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Superacid-catalyzed Friedel–Crafts cyclization of unactivated alkenes

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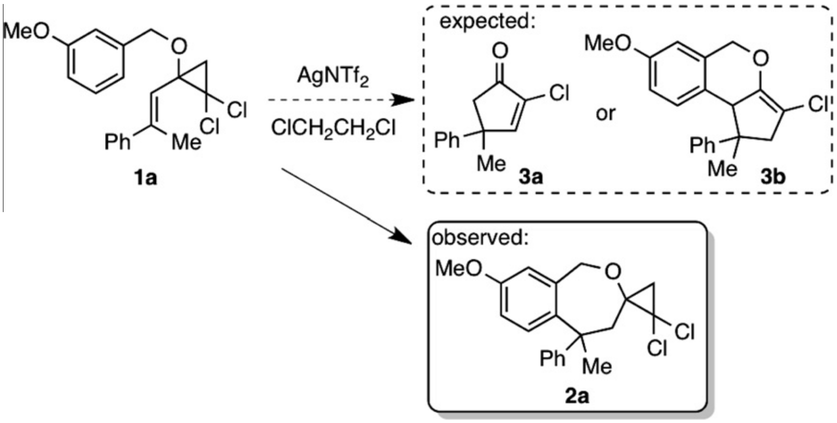
ABSTRACT

Trifluoromethanesulfonimide is an effective catalyst for Friedel–Crafts cyclizations of simple, nonpolarized alkenes with a variety of pendant arenes. A catalyst loading of 0.5 – 1.0 mol % effects clean cyclization to form 5- to 7-membered carbocycles with generally short reaction times and good to excellent yields under reflux or microwave heating.

The Friedel–Crafts reaction occupies a prominent position in the chemist's toolbox for the addition of carbon functionality to arene moieties, and intramolecular versions are well established. Alkenes can function as the electrophilic partners in intramolecular Friedel–Crafts reactions, though typically this is limited to Michael acceptor alkenes activated by Brønsted or Lewis acids.[1,2] This can necessitate additional steps to remove the activating group when it is not desired in the target molecule.[3] Historically, Brønsted acid mediated Friedel–Crafts reactions of simple alkenes have used one or more equivalents of acid to promote cyclization.[4] More recently, it was found that simple alkenes participate in these cyclizations in the presence of catalytic promoters such as $In(OTf)_3$,[5] $RuCl_3$,[6] Pt(II),[7] and $Bi(OTf)_3$.[8] Cyclization of less substituted alkenes is preferred when metals are used, so the use of Brønsted acids is



Scheme 1. Unexpected Friedel–Crafts reaction of **1a**.

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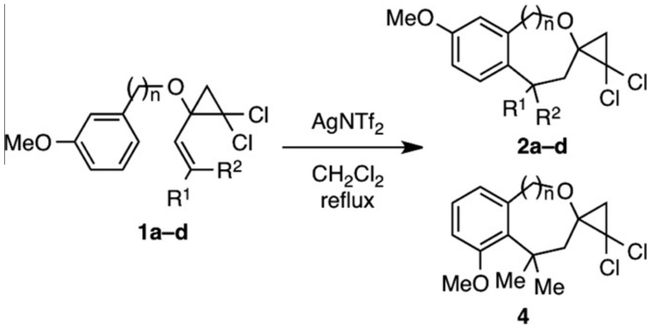
Table 1
Friedel–Crafts cyclization of dichlorocyclopropane substrates[a]



Entry	Substrate	R^1	R^2	*n*	Yield[b] (%)/product ratio
1	**1a**	Ph	Me	1	79/1.9:1[c]
2	**1b**	Me	Me	1	43/2.4:1[d]
3	**1c**	4-$MeOC_6H_4$	H	1	64/1:1[c]
4	**1d**	4-$MeOC_6H_4$	H	2	52/1:1[c]

[a] Conditions: substrates **1** were dissolved in DCM (0.05 M) with $AgNTf_2$ (10 mol %) and stirred at reflux until **1** was consumed (ca. 20 h).

[b] Yields given are for pure product after chromatographic purification.

[c] Ratio of diastereoisomers of **2**.

[d] Ratio of regioisomers **2b** and **4**.

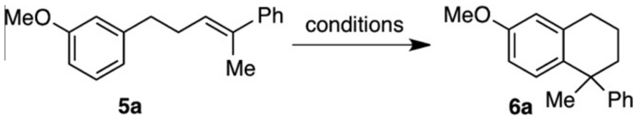
complementary with a preference for bond formation of more highly substituted alkenes. With the advent of modern ‘superacids’,[9] it stands to reason that the cyclization of simple alkenes should be amenable to catalysis, and this has been shown in an example of a triflic acid-catalyzed cyclization of arene–alkene units in a polymeric system.[10] However, to our knowledge there has been no definitive work on the optimization and scope of this reaction, despite the recent interest in the corresponding metal-catalyzed versions. Here we describe a Brønsted acid-catalyzed intramolecular Friedel–Crafts alkylation between various aromatic partners and simple alkenes. The reaction is high-yielding, convenient, and atom-economical.

