J|A|C|S COMMUNICATIONS

Published on Web 01/08/2010

Metal-Free Highly Regioselective Aminotrifluoroacetoxylation of Alkenes

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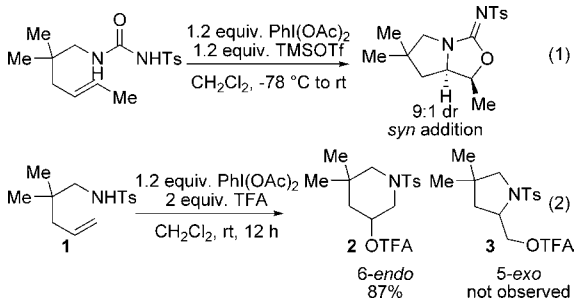
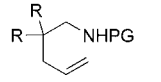
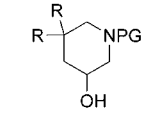
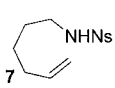
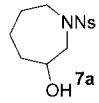
Selective oxidative difunctionalization of alkenes is an extremely powerful chemical transformation as evidenced by the extensive use of transformations such as the keystone Sharpless osmium-catalyzed dihydroxylations[1] and aminohydroxylations.[2] Despite the utility of these transformations in the construction of complex structures, alternative complementary methods are still needed. In recent years the application of hypervalent iodine(III) reagents to these oxidative processes has arisen as one such alternative.[3] Hypervalent iodine compounds have been shown to effect numerous useful chemical oxidations with the additional benefits of commercial availability, low cost, low toxicity, and convenient handling. In the area of alkene difunctionalizations, several groups have separately developed palladium-catalyzed methodologies with hypervalent iodine.[4] As a general rule, a metal catalyst in addition to the oxidant is required for efficient, desired reactivity. However, hypervalent iodine reagents have been shown to effect the intermolecular dihydroxylation of alkenes under metal-free conditions.[5]

Development of the associated *intramolecular* alkene aminohydroxylations would give concise routes to useful nitrogen-containing heterocycles while potentially allowing for increased regio- and stereocontrol during ring formation. With this objective, Donohoe and co-workers have performed a variety of osmium-catalyzed intramolecular oxidative cyclizations exhibiting high selectivity for *exo* ring closure.[6] Sorensen and co-workers have also described a promising palladium-catalyzed intramolecular oxyamination amenable to several alkene substitution patterns, albeit with moderate to poor regioselectivity.[7] Recently, we reported the generation of vicinal aminoalcohol derivatives via a diastereoselective, stereospecific metal-free oxidative cyclization (eq 1).[8] In the course of these studies, we discovered that treatment of sulfonamidoalkene **1** with $PhI(OAc)_2$ and TFA in the absence of any metal catalyst resulted in clean conversion to the *endo* aminotrifluoroacetoxylation product **2** (eq 2). This preferential formation of piperidine **2** over pyrrolidine **3** starkly contrasts with the 5-*exo* cyclizations observed under related oxidative conditions.[9] To our knowledge this is the first example of a highly *endo* selective aminohydroxylation.[10] The synthetic utility of such a rapid, regioselective generation of functionalized piperidines necessitated further development, and here we report our findings on this process.



Exploration of the scope of this transformation began with cyclization of several 1-sulfonamido-4-pentenes that provided piperidines **4a**−**6a** in excellent yields and regioselectivities (Table 1, entries 1−3). Other ring sizes could also be formed cleanly under the reaction conditions (Table 1, entries 4−5). As with the pentenyl substrates, hexenyl substrate **7** also exhibited high selectivity for 7-*endo* over 6-*exo* cyclization, forming the azepane almost exclusively.

Table 1. *Endo* Selective Aminotrifluoroacetoxylations of Alkenes

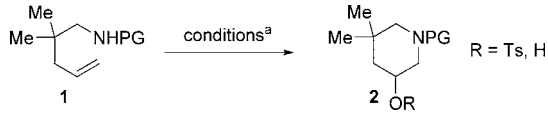
entry	alkene	product	cond.[a]	yield[b], (rs[c])
				
1	**4** R = Ph; PG = Ts	**4a**	A	99%, (>20:1)
2	**5** R = -C_5H_{10}-; PG = Ts	**5a**	A	99%, (>20:1)
3	**6** R = H; PG = 2-Ns	**6a**	C	95%, (14:1)
4	 **7**	 **7a**	B	81%, (15:1)
5	 **8**	 **8a**	B	82%

[a] Condition A: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (0.2 mmol), CH_2Cl_2 (1 mL), rt, 12 h. Condition B: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (1.2 mmol), CH_2Cl_2 (1 mL), rt, 24 h. Condition C: Alkene (0.1 mmol), $PhI(OTFA)_2$ (0.12 mmol), TFA (1.2 mmol), CH_2Cl_2 (1 mL), rt, 24 h. [b] Isolated yield of aminoalcohol(s) following saponification, K_2CO_3/MeOH, rt, 5 min. [c] rs = regioselectivity, determined by ^1H NMR spectroscopy.

