purification of products from triphenylphosphine oxide and dicarboxyhydrazine byproducts.[2] Despite significant advances,[3] alternative strategies are very much in demand.[4,5]

We recently disclosed a catalytic strategy for the promotion of dehydrative reactions[6] using simple cyclopropenones[7,8] as catalysts. This strategy, which relies on the facile formation of cyclopropenium cations for substrate activation,[9] was first demonstrated in the context of alcohol chlorodehydration using oxalyl chloride as the activating agent and source of nucleophile. Here, we advance this concept to the context of cyclopropenone catalyzed alcohol substitution with an acid anhydride.[10,11]

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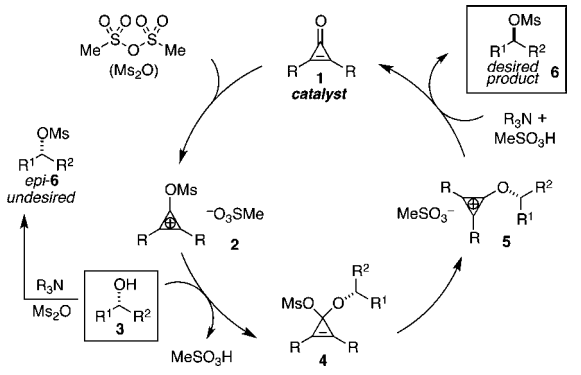
10.1021/ol302970c
Published on Web 12/13/2012

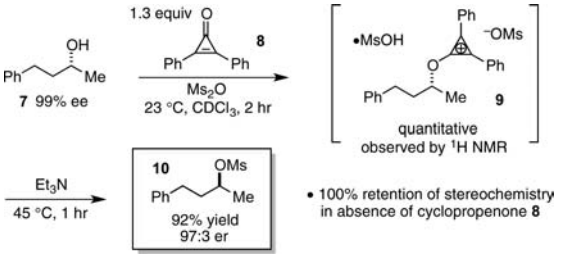
Scheme 1. Design of a Cyclopropenone Catalyzed Alcohol Inversion with Mesylate Ion



Our design of a cyclopropenone catalyzed alcohol inversion is shown in Scheme 1. In previous work by our group[9d] and others,[12] it has been demonstrated that a cyclopropenone **1** can undergo conversion to a cyclopropenium salt (**2**) by the action of acid anhydrides including methanesulfonic anhydride (Ms_2O). Alkylation of an alcohol substrate **3** by cyclopropenium ion, followed by reionization, leads to formation of the cyclopropenium activated intermediate **5**. We reasoned that nucleophilic displacement of the cyclopropenium alkoxide fragment of such intermediates by either the mesylate counterion or mesylate ion generated by the addition of base would produce the desired substitution product **6** with concomitant regeneration of the cyclopropenone catalyst. Of crucial importance to the proposed catalytic cycle is the successful competition of the desired pathway in preference to the direct mesylation of **3**, which would produce mesylate product *epi*-**6** with retention of stereochemistry.

To test this proposal, enantioenriched alcohol **7** was treated with 1.3 equiv of diphenylcyclopropenone[13] (**8**) and Ms_2O at 23 °C in $CDCl_3$ (Scheme 2). After 2 h, quantitative formation of cyclopropenium ether **9** was observed by ^1H NMR (see Supporting Information), as diagnosed by the significantly downfield shift of the methine proton. Extended monitoring of the reaction revealed minimal (< 10%) formation of mesylate products, suggesting that the mesylate counterion of **9** is not a competent nucleophile under these conditions. However, addition of triethylamine and warming to 45 °C resulted in facile conversion to product **10** in 92% isolated yield and 97:3 er with inversion of stereochemistry. In the absence of **8**, the mesylate product was isolated with 100% retention of stereochemistry, demonstrating that the proposed activation mode is essential to the desired outcome.

Scheme 2. Demonstration of Alcohol Inversion with Mesylate Ion via Cyclopropenium Activation



With the goal of catalysis, we optimized this inversion procedure with all components present from the beginning of the reaction (Table 1). Here, the use of triethylamine resulted in high yield but a preference for the undesired enantiomer (entry 1). More sterically demanding bases, such as 2,6-di-*tert*-butylpyridine (entry 2) and triisobutylamine (entry 3), offered significantly improved selectivities, presumably because they have poor capacity to effect direct mesylation of the alcohol but still serve as efficient proton sinks.[14] Interestingly, the exceedingly hindered base, pempidine, showed poor selectivity (entry 4). An examination of the anhydride stoichiometry (entries 3, 5, and 6) showed that higher amounts of Ms_2O resulted in not only minor improvements in yield but also a slight loss of er. Logically, additional anhydride would be expected to increase the rate of background alcohol mesylation, which would account for this outcome. In terms of reaction temperature (entries 3, 7–9), an increase to 55–65 °C led to shorter reaction times and appreciable improvements in selectivity. Lastly, dilution of the mixture correlated with an increase in not only er but also reaction time (entries 10–12). A concentration of 0.05 M was selected as an acceptable compromise.