We have previously shown that 2-alkenyl-1,1-dichloro-2-silyloxycyclopropanes undergo a domino process involving Ag(I)-promoted electrocyclic opening of the cyclopropane, followed by Nazarov cyclization of the resulting pentadienyl cation.[11] Moreover, the resulting cyclopentenyl cation can be intercepted by electrophilic aromatic substitution onto a pendent arene.[12] We initially set out to extend the generality of this latter process through the preparation of benzylic ether **1a** and examination of its behavior in the presence of 1 equiv of $AgNTf_2$ (Scheme 1). In the event, we found to our surprise that the sole product was intramolecular Friedel–Crafts alkylation product **2a**, a 1,3,4,5-tetrahydro-2-benzoxepin formed in moderate yield as a 1.2:1 mixture of diastereomers. No evidence was observed for the anticipated Nazarov process to produce either **3a** or **3b**. On further investigation, it was found that optimal Friedel–Crafts reactivity of **1a** could be realized using 10 mol % of $AgNTf_2$ in DCM at reflux, and these conditions were applied to several other substrates (Table 1) to afford benzo-fused 7- and 8-membered cyclic ethers **2a**–**d** (along with minor amounts of regioisomer **4** in the case of dimethyl-substituted **1b**, entry 2).

Given the prior observation that metal triflates and triflimides are known to form the corresponding Brønsted acids TfOH and Tf_2NH in the presence of water or other protic impurities,[13] we speculated that the observed Friedel–Crafts cyclization reactivity might arise from traces of $HNTf_2$. To probe the nature of the actual catalyst, we prepared the simplified substrate **5a**, and subjected it to cyclization conditions in the presence of $AgNTf_2$ with or without added water, $HNTf_2$, and other Brønsted acids (Table 2). When the reaction components were filtered through dry potassium carbonate under inert atmosphere to remove the residual water from the dichloromethane as well as any trace $HNTf_2$ that may be in the $AgNTf_2$, no reaction occurred upon extended stirring, supporting the need for trace acid to catalyze this reaction (entry 1). $HNTf_2$ itself proved to be a very effective catalyst for the process, and the reaction proceeded to completion within 1 h with only 0.5% loading of the acid (entry 2). Increasing the catalyst loading to 1% $HNTf_2$ has little effect on the yield of **6a**; however, the time required for the consumption of **5a** was significantly reduced (entry 3). Conversely, decreasing the catalyst to 0.1% led to an unacceptable reaction time and inconsistent yields.

A controlled amount of water was added to **5** and $AgNTf_2$ to demonstrate that hydrolysis of the silver salt by amounts of water available in ‘dry’ dichloromethane[14] can lead to generation of sufficient Brønsted acid active catalyst to effect conversion of **5a** to **6a**. In all of these cases, reactivity was at least partially restored, with 0.5 mol % water being optimal, and higher concentrations led to

Table 2
Effect of added water or Brønsted acid[a]



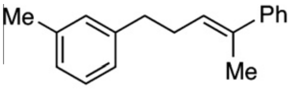
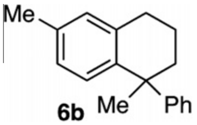
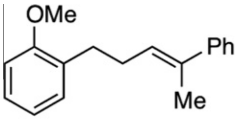
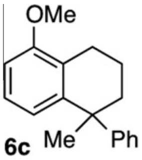
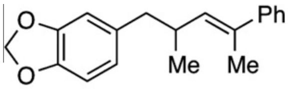
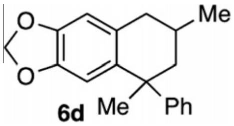
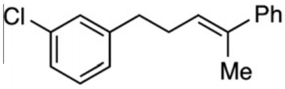
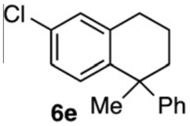
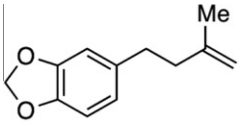
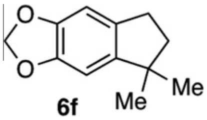
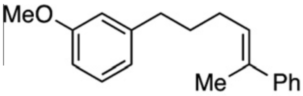
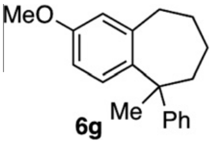
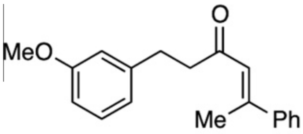
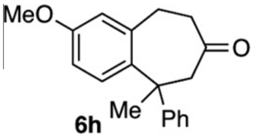
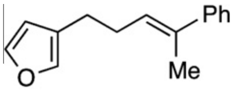
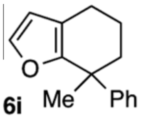
Entry	$AgNTf_2$ (mol %)	Brønsted acid (mol %)	H_2O (mol %)	Time (h)	Yield of **6a**[b] (%)
1	10	–	–	24	0
2	–	$HNTf_2$ (0.5)	–	1	94
3	–	$HNTf_2$ (1.0)	–	0.25	89
4	10	–	0.5	24	96
5	10	–	1	24	70[c]
6	10	–	10	24	36[c]
7	10	$HNTf_2$ (0.5)	–	1	96
8	–	$TsOH{\cdot}H_2O$ (0.5)	–	1	NR
9	–	MsOH (0.5)	–	1	NR
10	–	CSA (0.5)	–	1	NR
11	–	TfOH (0.5)	–	1	38[c]

[a] Reaction conditions: 0.05 M substrate in DCM at reflux. See Supplementary data for detailed procedure. Reactions were allowed to continue until consumption of **5a** (except for entries 1, 5, 6, 8–11).