Other sulfonamide protecting groups such as 2-nitrobenzenesulfonyl (2-Ns), 4-nitrobenzenesulfonyl (4-Ns), and trimethylsilylethanesulfonyl (SES) also afforded the 6-*endo* aminotrifluoroacetoxylation products[11] in excellent yields (Table 2). Acid incorporation also occurred when TsOH was used in place of TFA affording tosylate **2a** in good yield.

A variety of 1,1- and 1,2-disubstituted alkenes underwent cyclization under standard conditions to give aminotrifluoroacetoxylation products in good yields (Table 3). From this survey, several trends in regioselectivity were apparent. Unlike the monosubstituted pentenyl substrates, styrenyl substrates **9** and **10** provided the 5-*exo* cyclization products exclusively. Cyclohexenyl substrate **12** also selectively underwent 5-*exo* cyclization to form the 5,6 fused bicycle **12a** rather than a 6,6 bridged bicycle (entry 4). 1,2-Disubstituted alkenes with alkyl substituents (**13**, **14**), however, preferred *endo* cyclization, with the *Z* alkene exhibiting significantly better regioselectivity than the *E* isomer.[12] For the 1,1-disubstituted alkene **15**, piperidine **15a** was the only product observed (entry 7). In nearly every example, the trifluoroacetate is preferentially affixed

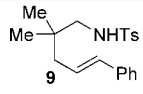
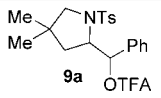
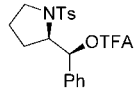
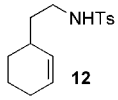
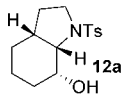
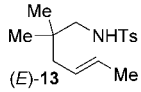
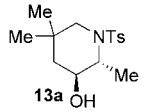
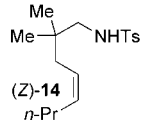
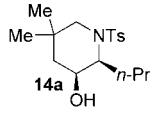
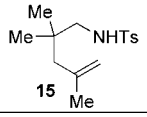
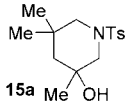
Table 2. *Endo*-Cyclization Protecting Group Assay



entry	alkene	PG	Oxidant	acid	product	% yield[b]
1	**1**	Ts	$PhI(OAc)_2$	TFA	**2**	88
2	**1**	Ts	$PhI(OAc)_2$	TsOH[c]	**2a**	82[d]
3	**1**	Ts	$PhI(OTFA)_2$	TFA	**2**	92
4	**1b**	2-Ns	$PhI(OTFA)_2$	TFA	**2b**	92
5	**1c**	4-Ns	$PhI(OTFA)_2$	TFA	**2c**	90
6	**1d**	SES	$PhI(OTFA)_2$	TFA	**2d**	94

[a] Reaction conditions: **1** (0.1 mmol), CH_2Cl_2 (1 mL), oxidant (0.12 mmol), acid (1.2 mmol), rt, 24 h. [b] Isolated yield of product following saponification, K_2CO_3/MeOH, rt, 5 min. [c] $TsOH \cdot H_2O$ (5 equiv). [d] Yield of tosylate (R = Ts).