With optimized conditions in hand, a catalytic version of this process was explored. Reaction of **7** using 10 mol % catalyst **8** resulted in formation of product **10** in 85% yield, but with nearly equal amounts of retention and inversion (Table 2, entry 1). We speculate that this lowered selectivity was due to a slow intermolecular substitution step, which effectively sequesters the catalyst and allows for competitive direct mesylation. To provide ample time for catalyst turnover, the alcohol and amine base were added as a solution over 12 h to a mixture of **8** and methanesulfonic anhydride (entry 2). In this case, the degree of inversion was improved dramatically to 94:6 er. Increasing the catalyst loading to 15 mol % (entry 3) and extending the addition time to 18 h (entry 4) offered additional improvements, to 97:3 er with an 85% isolated yield. This result demonstrates the feasibility of achieving

(10) For Mitsunobu reactions with sulfonate nucleophiles: (a) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461. (b) Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1996**, *61*, 7955. (c) Davis, A. P.; Dresen, S.; Lawless, L. J. *Tetrahedron Lett.* **1997**, *38*, 4305.

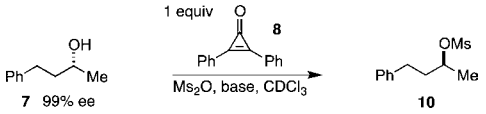
(11) A Mitsunobu procedure catalytic in diazodicarboxylate has been described. (a) But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636. (b) But, T. Y. S.; Lu, J.; Toy, P. H. *Synlett* **2010**, 1115.

(12) (a) Oda, M.; Breslow, R.; Pecoraro, J. *Tetrahedron Lett.* **1972**, *13*, 4415. (b) Stang, P. J.; Maas, G.; Fisk, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 6361. (c) Weber, H.-M.; Maas, G. *Synthesis* **1988**, 604.

(13) **8** is available from Sigma-Aldrich or may be readily synthesized on large scale. Breslow, R.; Posner, J. *Org. Synth.* **1967**, *47*, 62.

(14) For a study on the effect of base on mesylation selectivity, see: O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614.

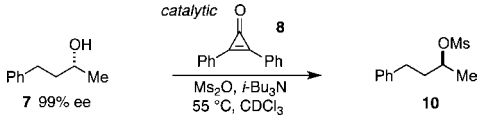
Table 1. Optimization of a One Step Cyclopropenone Mediated Alcohol Inversion with Mesylate Ion[a]



entry	base	Ms_2O (equiv)	temp (°C)	concn (M)	time (h)	yield (%)	er 10:*epi*-10
1	**Et_3N**	1.5	45	0.10	2.0	97	40:60
2	**2,6-(*t*-Bu)$_2$py**	1.5	45	0.10	2.0	82	87:13
3	***i*-Bu_3N**	1.5	45	0.10	2.0	94	91:9
4	**pempidine**[b]	1.5	45	0.10	2.0	97	36:64
5	*i*-Bu_3N	**1.2**	45	0.10	1.5	87	92:8
6	*i*-Bu_3N	**1.8**	45	0.10	1.0	93	91:9
7	*i*-Bu_3N	1.2	**35**	0.10	2.0	95	90:10
8	*i*-Bu_3N	1.2	**55**	0.10	0.8	78	94:6
9	*i*-Bu_3N	1.2	**65**	0.10	0.5	85	93:7
10	*i*-Bu_3N	1.2	55	**0.03**	19	76	96:4
11	*i*-Bu_3N	1.2	55	**0.05**	2.0	77	96:4
12	*i*-Bu_3N	1.2	55	**0.20**	0.8	74	90:10

[a] Reactions were performed by the addition of a $CDCl_3$ solution of 0.1 mmol of **7** and base (1.05 equiv) to a vial containing **8** (1.0 equiv) and Ms_2O in $CDCl_3$. Yields were determined on purified material. Enantiomeric ratios were determined by HPLC using a Chiralcel OD column. [b] 1,2,2,6,6-Pentamethylpiperidine.

