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A Direct and Stereoretentive Synthesis of Amides from Cyclic Alcohols

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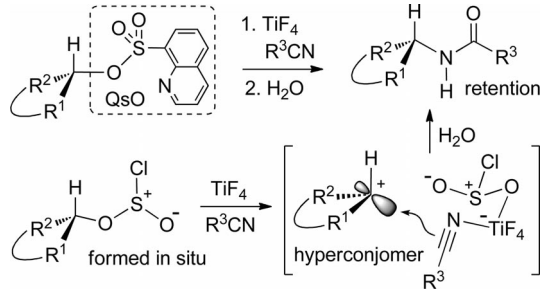
Keywords: Amides / Alcohols / Titanium / Chirality / Hyperconjugation

Chlorosulfites prepared in situ using thionyl chloride react with nitrile complexes of titanium(IV) fluoride to give a one-pot conversion of alcohols into amides. For the first time, amides are obtained from cyclic alcohols with stereoretention. Critical to the design of these new Ti^{IV} reactions has been the use of little-explored Ti^{IV} nitrile complexes that are thought to chelate chlorosulfites in the transition state to create a carbocation that is rapidly captured by the nitrile nucleophile through a front-side attack mechanism.

Introduction

Amides are among the most abundant functional groups in nature and, understandably, decades of creative research have been devoted towards their efficient synthesis with the majority of these studies centering on the dehydrative coupling of amines with carboxylic acids.[1] For the past few years, we have been in engaged in the development of methods to directly transform chiral secondary alcohols into new compound classes with retention of configuration, especially since non-racemic alcohols have become increasingly more available thanks to the development of recent powerful catalytic methods.[2] Recently, a metal-free procedure for the transformation of phenols into amides has been described with the use of a radical cascade reaction.[3] Primary alcohols have also been converted into amides via hemiaminal intermediates under catalytic dehydrogenation conditions.[4] As a tool for the direct conversion of alcohols to amides, the Ritter reaction has received substantial attention over the years. Excluding anchimeric assistance[5] or diastereomeric control,[6] this reaction is well known to proceed by a non-stereospecific carbocation mechanism and is often limited to alcohols where such intermediates are stabilized. However, two examples describing unexpectedly stereospecific Ritter amidations have been reported.[7] Nevertheless, most stereoselective approaches to amides from chiral alcohols require multistep procedures.[8]

As a complementary technique, we have previously reported a stereoretentive reaction by using a nucleophile-assisting leaving group (NALG) to position a Ti^{IV} azidation reagent for a front-face attack.[9] Using a designed chelating leaving group,[10] we fortuitously discovered a more direct stereospecific Ritter-type amidation reaction for cyclic alcohols. This initial observation involved the reaction of an 8-quinoline sulfonate (quisylate, QsO) with titanium(IV) fluoride in the presence of alkyl or aryl nitriles (Scheme 1). We next thought to extend the concept of chelating leaving groups to chlorosulfites, which can be generated in situ. To the best of our knowledge, chlorosulfites have not been exploited as leaving groups and are primarily relegated to use as intermediates in the classic $SOCl_2$ chlorination reaction. In this communication, we report our success in utilizing chlorosulfites for one-pot, two-step reactions of cyclic alcohols to yield amide products with predominant retention of configuration (Scheme 1). Importantly, these findings appear to be the first experimental verification of secondary hyperconjomers,[11] a theory of non-planar carbocations developed by Sorensen and Schleyer.[12,13]



Scheme 1. One-pot, stereoretentive amidation reaction of cyclic alcohols.

Results and Discussion

The initial inclination to use titanium(IV) fluoride in reactions with chelating leaving groups was based on our desire to develop a stereoretentive fluorination reaction as a follow-up to our success with chlorinations[14] and brominations[9] by using the corresponding Ti^{IV} halogen reagents.