Table 3. Effects of Alkene Substitution

entry	alkene	product	conditions[a]	yield[b]
1	 **9**	 **9a**	**B**	62%, >20:1 rs[c] 19:1 dr
2	 (*Z*)-**10** (1:19 E:Z)	 **10a**	**B**	56%, >20:1 rs 5:1 dr[d]
3	(*E*)-**10** (9:1 E:Z)	**10a**	**B**	49%, >20:1 rs 5:1 dr[d]
4	 **12**	 **12a**	**A**	86%, 7:1 rs >20:1 dr[e]
5	 (*E*)-**13**	 **13a**	**B**	69%, 2:1 rs >20:1 dr[e]
6	 (*Z*)-**14**	 **14a**	**B**	90%, 19:1 rs >20:1 dr[e]
7	 **15**	 **15a**	**A**	92%, >20:1 rs

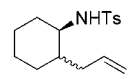
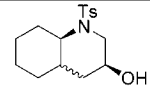
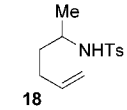
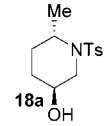
[a] Condition A: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (0.2 mmol), CH_2Cl_2 (1 mL), rt, 12 h. Condition B: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (1.2 mmol), CH_2Cl_2 (1 mL), rt, 24 h. [b] Isolated yield of aminoalcohol(s) following saponification, K_2CO_3/MeOH, rt, 5 min. [c] rs = regioselectivity - *endo*/*exo* cyclization; determined by ^1H NMR spectroscopy. [d] Major diastereomer determined by literature comparison.[20] [e] Major diastereomer determined by ^1H NMR spectroscopy.

to the carbon better able to stabilize a carbocation, providing a reliable predictor of regioselectivity. Substituents on the tether had little effect on this preference, with the exception of substitution alpha to the sulfonamide (Table 4), which gave significantly lower regioselectivities.

Several trends in diastereoselectivity were also evident. Styrenyl substrates **9** and **10** gave aminotrifluoroacetoxylation products in good to excellent diastereoselectivity. Interestingly, both *E* and *Z* geometries of **10** afforded the same major stereoisomer. The matching selectivity for the *cis*/*trans* pair may be due to *in situ* *cis*−*trans* alkene isomerism.[13] The configuration of the major stereoisomers of **10a** and **12a** show that 5-*exo* cyclizations appear to be selective for *syn* addition products. On the other hand, *E* and *Z* alkyl-substituted alkenes **13** and **14** did not converge to the same relative stereochemistry upon cyclization. The *E* alkene gave exclusively the *trans* hydroxypiperidine, and the *Z* alkene gave only the *cis*, indicating that the reaction took place stereospecifically. Unlike the 5-*exo* cyclizations, these 6-*endo* cyclizations exhibited *anti* selectivity during the aminotrifluoroacetoxylation.

The effects of backbone substitution on diastereoselectivity were also examined (Table 4). Substitution alpha to the sulfonamide resulted in good selectivity for the *trans* product, whereas substitution in the beta position gave mostly *cis* stereochemistry. In the fused cyclohexene substrates **16** and **17**, selectivities were modest and appeared to be controlled mostly by the stereocenter alpha to the sulfonamide.

Table 4. Diastereoselectivity from Backbone Substitution

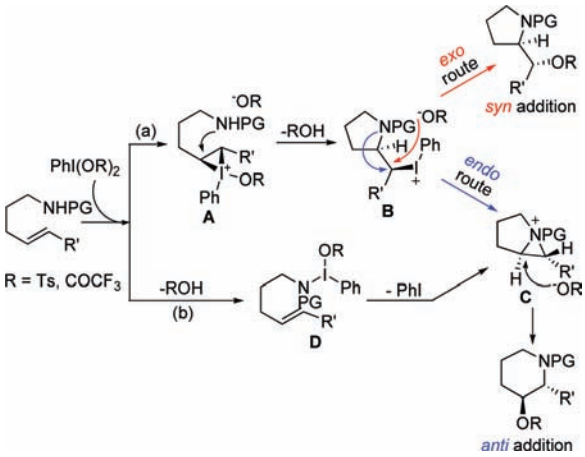
entry	alkene	product	conditions[a]	yield[b]
1	 **16** *trans*	 **16a**	**A**	61%[c], 3:1 dr[d]
2	**17** *cis*	**17a**	**A**	83%, 2:1 dr[d]
3	 **18**	 **18a**	**A**	67%, 2:1 rs 3.5:1 dr[d]
4	**19** R = Ph, PG = Ts	**19a**	**B**	91% (68%[e]), 19:1 rs, 4:1 dr[d]
5	**20** R = Me, PG = 2-Ns	**20a**	**B**	74%, >20:1 rs 3:1 dr[d]

[a] Condition A: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (0.2 mmol), CH_2Cl_2 (1 mL), rt, 12 h. Condition B: Alkene (0.1 mmol), $PhI(OAc)_2$ (0.12 mmol), TFA (1.2 mmol), CH_2Cl_2 (1 mL), rt, 24 h. [b] Isolated yield of aminoalcohol(s) following saponification, K_2CO_3/MeOH, rt, 5 min. [c] Isolated yield of major stereoisomer. [d] Major diastereomer determined by ^1H NMR spectroscopy. [e] rs = regioselectivity - *endo*/*exo* cyclization; determined by ^1H NMR spectroscopy.