Table 2. Optimization of a Cyclopropenone Catalyzed Alcohol Inversion with Mesylate Ion[a]



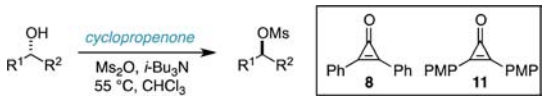
entry	catalyst **8** (mol %)	addition time (h)	reaction time (h)	yield (%)	er 10:*epi*-10
1	10	--	2.5	85	46:54
2	10	12	1.0	73	93:7
3	15	12	1.0	75	95:5
4	15	18	1.0	85	97:3

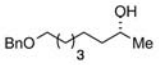
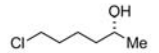
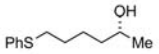
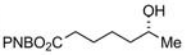
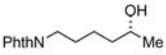
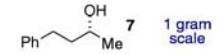
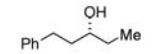
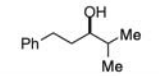
[a] Reactions were performed by the addition of a $CDCl_3$ solution of 0.1 mmol of alcohol **7** and *i*-Bu_3N (0.95 equiv) by syringe pump over the indicated time to a vial containing cyclopropenone **8** and Ms_2O (1.5 equiv) in $CDCl_3$, followed by the addition of another 0.25 equiv of *i*-Bu_3N. The solution was then stirred for the additional reaction time indicated. Yields were determined on isolated and purified material. Enantiomeric ratios were determined by HPLC using a Chiralcel OD column.

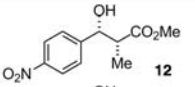
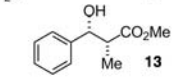
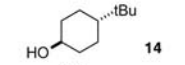
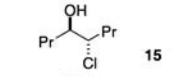
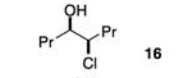
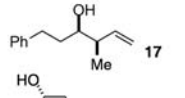
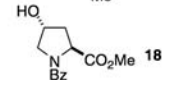
cyclopropenone catalyzed alcohol inversion with a simple acid anhydride.

The results of our substrate scope studies, under the conditions identified above, are provided in Table 3. High degrees of inversion can be obtained for certain substrates with either the catalytic or stoichiometric protocols, although yields are generally greater with the use of 100 mol % cyclopropenone. A range of functionality, including

Table 3. Substrate Scope Studies for Cyclopropenone Catalyzed/Mediated Alcohol Inversion with Mesylate Ion[a]



entry	substrate	15 mol% **8**[b] yield (%)	er	100 mol% **8**[c] yield (%)	er
1		75	97:3	91	95:5
2		77	95:5	92	96:4
3		72	96:4	83	94:6
4[d]		81	95:5	98	97:3
5		74	96:4	77	95:5
6[e]	 1 gram scale	88	96:4	77	96:4
7		83	96:4	84	94:6
8		45	91:9	68	85:15

entry	substrate	cyclopropenone[f] (equiv)	yield (%)	*syn*:*anti*
9	 **12**	**11** (1.1)	72	<2:98
10	 **13**	**11** (1.1)	64[g]	12:88
11	 **14**	**11** (1.1)	74	96:4
12	 **15**	**8** (1.8)	82	97:3
13	 **16**	**8** (1.8)	75	5:95
14	 **17**	**8** (1.1)	--	--
15	 **18**	**8** (1.5)	77	97:3

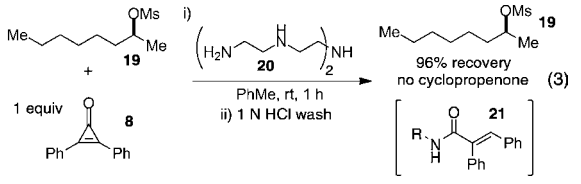
[a] Yields were determined on isolated and purified material. Enantiomeric ratios were determined by HPLC using a Chiralcel OD column. Diastereomeric ratios were determined by ^{1}H NMR on crude reaction mixtures. [b] For entries 1–8 using 15 mol % cyclopropenone, the reactions were performed according using the conditions shown in Table 2, entry 4. [c] For entries 1–8 using 100 mol % cyclopropenone, reactions were performed using the conditions shown in Table 1, entry 11. [d] PNB = *p*-nitrobenzyl. [e] Gram scale reaction performed under catalytic conditions. [f] For experimental details for entries 9–15, see Supporting Information. [g] Yield determined by ^{1}H NMR vs Bn_2O as an internal standard.

ether, alkyl halide, thioether, ester, and phthalimide groups, is accommodated by this procedure (entries 1–5). The degree of steric hindrance near the reactive hydroxyl group

was found to significantly impact the efficiency of the substitution. Thus, in an examination of a series of methyl, ethyl, and isopropyl substituted alcohols (entries 6–8), increasing steric hindrance led to a corresponding decrease in reaction efficiency. For appropriate substrates this catalytic procedure was found to be viable on a preparative scale, as demonstrated by the reaction of 1 g of **7** (entry 6).

