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Hydroamination and Hydroalkoxylation Catalyzed by Triflic Acid. Parallels to Reactions Initiated with Metal Triflates

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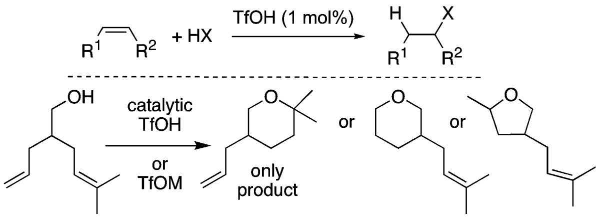
ABSTRACT



Intermolecular additions of the O–H bonds of phenols and alcohols and the N–H bonds of sulfonamides and benzamide to olefins catalyzed by 1 mol % of triflic acid and studies to define the relationship between these reactions and those catalyzed by metal triflates are reported. Cyclization of an alcohol containing pendant monosubstituted and trisubstituted olefins catalyzed by either triflic acid or metal triflates form products from addition to the more substituted olefin, and additions of tosylamide catalyzed by triflic acid or metal triflates form indistinguishable ratios of the two *N*-alkyl sulfonamides.

Mild, metal-catalyzed additions of N−H and O−H bonds across olefins have been sought for decades, and efforts to develop such processes have intensified in recent years. During the past 5 years, we have reported catalysts for intermolecular additions of amines to vinylarenes and additions of amines and phenols to dienes.[1] In parallel with this work on metal-catalyzed reactions, we reported that triflic acid and sulfuric acid catalyze the intramolecular additions of the N−H bond of sulfonamides, carbamates, acetamides, and benzamides across the C−C double bond of alkenes and vinylarenes.[2] Of course, related acid-catalyzed additions of alcohols to alkenes are classic reactions in organic chemistry.[3]

Many of the catalysts for intermolecular additions of N−H and O−H bonds across alkenes that have been reported recently are either metal triflates or combinations of metal halides and silver triflate.[4−10] These catalysts include copper, silver, gold, ruthenium, platinum, and palladium complexes.

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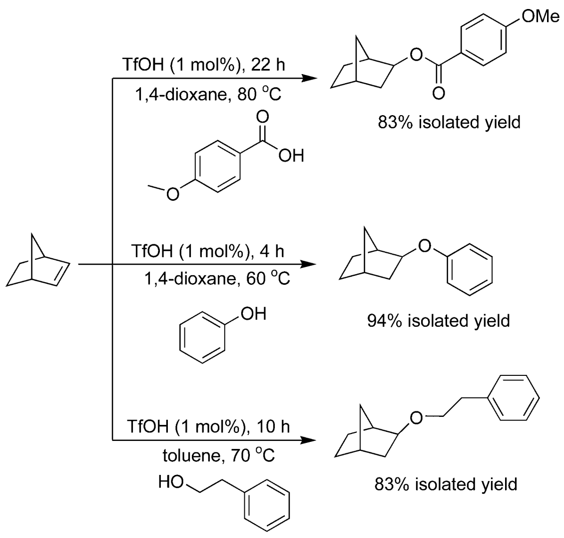
Our current work originated from an unpublished observation that the addition of cyclohexanol to styrene in the presence of a combination of a ruthenium precursor and triflic acid was more likely catalyzed by a phosphonium triflate, generated from the metal−phosphine complex and acid, than by a ruthenium complex.[11] At a similar time, Spencer reported that acid can be the true catalyst in Michael additions of heteroatom nucleophiles to acrylic acid derivatives conducted with catalytic amounts of metal complexes.[12]

With these results as a backdrop, we have explored the addition of various alcohols, carboxylic acids, phenols, carbamates, and sulfonamides to alkenes and vinylarenes catalyzed by triflic acid alone.[13,14] In addition to exploring the scope of acid-catalyzed additions, we have compared the rates, side products, and selectivities of the acid-catalyzed reactions to those of some of the reactions run with catalytic amounts of metal triflates. These data show that most reactions reported with metal triflates as catalyst also occur with triflic acid as catalyst, that limiting the quantity of acid is crucial to observing additions in high yields in some cases, and that the selectivities and side products of the reactions catalyzed by triflic acid often mirror those observed during the reactions initiated with metal triflates. These results led us to develop a substrate that can also help distinguish between additions of X−H bonds to olefins that occur intramolecularly and that could be catalyzed by metal complexes or by acid.

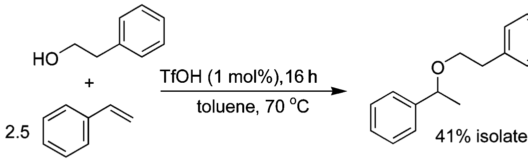
Our studies began with an exploration of the additions of carboxylic acids, phenols, and alcohols to norbornene. These reactions are summarized in Scheme 1. Several papers have stated that products from the additions of these reagents to olefins form in low yield in the presence of 10−15 mol % of triflic acid,[6,8,9] and we found the same result when a large loading of acid is used. However, these conditions do consume the olefin. We found that some addition product forms at early times, but that this product undergoes decomposition in the presence of the large amount of acid.