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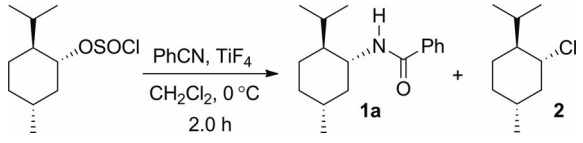
Although currently under study by various groups for use in dental varnishes,[15] titanium(IV) fluoride has received only modest attention from the organic synthesis community[16] probably due to its moderate complexing ability,[17] propensity for oligomer complex formation, and sparing solubility in typical reaction solvents. Following up on a report indicating that TiF_4 can be solubilized as nitrile complexes,[18] we hypothesized that a fluorination reaction might still be possible with added nitrile. To our surprise, the subsequent reaction of this solubilized reagent with the chlorosulfite ester of L-menthol failed to give the expected fluoride but instead afforded amide product **1a** after aqueous workup with complete retention of configuration (Table 1). The major side product in this reaction was chloride **2**. Interestingly, the chlorosulfite of menthol failed to yield product **2** at a reaction temperature of 0 °C, except in the presence of the Ti^{IV} reagent. Indeed, our subsequent studies revealed that a number of Ti^{IV} species can be used to catalyze halosulfite reactions leading to alkyl halides in excellent yields under mild conditions with nearly exclusive retention of configuration.[19] On the basis of previous studies,[18] we suspected that multiple equivalents[20] of TiF_4 and nitrile would be necessary for our amidation reaction. Indeed, the optimal ratio of benzonitrile/TiF_4 appears to be 4:1. Using 10 equivalents of TiF_4 (2.5 M) led to an 84% yield of amide **1a**.[21] Further studies with the L-menthol substrate revealed that the stereoretentive amidation reaction is successful with both aromatic and aliphatic nitriles (Table 2). The primary limitation appears to be with strongly electron-deficient nitriles such as trichloroacetonitrile (Table 2, Entry 5) presumably due to their poor liganding ability. We note that acetamide product **1g** was produced in an excellent yield of 92% (Table 2, Entry 6).

Table 1. Effect of Ti^{IV} concentration on amidation yields.

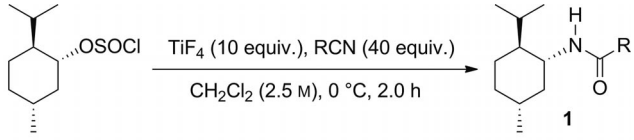


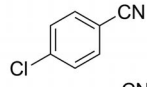
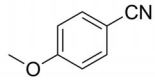
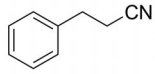
Entry	PhCN [equiv.]	TiF_4 [equiv.]	Conc. of TiF_4 [M]	Yield [%][a] 1a	2[b]
1	4	2	0.2	30	55
2	4	2	1.0	45	43
3	8	4	1.0	52	35
4	8	4	2.5	56	33
5	16	4	2.5	62	25
6	24	6	2.5	67	22
7	32	8	2.5	75	13
8	40	10	2.5	84	5

[a] Isolated yield. [b] Chlorides formed with complete stereoretention.

Using benzonitrile as a convenient coupling partner, a variety of substrate alcohols were examined by using our optimized amidation conditions (Table 3). Very similar to the previously mentioned menthol example, we observed that a number of cyclic chiral alcohols were converted into amide products with complete retention of configuration

Table 2. Nitrile generality for stereoretentive amidation.



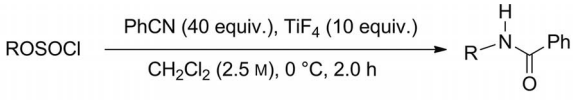
Entry	RCN	Product	Yield[a]
1		**1b**	65[b]
2		**1c**	72[b]
3		**1d**	85
4		**1e**	80
5	Cl_3CCN	**1f**	NR
6	H_3CCN	**1g**	92

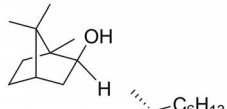
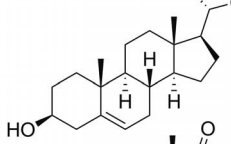
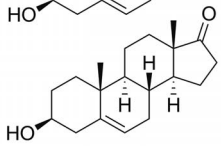
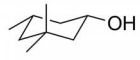
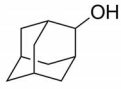
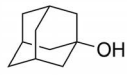
[a] Isolated yield. [b] Reactions 1.0 M in TiF_4.

(Table 3, Entries 1–4). In some cases, a significant amount of inversion product (≈25%) was observed under these reaction conditions (Table 3, Entry 5). In particular, the reaction outcome of cholestanol (a saturated derivative of **5**) led to a mixture of retention/inversion products (not shown). This attracted our attention, because others have commented that this substrate should proceed by a different mechanism in our system due to the absence of a nearby double bond.[22] We recently achieved a high-yielding chlorination of cholestanol by using a closely related Ti^{IV} reaction with exclusive retention of configuration.[19,23] Nevertheless, this less stereospecific result with the present amidation reaction prompted us to further examine our mechanistic hypotheses for these titanium(IV) reactions as discussed below.

