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Brønsted Acid Catalyzed Addition of Phenols, Carboxylic Acids, and Tosylamides to Simple Olefins

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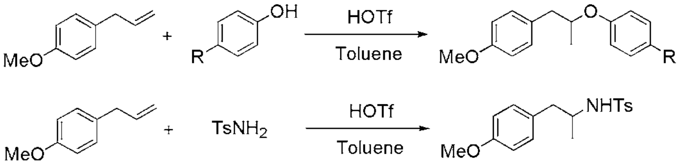
ABSTRACT



Intermolecular addition of phenols, carboxylic acids, and protected amines to inert olefins can be catalyzed by low concentrations (1–5%) of triflic acid. Functional groups, such as the methoxyl substitution on aromatics, could be tolerated if the concentration of triflic acid and the reaction temperature are controlled appropriately. This reaction provides one of the simplest olefin addition methods and is an alternative to metal-catalyzed reactions.

Nucleophilic addition of phenols, carboxylic acids, and protected amines to unsaturated carbon−carbon bonds provides one of the simplest methods to construct valuable synthetic building blocks.[1] Continuous efforts have been made in this field with various methods developed, particularly, in the past decade. Most of these methods use expensive and often toxic metal catalysts, including palladium,[2] rhodium,[3] ruthenium,[4] lanthanides,[5] main group metals,[6] and most recently, platinum and gold.[7] The employment of metal-based catalysts offers promises to perform enantioselective additions and to tolerate labile functional groups; however, it also limits large-scale applications of these reactions and often generates heavy metal impurities in the product. Direct use of simple Brønsted acids under relatively mild conditions may overcome these shortcomings.

Various Brønsted acids have been found to catalyze hydroamination, hydrophosphonylation, aziridination, and transfer-hydrogenation of imines.[8] Even though Brønsted acid

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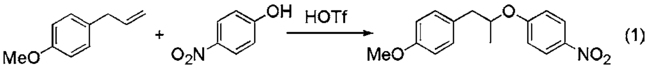
mediated olefin hydration was known over 50 years ago,[9] other acid-catalyzed additions to simple olefins have been studied to a less extent.[10] Direct addition of nitrogen, oxygen, and sulfur nucleophiles to α,β-unsaturated ketones catalyzed by Brønsted acid was reported recently.[11] Hartwig et al. reported in 2002 an intramolecular hydroamination of olefins catalyzed by Brønsted acids.[12] Bergman et al. also described an acid-catalyzed hydroamination of activated alkenes with anilines.[13] Herein, we report a simple, efficient nucleophilic intermolecular addition of phenols, carboxylic acids, and tosylamides to unactivated olefins catalyzed by trifluoromethanesulfonic acid (HOTf, triflic acid). Our modified reaction conditions can tolerate some substrates that were previously regarded as incompatible with strong Brønsted acids.

The methoxyl substitution on aromatic systems is typically considered unstable under strong Brønsted acid conditions in nucleophilic addition reactions. Most previous experiments employed 20% acid that led to decomposition of this group. We tested a reaction between allylanisole and *p*-nitrophenol with lower concentrations of triflic acid at various temperatures. As summarized in Table 1, the use of 1, 2, and 5% HOTf gave almost identical results at 85 °C: a small amount of the addition product was observed with most allylanisole decomposed (Table 1, entries 1−3). Decreasing the reaction temperature increased the product yield. Almost quantitative conversion (based on the phenol nucleophile) to the ether product was achieved if the reaction was run at room temperature for 48 h (Table 1, entry 6).

With 2−5% HOTf as the Brønsted acid catalyst, we tested the additions of *p*-nitrophenol and *p*-methoxyphenol to various olefins. Good to excellent conversions were observed for most substrates (Table 2, the excess of olefins are stable in these reactions at room temperature). An electron-donating substitution on both substrates seems to enhance the activity.