[b] Yields given are for pure product after chromatographic purification.

[c] Product yield was calculated using the ^1H NMR ratio of an inseparable mixture of **6a** and unconsumed **5a**.

Table 3
Scope of Friedel–Crafts cyclization of simple arene-tethered olefins

Entry	Substrate	Reaction conditions	Product	Yield[a] (%)
1	 **5b**	0.5 mol % $HNTf_2$, DCM, reflux, 2 h	 **6b**	92
2	 **5c**	1.0 mol % $HNTf_2$, DCE, 180 °C (microwave), 20 min	 **6c**	80
3	 **5d**	1.0 mol % $HNTf_2$, DCE, 180 °C (microwave), 15 min	 **6d**	90 (2.8:1 dr)
4	 **5e**	1.0 mol % $HNTf_2$, DCE, 180 °C (microwave), 2 h	 **6e**	87
5	 **5f**	1.0 mol % $HNTf_2$, DCE, 180 °C (microwave), 15 min	 **6f**	74
6	 **5g**	1.0 mol % $HNTf_2$, DCM, reflux, 20 h	 **6g**	60
7	 **5h**	1.0 mol % $HNTf_2$, CD_2Cl_2, reflux, 21 h; then 100 °C (microwave), 30 min	 **6h**	NR
8	 **5i**	1.0 mol % $HNTf_2$, DCE, 180 °C (microwave), 5 min	 **6i**	56

[a] Yields given are for pure product after chromatographic purification.

apparent inhibition of the reaction (entries 4–6). In entry 7, $AgNTf_2$ was used in combination with $HNTf_2$ to check for an additive effect; however, the results did not differ significantly from the use of $HNTf_2$ alone. Finally, other strong Brønsted acids failed to catalyze the cyclization, with the exception of triflic acid in moderate yield.

When these optimized reaction conditions were applied to other substrates, it was found that in the majority of cases it was necessary to increase the catalyst loading to 1% and employ microwave heating in dichloroethane to encourage expedient and complete reaction of the substrate (Table 3). Methyl-substituted **5b** cyclized cleanly to provide **6b** in excellent yield (entry 1), whereas **5c** required more forcing conditions to form the congested 1,2,3-trisubstituted benzene moiety **6c** in 80% yield (entry 2). Branched substrate **5d** was cyclized to **6d** in 90% yield with an unremarkable 2.8:1 ratio of diastereomers[15] (entry 3). Electron-deficient 3-chloro substrate **5e** was cleanly converted into tetralin **6e** in excellent yield under the microwave conditions (entry 4). The noteworthy tolerance of halogen substitution[16] suggests the possibility of sequential C–C bond formation by Friedel–Crafts alkylation followed by various transition metal-catalyzed cross-coupling processes.[17]

1,1-Disubstitution on the alkene effects a reversal in cyclization regiochemistry (entry 5), affording indane **6f** in good yields. Extension of the tether provides benzocycloheptene **6g** in moderate yield (entry 6). The analogous enone **5h** was unreactive under the conditions employed, which may arise from a preference for the *s*-cis conformation by the enone moiety.[18,19] Furan **5i** underwent cyclization with microwave heating to afford tetrahydrobenzofuran **6i** (entry 8). No competing cyclization at C-4 to afford the tetrahydroisobenzofuran isomer was observed.

Friedel–Crafts cyclization of unactivated alkenes proceeds readily under superacid catalysis. This is an improvement over the classical reagents with respect to milder conditions and decreased acid waste, and should be more amenable to highly functionalized substrates. Electron-rich and electron-poor arenes as well as furans are compatible, and 5-, 6-, and 7-membered rings are formed with excellent regioselectivity in good to excellent yields with the creation of a quaternary center.

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Supplementary data

Supplementary data (Experimental procedures, physical data, and NMR spectra for **1a**–**d**, **2a**–**d**, **4**, **5a**–**i**, **6a**–**g**, **6i** and synthetic intermediates, and X-ray crystallographic data for **2d**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.082.

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19. Substrates **5g** and **5h** were unreactive under the conditions successfully applied to **5b**, and the reactions were subjected to extended heating in CD_2Cl_2 with periodic NMR analysis. Longer reactions times furnished **6g** in acceptable yield, and the reaction was scaled up using DCM. However, **5h** remained unconsumed under all conditions examined.