In general, this amidation reaction gives high-yielding results with cycloalkanols of varying ring sizes under mild conditions (Table 3, Entries 6–9). However, with the exception of 1-adamantanol (Table 3, Entry 10), our conditions failed to yield amides with tertiary alcohol substrates, giving the chloride products instead. Given the preference of our reaction for secondary substrates, we deem this reactivity profile complementary to that of the classic Ritter reaction, which is generally only useful in easily ionized systems such as tertiary alcohols. In light of our emerging mechanistic conception for this reaction (discussed below), we were not surprised to observe that the stereospecificity of the present amidation reaction does not extend to acyclic systems. We conducted a study of acyclic alcohols by using (*S*)-2-octanol and (*S*)-1-phenylethanol.[22] In a reaction of the non-racemic phenylethanol with benzonitrile and TiF_4, amide **13** was obtained entirely as the racemate (Scheme 2). It should be noted that the chlorosulfite of phenylethanol readily converts into the chloride product at 0 °C. Accord-

Table 3. Substrate generality for stereoretentive amidation.

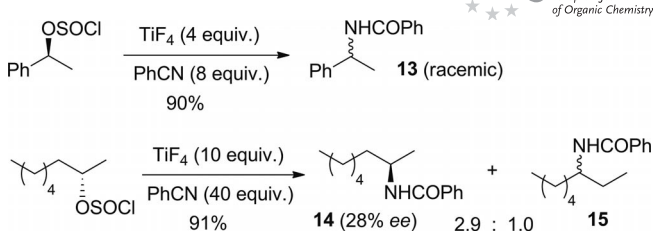


Entry	ROH	Product	Yield[a]
1		**3**	88
2		**4**	94
3[b]		**5**	75
4[b]		**6**	76
5		**7**	63[c]
6		*n* = 2 **8**	90
7		*n* = 3 **9**	80
8[b]		*n* = 7 **10**	65
9		**11**	90
10[b]		**12**	40
11		–	NR

[a] Yield of retention product only. [b] Intermediate chlorosulfite prepared at –78 °C with TiF_4 concentration maintained at 1.0 M. [c] Inversion product produced in 26% yield.

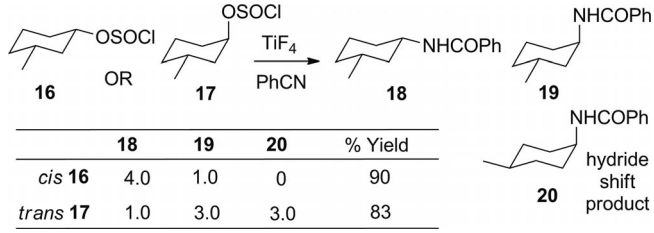
ingly, the chlorosulfite was prepared at –78 °C and then added to a Ti^{IV} solution. The amidation reaction with 2-octanol produced a mixture of direct substitution product **14** and hydride-shifted product **15** (2.9:1). Polarimetry measurements of purified hydride-shifted product **15** indicated that it was essentially racemic. However, direct substitution product **14** gave an enantiomeric excess of 28% favoring inversion (Scheme 2).[24] Finally, primary alcohols (Table 3, Entry 11) reacted very slowly, which is consistent with our previous work with titanium(IV)-mediated reactions.[9]

In our previous communications involving titanium(IV) reagents, we suggested that stereoretentive products are likely achieved through an S_Ni mechanism.[9,14] However, the recent work of Braddock (Imperial College London) and Burton (Oxford) provide convincing evidence that an S_N1-type mechanism may also be operative in NALG/Ti^{IV} reactions.[22] Specifically, the British researchers argue that these Ti^{IV}-mediated reactions proceed via carbocation intermediates whose nucleophilic capture is under diastereomeric control. They further point out that, in some cases, carbocations are not completely dissociated from the leaving group, leading to tight ion-pair formation and thus attack is favored from the less-hindered backside.



Scheme 2. Amidation of acyclic alcohols.

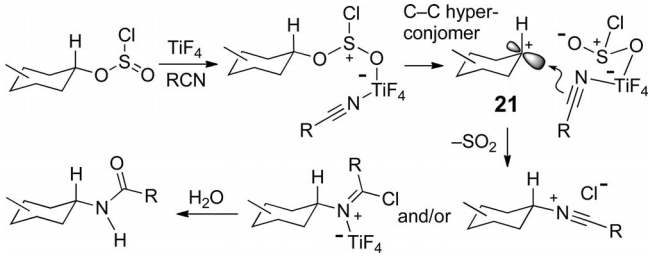
To help distinguish between the various mechanistic possibilities in the present amidation reaction, we closely examined *trans*- and *cis*-3-methylcyclohexanol. If the reactions of these isomeric alcohols proceed through a classical S_N1 mechanism they should form the same carbocation intermediate. Attack of this intermediate should then lead to the same product outcome. This was not the case. Instead, we observed a clear preference for retention products in these amidation reactions (Scheme 3). Thus *cis*-3-methylcyclohexanol (**16**) led primarily to *cis* product **18** (4:1) and the *trans* substrate (i.e., **17**) led to mainly *trans* product **19** (3:1). Though no hydride shift product was observed for *cis*-3-methylcyclohexanol, the chlorosulfite of *trans*-3-methylcyclohexanol (**17**) gave hydride-shift product **20** with the amide group exclusively as the *trans* isomer.