Scheme 1

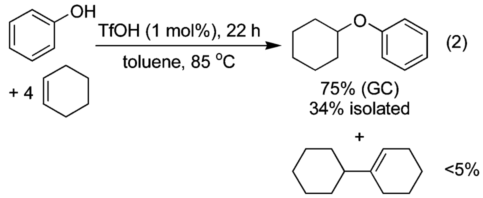


In contrast, reactions of carboxylic acids, phenols, and alcohols occurred cleanly in the presence of a smaller, 1 mol % quantity of triflic acid, as shown in Scheme 1. With this amount of acid catalyst, addition of anisic acid occurred within a day at 80 °C, the addition of phenol occurred after heating at 60 °C for 4 h, and the addition of β-phenethyl alcohol occurred after 10 h at 70 °C in high isolated yields.

These additions of O−H bonds to olefins catalyzed by triflic acid were not limited to reactions of the strained norbornene. Addition of β-phenethyl alcohol to a small excess of styrene formed the addition product in 41% isolated yield. When this reaction was conducted for 1 day at 70 °C, significant decomposition of the product occurs, and the product from dimerization of styrene increases. Addition of phenol to cyclohexene formed the addition product in 34% isolated yield, with the product from hydrovinylation of cyclohexene comprising less than 5% of the product mixture.



(1)



(2)

Additions of aliphatic amines to olefins in the presence of acid do not occur under mild conditions, presumably because of the leveling effect of the amine. The reactions of olefins with arylamines can be catalyzed by acid, but significant amounts of hydroarylation product are formed in combination with the hydroamination product.[14] Further, control reactions on the addition of aniline to vinylarenes and dienes did not occur with triflic acid, at least at the temperatures of the metal-catalyzed processes.[1b] The sole production of N−H addition products from reactions catalyzed by $L_2Pd(OTf)_2$ or Pd(0) complexes with triflic acid as cocatalyst[1j] and the absence of addition product with HOTf as catalyst alone, as well as the observation of substantial enantiomeric excess for some additions,[1i,j] imply that the Pd-catalyzed hydroaminations of vinylarenes and dienes are truly metal catalyzed.[1b]

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(10) Zhang, J. L.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

(11) Utsunomiya, M.; Hartwig, J. F. Unpublished results.

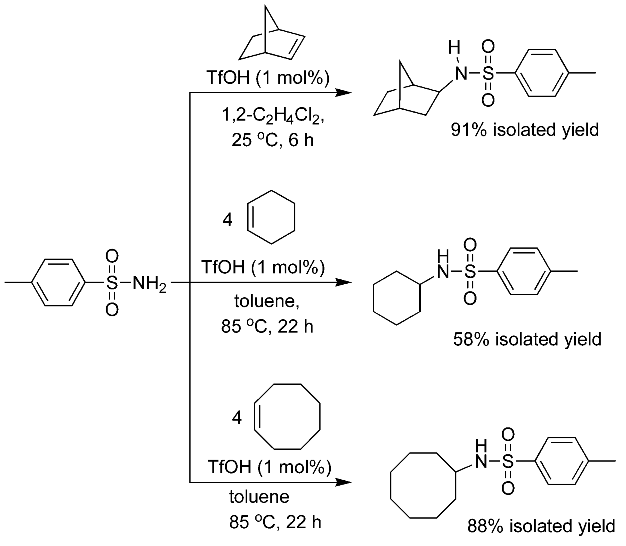
(12) (a) Wabnitz, T. C.; Yu, J. Q.; Spencer, J. B. *Chem.*−*Eur. J.* **2004**, *10*, 484. (b) For a similar study on the additions of arene C−H bonds to α,β-unsaturated ketones catalyzed by Au(III) and HBF_4, see: Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247.

(13) For reactions of anilines with norbornene and vinylarenes catalyzed by acids with tetraarylborate anions, see ref 14.

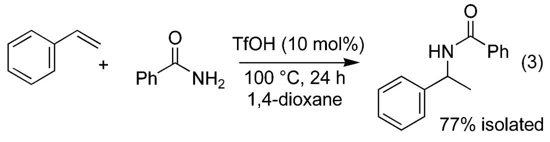
(14) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

However, less basic reagents with N−H bonds, such as amides, carbamates, and sulfonamides, do add to olefins under acid-catalyzed conditions. Our past intramolecular additions of sulfonamides, carbamates, acetamides, and benzamides and the use of metal triflates for additions of these reagents to alkenes led us to investigate intermolecular additions of these reagents to alkenes catalyzed by triflic acid alone. These results are summarized in Scheme 2.