Table 1. Addition of *p*-Nitrophenol to Allylanisole

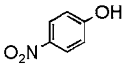
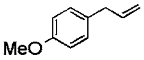
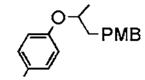
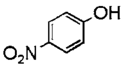
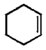
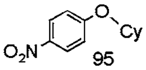
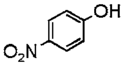
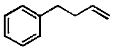
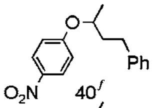
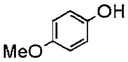
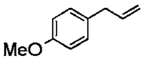
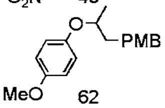
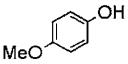
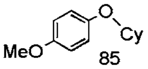
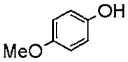
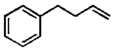
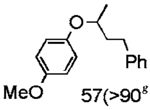
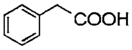
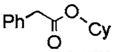
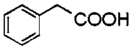
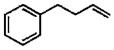
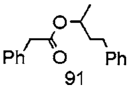


entry	condition[a]	olefin recovery[b]	phenol recovery[b]	product (%)[b]
1	1% HOTf, 85 °C	N	Y	trace
2	2% HOTf, 85 °C	N	Y	trace
3	5% HOTf, 85 °C	N	Y	trace
4	2% HOTf, 50 °C	N	Y	<60
5	1% HOTf, 50 °C	N	Y	<60
6	2% HOTf, rt	Y	N	>95[c]

[a] All reactions were carried out under N_2 in 2 mL of toluene overnight. Phenol:olefin = 1:4 at 1 mmol scale. [b] Determined by ^{1}H NMR. [c] After 48 h.

The addition of *p*-methoxyphenol to olefins can be achieved at room temperature (Table 2, entries 4−6); however, elevated temperatures are required for additions of *p*-nitrophenol to unactivated olefins (Table 2, entries 2 and 3, no reaction occurred at room temperature after 24 h for these two cases). Carboxylic acids could also be efficiently added to olefins at 50 °C (Table 2, entries 7 and 8).

Table 2. Addition of Phenols and Carboxylic Acid to Olefins[a]

entry	phenol	olefin	temperature[b]	product(%)[c]
1[d]			rt	 93
2[d]			50 °C	 95
3[e]			50 °C	 40[f]
4[d]			rt	 62
5[d]			rt	 85
6[d]			rt	 57(>90[g])
7[d]			50 °C	 94(70[h])
8[e]			50 °C	 91

[a] All reactions were carried out with nucleophile:olefin = 1:4 at 1 mmol scale in 2 mL of toluene. [b] All reactions at rt were run for 48 h; all reactions at 50 °C were run for 16−24 h. [c] Isolated yield. [d] A large amount of olefin remains after reactions. [e] All remaining olefin migrates; see Scheme 1. [f] Yield based on ^{1}H NMR. [g] An overnight reaction at 50 °C afforded >90% conversion, but with isomers and byproducts. [h] After an overnight reaction at 85 °C.

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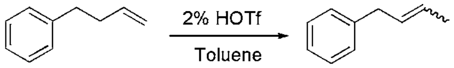
Temperature is a key factor in controlling the addition reactions reported here. Degradation of olefins occurs at high temperatures.[14] The stability of 4-phenyl-1-butene was tested in toluene with 2% triflic acid at different temperatures (Scheme 1). This substrate was stable at room temperature for 24 h without noticeable change of its ^{1}H NMR spectrum. Heating the substrate overnight at 50 °C led to ~50% degradation and ~50% migration of the olefin. Complete degradation of this olefin was observed after heating at 85 °C overnight. It should be noted that addition of phenylacetic acid to 4-phenyl-1-butene at 50 °C gave 91% isolated product without migration (Table 2, entry 8). Apparently, the addition step is faster than olefin migration in this case; the addition of carboxylic acids to olefins did not occur at room temperature.

Scheme 1. Triflic Acid Catalyzed Olefin Rearrangement



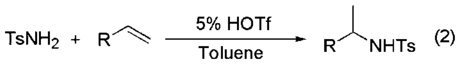
rt	no reaction[a,b]
50 °C:	~50% rearranged product + degradation[c]
85 °C:	complete degradation[c]

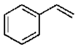
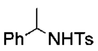
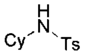
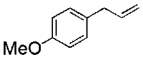
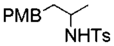
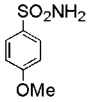
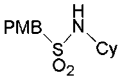
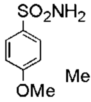
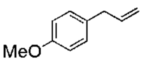
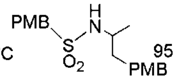
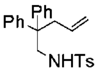
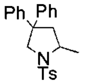
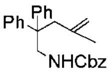
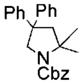
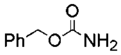
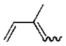
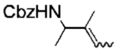
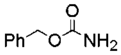
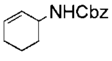
[a] Reactions were monitored by 1H NMR. [b] 24 h reaction. [c] An overnight reaction.