	18	19	20	% Yield
cis **16**	4.0	1.0	0	90
trans **17**	1.0	3.0	3.0	83

Scheme 3. Amidation in *cis*- and *trans*-3-methylcyclohexanol.

Our experimental results with other cyclic alcohols (Tables 1–3) also suggest that amidation reactions giving predominantly retention of configuration may not proceed by a classical S_N1 mechanism. Indeed, amidation studies of L-menthol under typical Ritter conditions (well known to proceed via classical carbocation intermediates) afforded amide products arising from a tertiary carbocation.[21] Such products have never been observed in our studies of 2-substituted cyclic alcohols. Instead, we suggest that our amidation reactions may involve a fast front-side attack of a carbocation intermediate such as **21** possessing pyramidal geometry, as theorized by Sorensen and Schleyer (Scheme 4).[12,13] Importantly, the cationic center in **21** is expected to maintain its configuration (as a single hyperconjomer) through hyperconjugative stabilization.[25] By contrast, there appears to be less of a barrier to carbocation planarization in acyclic systems, possibly explaining the lack of stereospecificity in their amidation reactions.



Scheme 4. Proposed mechanism and intermediates for the observed amidation reaction.

Conclusions

We have discovered an exciting variation of the Ritter reaction by using an inexpensive and unexplored Ti^{IV}/nitrile reagent to prepare amides directly from cyclic secondary alcohols. Critical to the design of this new reaction is the first-ever use of chlorosulfites, formed by the well-known reaction of alcohols and thionyl chloride, as in situ formed chelating leaving groups. Further mechanistic studies on this system are currently underway especially with a view to achieve substoichiometric use of the reagents involved.

Experimental Section

General Procedure for Stereoretentive Amidation Reactions: To an ice-cold solution of alcohol (1.0 equiv.) in dichloromethane (1.0 M) was added thionyl chloride (1.5 equiv.) followed by stirring for 1 h to form the chlorosulfite. In a separate reaction vessel, nitrile (40 equiv.) was added to a TiF_4 (10 equiv.) suspension in dichloromethane (4.0 M) and allowed to stir at room temperature until complete dissolution (≈15 min). Because TiF_4 is fairly moisture sensitive, it was quickly transferred to a reaction vessel under an atmosphere of argon and then weighed. The amount of each remaining reagent was then based on the weight of TiF_4. The titanium/nitrile solution was then cooled to 0 °C, and to this solution was added the previously prepared chlorosulfite, transferring by cannula under argon pressure. The chlorosulfite-containing vessel was further washed with an amount of dichloromethane necessary to bring the final concentration of TiF_4 in the other vessel to the desired concentration (2.5 M). After stirring for 2 h, the reaction was quenched with deionized water and stirred (≈30 min) until the organic layer became clear. The organic layer was removed, and the aqueous layer was extracted with dichloromethane (2×). All organic layers were combined, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (ethyl acetate/hexane).

Supporting Information (see footnote on the first page of this article): Characterization data for compounds **1a**–**e**, **1g**, **3**–**7**, and 5α-cholestan-3β-chloride; copies of the ^1H and ^{13}C NMR spectra for compounds **1**, **3**–**7**, and **8**, **10**, and **11**; NMR spectra of product mixtures for variously substituted cyclohexanols.

Acknowledgments

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[20] Although a large excess of TiF_4 is used in this reaction, we note that the reagent is very inexpensive (≈1 USD/g) and environmentally benign.
[21] For perspective, this yield represents a sixfold increase over the highest yield achieved in the literature by using a Lewis acid assisted Ritter reaction with menthol, which is considered a problematic substrate: P. B. Shrestha-Dawadi, J. Jochims, *Synthesis* **1993**, 426–432.

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[23] Starting from the in situ formed chlorosulfite of cholestanol (0.1 M in CH_2Cl_2) and using $TiCl_4$ (5 equiv.) at 0 °C, the direct substitution chloride product was formed in 15 min as a single product in 80% yield with complete retention of configuration (see the Supporting Information).
[24] A rotation value –4.4 (c = 5.5, $CHCl_3$). Pure inversion product was made by an alternative route in four steps from (*S*)-2-octanol through an S_N2 mechanism, giving an optical rotation of –15.7 (c = 3.55, $CHCl_3$).
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