Several possible mechanisms could be operative in this system. In our previous acid-promoted oxyamination of alkenyl ureas, we had proposed that cyclization occurred via successive displacements of an iodonium intermediate based on the observed stereospecific *syn* addition.[8] In this transformation, the stereochemical outcome is more ambiguous, appearing to favor *syn* addition in *exo* selective cyclizations (Table 3, entry 4) and *anti* in *endo* selective cyclizations (entries 5, 6). Such a reversal of the stereospecificity during piperidine formation suggests the cyclization does not solely proceed through a typical three-membered iodonium ion species, which favors the kinetic, *exo* ring closure.[9,14] It is known that aziridines can be oxidatively formed from alkenes and sulfonamides under various conditions,[15] and we propose that aziridinium ion formation is responsible for the observed overall *endo* and *anti* selectivity of this transformation. A plausible reaction mechanism to account for the observed selectivities is outlined in Scheme 1. First the alkene may be oxidized to generate an iodonium ion, **A** (pathway a). This intermediate may then be intramolecularly attacked by the sulfonamide to form the kinetically preferred intermediate **B**. For the more

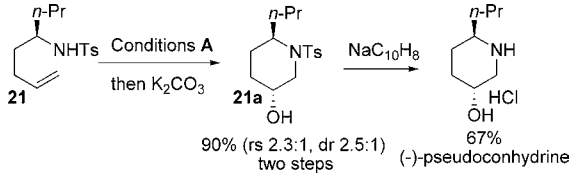
reactive styrenyl substrates **9**−**11** or for strained structures such as **12**, **B** is then rapidly trapped by the trifluoroacetate counterion to form the 5-*exo* products. The observed *syn* selectivity of substrates **10a** and **12a** is consistent with this double displacement mechanism. For less strained and reactive substrates such as **13**−**20**, the nitrogen may eventually displace the iodine to generate an aziridinium ion, **C**.[9c,16,17] Subsequent nucleophilic attack onto the more substituted carbon of **C** would then generate the *endo* cyclized products with *anti* selectivity. Alternatively, the sulfonamide may be directly oxidized prior to formation of the aziridinium ion (pathway b). Either oxidation pathway would converge to aziridinium ion, **C**, leading to an *endo* cyclization. The observation that there is no apparent difference in the rate of reaction of the Ns and Ts substituted substrates would appear to favor an alkene oxidation mechanism (pathway a) over a sulfonamide oxidation mechanism (pathway b).

Scheme 1. Proposed Reaction Mechanism



The utility of this transformation for the rapid construction of functionalized nitrogen heterocycles was demonstrated by its use in the concise total synthesis of (−)-pseudoconhydrine (Scheme 2).[15b,18] The oxidation substrate **21**[19] was made in three steps from D-norvalinol and subjected to the aminotrifluoroacetoxylation reaction. Following cyclization and saponification, purified **21a** was deprotected to provide (−)-pseudoconhydrine in only six steps and an unoptimized 22% overall yield.

Scheme 2. Total Synthesis of (−)-Pseudoconhydrine



In conclusion, we have developed a broadly applicable, high yielding oxyamination reaction of alkenes promoted by a Brønsted acid. High regioselectivities were observed for *endo* cyclizations of a wide range of substrates with good to excellent diastereoselectivities.

Acknowledgment. We thank the University of Washington for financial support of this project.

Supporting Information Available: Representative experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Following submission of this manuscript for publication, related work by Wardrop and coworkers was published in this journal: Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2009**, ASAP (DOI: 10.1021/ja9069997).
(11) Some hydrolysis of the trifluoroacetates was observed upon standing. Therefore, the aminotrifluoroacetoxylation products were intentionally saponified to the aminoalcohols during isolation.
(12) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun.* **2006**, 2156–2158.
(13) Cyclizaton of ***E*-14** also gave a mixture of regioisomers.
(14) Some *cis*/*trans* isomerism was observed in the presence of acid alone.
(15) When the iodoamination is performed with NIS, only the 5-*exo* pyrrolidine product is observed.
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JA906648W