Triflic acid at low concentrations is also capable of mediating hydroamination of simple olefins under relatively mild conditions (Table 3). In contrast to phenols and carboxylic acids, addition of $TsNH_2$ to unactivated olefins requires a higher temperature (60−85 °C) to afford good conversions. A methoxyl substitution on the nucleophile could be tolerated with the use of 1% to 5% HOTf (Table 3, entries 4 and 5); however, the use of 20% HOTf led to decomposition of the starting material and observation of a trace amount of the addition product, demonstrating the effect of the acid concentrations on these reactions. Not surprisingly, intramolecular hydroamination with both TsNH− and CbzNH− moieties as nucleophiles worked efficiently with 5% triflic acid at 85 °C (Table 3, entries 6 and 7). $CbzNH_2$ could be added to 1,3-dienes to afford allylamines in good yields (Table 3, entries 8 and 9). Thus, both methoxyl and Cbz groups can be tolerated with 5% triflic acid in these reactions.

Triflic acid appears to be more active than cationic gold(I) we previously employed for catalyzing this type of transformation.[7d−f] It works at a lower temperature; however, it also generates more side products at elevated temperatures (Table 4). HOTf could catalyze reactions at room temperature, while $Ph_3PAuOTf$ was completely inactive. Similar results were described in other gold-mediated reactions.[15] The use of $Ph_3PAuOTf$ afforded good conversions to the addition products at 85 °C, while HOTf led to degradation of the "labile" substrate. This result is in agreement with the olefin migration reaction shown in Scheme 1. At elevated temperatures (80−85 °C), HOTf completely decomposed the olefin, whereas $Ph_3PAuOTf$ gave a clean 75% migration.

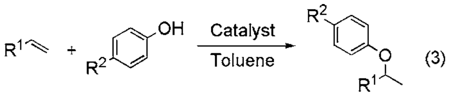
Table 3. Hydroamination of Olefins and 1,3-Dienes[a]

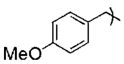
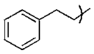


entry	amine	olefin	temperature	product	(%)[b]
1	$TsNH_2$		85 °C		70
2	$TsNH_2$		85 °C		85
3	$TsNH_2$		60 °C		88
4			85 °C		95[c]
5[d]			60 °C		95
6			85 °C		90
7			85 °C		81
8[e]			rt		83
9[e]			50 °C		71

[a] All reactions were carried out with nucleophile:olefin = 1:4 (1:1.2 for entries 8 and 9) at 1 mmol scale in 2 mL of toluene overnight. [b] Isolated yield. [c] 20% HOTf led to decomposition of the nucleophile. [d] 48 h reaction. [e] 1% HOTf was used with dichloroethane as the solvent.

Table 4. Temperature Difference in HOTf- and $Ph_3PAuOTf$-Catalyzed Reactions



R^1	R^2	temperature	HOTf (5%)	$Ph_3PAuOTf$ (5%)[a]
	NO_2	rt	93%[b]	no reaction[c]
		85 °C	trace[d]	81%[b, e]
	OMe	rt	57%[b]	no reaction[c]
		85 °C	trace[d]	58%[b, e]

[a] $Ph_3PAuOTf$ was generated in situ by mixing Ph_3PAuCl and AgOTf. [b] Isolated yield. [c] No reaction after 24 h. [d] ^{1}H NMR conversion. [e] Cited from ref 7d.

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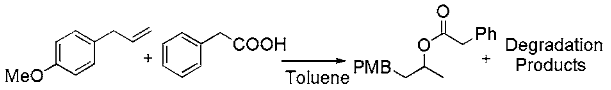
[14] Friedel−Crafts products from toluene addition were observed.

[15] (a) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247−1252. (b) Hashmi, A. S. K.; Schwarz, L.; Rubenbauer, P.; Blanco, M. C. *Adv. Synth. Catal.* **2006**, *348*, 705−708.