Although catalysis is limited to substrates with relatively low steric demand, the stoichiometric procedure is effective with more challenging substrates. The aldol adduct **12** underwent mesylation with stereospecific inversion in good yield (entry 9). Here, 2,3-bis(*p*-methoxyphenyl)-cyclopropenone (**11**) provided efficiency and stereospecificity superior to those of the diphenyl reagent **8**.[15] On the other hand, an electronically neutral benzylic alcohol **13** reacted with subpar selectivity (entry 10), likely due to benzylic C–O bond heterolysis/recombination of the cyclopropenium activated intermediate. Inversion of cyclic alcohols such as the conformationally locked cyclohexanol **14** was feasible, again with optimal results arising from use of electron-rich cyclopropenone **11**. It should be noted that the desired product was accompanied by ~17% elimination product. The diastereomeric chlorohydrins **15** and **16** underwent efficient, stereospecific inversion using **8**, with no observed complications arising from epoxide formation (entries 12 and 13). Due to the reduced nucleophilicity of these substrates, higher loadings of cyclopropenone (1.8 equiv) were used to ensure full activation. A limitation of the current method was found in the attempted reaction of homoallylic alcohol **17** (entry 14), which resulted in a complex mixture of products, presumably arising from alkene-assisted ionization of the cyclopropenium activated intermediate of this substrate.[16] Finally, the hydroxyproline derivative **18** underwent facile mesylation with inversion of configuration (entry 15).

cyclopropenone scavenge



One of the most commonly encountered complications of Mitsunobu procedures arises from difficulties in product purification,[2] due to the presence of the stoichiometric byproducts mentioned above. For the same reason, we felt it was important to demonstrate that the cyclopropenone reagent/catalyst from our procedure could be readily removed from the desired products. As a matter of fact, obtaining yields for three of the entries in Table 3 (4, 5, and 13) was initially complicated by the fact that diphenylcyclopropenone coelutes with these mesylate adducts during chromatographic purification. To remedy this situation, we developed a simple procedure to scavenge the cyclopropenone by making use of their known propensity to undergo nucleophilic ring opening (eq 1).[17] Thus, the addition of commercially available tetraethylenepentamine (**20**) to an equimolar mixture of diphenylcyclopropenone (**8**) and mesylate **19** resulted in quantitative removal of the ketone, after a 1 N HCl wash, presumably by conversion to the corresponding ring-opened acrylamide **21**. Importantly, the mesylate **19** was recovered in 96% yield. As further evidence of the viability of this purification strategy, the yields reported for entries 4, 5, and 13 in Table 3 were obtained with the application of this scavenging procedure.

In conclusion, we have developed a catalytic strategy that allows for alcohol inversion by a mesylate ion, using only methanesulfonic anhydride and a simple tertiary amine base. This procedure avoids the generation of offensive byproducts and utilizes a catalyst that can be readily scavenged from solution, making purification straightforward. Importantly, the conceptual principles embodied in this protocol may be applicable to the use of other activating agents or nucleophiles, which would offer additional alternatives for alcohol substitution.

Acknowledgment. T.H.L. is grateful for an Alfred P. Sloan Research Fellowship and an Ely Lilly Grantee Award. We also thank the Sames and Norton groups (Columbia University) for use of their instrumentation.

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

(15) The more electron-rich cyclopropenone **11** increases the rate of formation of the cyclopropenium activated intermediate (cf. **5**, Scheme 1) and, thus, helps to outcompete direct mesylation with certain hindered substrates. However, relative to cyclopropenone **8**, **11** also dramatically slows the mesylate displacement event (the rate-limiting step) and, thus, has not proven to be viable for the catalytic process.

(16) For reviews on this well-known reactivity, see: (a) Hanack, M.; Schneide, H. J. *Angew. Chem., Int. Ed.* **1967**, *6*, 666. (b) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623.

(17) (a) Dehmlow, E. V. *Tetrahedron Lett.* **1967**, *8*, 5177. (b) Eicher, T.; Böhm, S.; Ehrhardt, H.; Harth, R.; Lerch, D. *Liebigs Ann. Chem.* **1981**, 765.

The authors declare no competing financial interest.