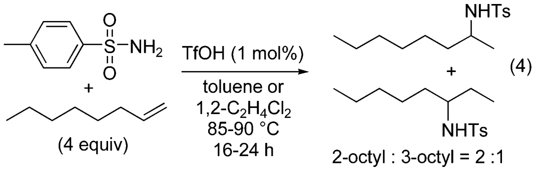
Scheme 2



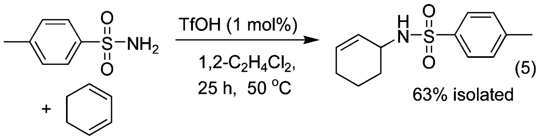
The addition of *p*-toluenesulfonamide ($TsNH_2$) to norbornene occurred within hours at room temperature in dichloroethane solvent to form the exo addition product in 91% yield. Like the reactions of alcohols catalyzed by triflic acid, the reactions of sulfonamides catalyzed by acid were not limited to additions to the strained norbornene. The addition of $TsNH_2$ to cyclohexene and cyclooctene occurred within a day at 85 °C in 58 and 86% isolated yield. The addition of benzamide to styrene also occurred at 100 °C in dioxane solvent over 24 h in 77% yield (eq 3).



The reaction between $TsNH_2$ and an excess (4 equiv) of 1-octene occurred to high conversion at 85−90 °C over 16−24 h in toluene to form an approximately 2:1 ratio of the 2- and 3-*N*-octyl tosylamides. The same mixture of isomers in toluene also formed from reactions conducted in the presence of catalytic amounts of $(Ph_3P)AuOTf$.[10] The formation of these isomers upon acid-catalyzed chemistry implies that a carbocation is generated and a 1,2-hydrogen shift competes with trapping of the carbocation by the sulfonamide.



Several reports of the addition of sulfonamides to dienes catalyzed by metal triflates have appeared recently.[7,15] We found that $TsNH_2$ adds to cyclohexadiene in the presence of 1 mol % of triflic acid, and that this reaction was nearly complete after 25 h at 50 °C to form the addition product in 63% isolated yield (eq 5).



Because the scope of the reactions catalyzed by HOTf and metal triflates is closely related, we also compared qualitatively the rates of the additions in the presence of catalytic amounts of triflic acid to the rates of additions in the presence of catalytic amounts of several metal triflates. These comparative studies showed that the rates of reaction catalyzed by 1 mol % of triflic acid were similar to the rates of reactions catalyzed by metal triflates in equal to or greater amounts.

In particular, reactions of β-phenethyl alcohol with styrene and norbornene conducted with the combination of 2 mol % of $Cp^*Ru(PPh_3)Cl_2$ and 4 mol % of AgOTf as catalyst required 48 h at 70 °C,[6] whereas these two reactions occurred over 10−16 h at 70 °C when conducted with only 1 mol % of HOTf. The addition of 4-*tert*-butyl phenol to cyclohexene occurred at 85 °C over 15 h in the presence of 2 mol % of $(Ph_3P)AuOTf$,[9] whereas the addition of phenol to cyclohexene occurred at 85 °C over a similar time frame (22 h) with only 1 mol % of HOTf. Likewise, the addition of *p*-anisic acid or phenol to norbornene occurred over 18 h at 80 °C with 2.5 mol % of $Cu(OTf)_2$[8] and occurred under the same conditions providing similar yields with 1 mol % of HOTf. Further, the reaction of $TsNH_2$ with norbornene catalyzed by 1 mol % of HOTf occurred at room temperature instead of the elevated temperatures and higher loadings of metal triflates.[5,10]

The reaction between a large number of N−H and O−H bond donors and olefins catalyzed by metal triflates has been published, and it is beyond the scope of this work to analyze each of these processes. However, the side products formed during some of these reactions and the acid-catalyzed reactions shed some light on the relationship between these two processes.

For example, the reactions between phenol and cyclohexene and between $TsNH_2$ and cyclohexene or cyclooctene in the presence of triflic acid formed a set of side products with masses equal to twice the mass of the olefin. We presume these products are regioisomers formed by trapping of the

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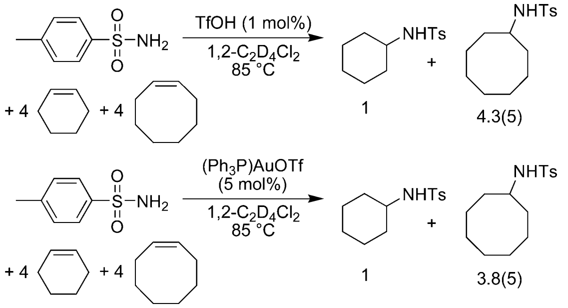
(15) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744.

carbocation intermediate with the excess of olefin. This reaction of the carbocation apparently competes with trapping of the carbocation by the phenol or the sulfonamide. Most important for assessing the relationship between acid- and metal-catalyzed reactions, these same side products were formed during the reaction of cyclohexene and cyclooctene with TsNH$_2$ conducted with catalytic amounts of (Ph$_3$P)AuOTf.