The difference is further shown in a reaction between allylanisole and phenylacetic acid: 2% triflic acid gave the expected addition product (∼60% ^{1}H NMR yield) at 50 °C and decomposition of most of the allylanisole at 85 °C.[16] $Ph_3PAuOTf$ is inactive at 50 °C but can catalyze the addition reaction to afford 95% isolated product at 85 °C.

Table 5. Different Reactivity between HOTf and $Ph_3PAuOTf$

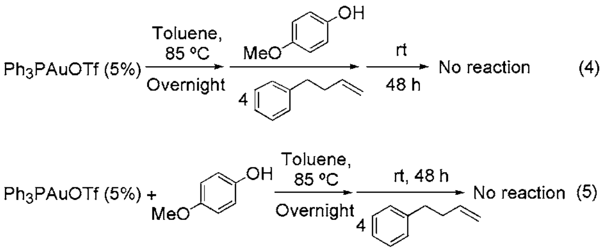


temperature	HOTf	$AuPPh_3OTf$
rt	no reaction[a]	no reaction[a]
50 °C	60% conversion[b]	no reaction[a]
85 °C	trace[b]	95%[c]

[a] No reactions after 24 h. [b] ^{1}H NMR yield. [c] Isolated yield, cited from ref 7d.

Could the gold-mediated reactions be catalyzed by acid generated from reacting gold(I) with nucleophile? Our results do not support such a possibility. (i) In the absence of proton source, we heated 4-phenyl-1-butene in the presence of 1 mol % of $Ph_3PAuOTf$ at 85 °C in toluene to afford approximately 75% of 4-phenyl-2-butene in a 2.2:1 *E*:*Z* ratio. Triflic acid completely decomposes the olefin under the same conditions. (ii) Reactions catalyzed by gold(I) showed functional group tolerance at 85 °C, while triflic acid led to complete decomposition of substrates, such as allylanisole. (iii) Our previous ^{31}P NMR study did not detect formation of $Ph_3PAuNHTs$ when $Ph_3PAuOTf$ was heated with $TsNH_2$ at 85 °C, while $Ph_3PAuNHTs$ reacts with HOTf readily to release $Au(PPh_3)OTf$ and $TsNH_2$ as monitored by NMR experiments (Supporting Information). A soft gold(I) ion will not react with $TsNH_2$ to give $Ph_3PAuNHTs$ and a strong acid. The reverse reaction is highly preferred.[17] (iv) When $Ph_3PAuOTf$ was heated overnight with or without phenol nucleophile and then reacted with an olefin (plus phenol if not already added) for 2 days at room temperature, no reaction was detected (gold will not mediate this reaction at room temperature), while 2% HOTf gave 57% isolated yield for the same reaction after 2 days at room temperature (Scheme 2 and Table 2, entry 6).

Scheme 2



We propose that the cationic gold(I), preferring a linear two-coordinate geometry, may activate the olefin to generate an incipient carbon cation that traps weak nucleophiles[7c] similar to an acid-catalyzed process. We do not think acid could be generated as the catalyst in gold(I)- or platinum-(II)-mediated reactions.[7] With hard, highly positively charged metal cations, that would be a concern.

In conclusion, we show here that HOTf can efficiently catalyze the addition of phenols, carboxylic acids, and tosylamides to simple olefins under mild conditions. Some functional/protecting groups, such as the methoxyl substitution on arenes and Cbz, can be tolerated if the concentration of the Brønsted acid and the reaction temperature are controlled appropriately. The use of HOTf for these reactions provides a simple alternative to toxic and precious metals.

Acknowledgment. This research is supported by the University of Chicago. C.H. is also a recipient of a Research Innovation Award (RI1179) from Research Corporation and an Alfred P. Sloan Research Fellowship.

Supporting Information Available: Representative experimental procedure and the characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) At 50 °C, product could not be isolated from other byproducts.

(17) Perevalova, E. G.; Struchkov, Yu. T.; Kravtsov, D. N.; Kuz'mina, L. G.; Smyslova, E. I.; Kalinina, O. N.; Dyadchenko, V. P.; Voevodskaya, T. I. *Zh. Obshch. Khim.* **1988**, *58*, 62−71.