Considering the potential that the metal complexes serve as precatalysts for the formation of a protic acid catalyst, we sought to develop protocols to distinguish between these two types of additions. One protocol involves measuring the ratios of products formed between an N−H and O−H bond donor and two different olefins. The second protocol allows analysis of intramolecular reactions and involves the addition of an O−H bond across two different olefins that are distinct in their steric properties and ability to stabilize a carbocation.

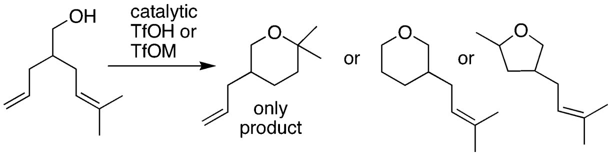
Scheme 3



Results from the first protocol are shown in Scheme 3. The reaction of TsNH$_2$ with 4 equiv each of cyclohexene and cyclooctene was conducted. The reaction in the presence of 1 mol % of triflic acid led to a 1:4 ratio of the product from addition of cyclohexene and cyclooctene. The ratio of products fluctuated during the course of the reaction, but by no more than 15% of the average value. The measured ratios for the addition products appeared to reflect the kinetic ratio because addition of 3 equiv of cyclooctene and 1 mol % of triflic acid to *N*-cyclohexyl-*p*-toluenesulfonamide did not produce any detectable *N*-cyclooctyl-*p*-toluenesulfonamide after 12 h at 90 °C and 4 h at 120 °C. The ratio of these two products formed from the same reaction catalyzed by (Ph$_3$P)AuOTf (Scheme 3) is clearly similar to the ratio formed from the acid-catalyzed process.[16]

The second protocol involves cyclization of an alcohol containing a monosubstituted and a 2,2-disubstituted olefin, with this reaction being shown in Scheme 4. We assume that metal-catalyzed O−H or N−H additions by a combination of olefin coordination and insertion or by a combination of olefin coordination and nucleophilic attack would be faster to the less substituted olefin than to the more substituted olefin; complexes of less substituted olefins are more stable than complexes of more substituted olefins. Of course, the acid-catalyzed addition would occur faster to the 2,2-disubstituted olefin than to the monosubstituted olefin because it would form a more stable carbocation intermediate. Indeed, cyclization of this substrate in the presence of 1 or 10 mol % of triflic acid for 12 h in toluene at 80 °C formed only the product from cyclization at the more substituted olefin. This product was isolated in 61% yield from a reaction conducted with 1 mol % of HOTf. The reactions initiated with 2.5 mol % of Cu(OTf)$_2$; with 10 mol % of AgOTf; with 2 mol % of [Cp*RuCl$_2$]$_2$, 4 mol % of PPh$_3$ and 2.5 mol % of AgOTf; with 5 mol % of (Ph$_3$P)AuCl and 5 mol % of AgOTf; and with 10 mol % of FeCl$_3$ under conditions published for the reactions of alcohols with olefins also formed the product from cyclization at the more substituted olefin.

Scheme 4



Thus, we have shown that triflic acid in weakly basic solvents catalyzes the additions of a broad range of O−H and N−H bond donors to unactivated alkenes. The rates and product ratios from reactions catalyzed by acid and metal triflates were similar, and cyclization of a diene resulted in the same product from reaction at the more substituted of the olefins when metal triflate or triflic acid alone was used as catalyst. Therefore, one must consider carefully whether the additions of weakly basic substrates with N−H and O−H bonds to olefins catalyzed by metal triflates are true metal-catalyzed processes or if the metal simply generates a protic acid.

Acknowledgment. We thank the NIH (GM-55382) for support of this work. M.U. thanks Mitsubishi Chemicals for support.

Supporting Information Available: Reaction procedures, substrate synthesis, and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) One could also envision using the ratio of endo and exo isomers formed from addition of O−H and N−H bond donors to norbornene catalyzed by acid and by a metal complex to distinguish the two pathways. Although a mixture of endo and exo isomers was stated to be observed from the addition catalyzed by 10 mol % of triflic acid after 18 h at 80−85 °C,[7,9] we have observed greater than 95% of the exo isomer after 95% conversion of the olefin (4 h, 90 °C) during reactions conducted with 1, 2, or 5 mol % of triflic acid, with 5 mol % of (Ph$_3$P)AuCl/AgOTf in toluene, or 2.5 mol % of Cu(OTf)$_2$ in dioxane for 2−4 h. At longer reaction times (ca. 22 h), we began to observe an increase in the amount of endo isomer.