Stereoretentive Copper(II)-Catalyzed Ritter Reactions of Secondary Cycloalkanols

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Abstract: A Ritter-like coupling reaction of cyclic alcohols and both aryl and alkyl nitriles to form amides catalyzed by copper(II) triflate is described. These reactions proceed in good yields under mild and often solvent-free conditions. With 2- and 3-substituted cycloalkanols, amide products are formed with near complete retention of configuration. This is likely due to fast nucleophilic capture of non-planar carbocations (hyperconjomers) stabilized by ring hyperconjugation. A critical aspect of this novel catalytic cycle is the *in situ* activation of the alcohol substrates by thionyl chloride to form chlorosulfites.

Keywords: amides; carbocations; catalytic reaction; hyperconjomers; Ritter reaction; stereoretentive reaction

Introduction

The dehydrative coupling of an amine with a carboxylic acid continues to be the method of choice for amide bond formation. Such a step is usually achieved through activation of the acid:^[1] however, due to the reactivity of acid derivatives and other issues, numerous alternative strategies have been developed.^[2] Examples include the use of azides as an amine precursor as in the modified Staudinger reaction,^[3] the Schmidt reaction,^[4] and the Beckmann rearrangement.^[5] More recently, oxidative amidation, a highly atom-economical approach, has been developed allowing the formation of amides from readily available starting materials.^[6] This promising approach usually requires the use of heat, a stoichiometric amount of oxidant, and relatively expensive reagents.^[7] The wellknown Ritter reaction affords amides from the coupling of nitriles with alcohols and alkenes. However, this method is practically limited to tertiary and activated alcohols.^[8] Nevertheless, this classic reaction continues to be the subject of continued investigation, especially for diastereoselective amide formation^[9] with very recent successes using benzylic alcohols.^[10,11]

Recently, our group developed a new method for a one-pot stereoretentive amidation reaction of cyclic alcohols (Scheme 1).^[12] In this method, thionyl chlo-



Scheme 1. Stereoretentive amidation *via* a non-planar hyperconjomer-stabilized carbocation intermediate.

ride was used for the first time for the *in situ* generation of a chlorosulfite leaving group for a non-chlorination reaction. The absolute stereochemistry of the resultant amide is that of the alcohol substrate; the reaction proceeds with retention of configuration. Such selectivity was suggested to be the first experimental verification of cyclohexyl cation hyperconjomers,^[13] achieved *via* the formation of non-planar carbocations, a theory developed by Sorensen and Schleyer.^[14,15] Although the method is fairly general with respect to nitriles and cyclic alcohols substrates, the use of large excess of nitrile (40 equiv.) and the TiF₄ coupling agent (10 equiv.) greatly limits its utility. In the present communication, we detail our development of a catalytic version of this unique stereoretentive amidation reaction.

Results and Discussion

We began our investigation by examining the effectiveness of various leaving groups using our previously developed titanium(IV) fluoride conditions (Table 1).^[12] Interestingly, our previously described

Table 1. Leaving group study using TiF₄.



Entry	R	Compound	10:11	Yield [%] ^[a]
1	-	1	10	88
2	-	2	8.3	41
3	8-quinoline	3	7.1	80
4	2-nitrobenzene	4	6.2	55
5	4-nitrobenzene	5	4.8	54
6	2-trifluoromethyl benzene	- 6	6.3	48
7	4-trifluoromethyl benzene	- 7	6.7	61
8 9	toluyl trifluoromethyl	8 9	3.6 0.2	57 18

^[a] Isolated yields.

^[b] Ratio determined using ¹H NMR

nucleophile assisting leaving group (NALG) containing a diethylene oxide chelating arm (compound 2)^[16] gave a similar diastereoselectivity but much poorer yield than other chelating leaving groups such as chlorosulfite 1 and 8-sulfonylquinoline 3. Poorer results were observed with other leaving groups (entries 4–8). Surprisingly, substrate 9 containing the trifluoromethanesulfonate (triflate) leaving group gave the inverted amide product as the major diastereomer under the action of TiF₄ (entry 9). Our leaving group study clearly suggested that the *in situ* formed chlorosulfite 1 would be the optimal starting point in our goal to develop a catalytic form of this stereoretentive Ritter reaction.

We next examined various metal salts (Table 2) in an attempt to realize catalytic conditions for this amidation reaction. In our previous work, TiF_4 was chosen due to its modest Lewis acidity and essentially non-reactive fluoride ligands. However, this reagent formed oligomeric complexes requiring the use of large excesses to bring about reasonable yields. By contrast, catalytic TiCl₄ (and its bromide analog)

Table 2.	A survey	of metal	salt reactiv	ity.
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osoci		MX _n (50%) PhCN (1.1 equiv.)	H N Ph	
\smile		CH ₂ Cl ₂	0	
		0 °C to r.t.	10/11	
	Entry	MXn	Yield [%] ^[a]	
	1	Sc(OTf) ₃	34	
	2	Cu(OTf) ₂	32	
	3	Cu(CO ₃) ₂	17	
	4	Co(NO ₃) ₂	19	
	5	AgNO ₃	13	
	6	KOTf	0	

^[a] Isolated yields.

reacts rapidly with chlorosulfites to give exclusively halide products in high yields.^[17] Martin and co-workers have reported similar results using Fe(III) halides in related systems.^[18] Accordingly, we choose to study metal salts possessing non-nucleophilic ligands. The readily available triflate salts of copper(II) and scandium(III) afforded amide product, albeit with a high catalyst loading of 50%. Copper(II) carbonate gave a significantly lower yield than Cu(OTf)₂ although this result may be due to poor solubility. To rule out the role of triflate as anything other than a spectator ion, KOTf was used (entry 6); however, no amide product was observed.^[19] We also observed product formation with other metal salts including those of Co(II) and Ag(I) which afforded only modest yields (entries 4 and 5). We proceeded to further study the present amidation reaction using copper(II) triflate due to its lower toxicity and cost relative to the scandium reagent.

We chose to proceed with copper(II) triflate despite some drawbacks. Literature evidence suggests that copper(II) is destroyed in the presence of sulfur dioxide gas which is a by-product of the present reaction.^[20] Furthermore, this metal salt is relatively insoluble in all but coordinating solvents; however, stereoretention is only observed in non-coordinating solvents such as dichloromethane.

This led us to try reactions in which the nitrile coupling partner would serve as both reagent and solvent in this system (virtually solvent-free conditions). This approach also allowed for easier removal of SO_2 likely generated during the course of the reaction by flushing the head-space in the reaction vessel with argon. In some cases, a small amount of CH_2Cl_2 (1M) was used to further solubilize the reactants. These minimal-solvent conditions with 20% catalyst afforded a 71% of amide **10** from *trans*-2-methylcyclohexanol with complete retention of configuration. Catalyst load and nitrile stoichiometry studies were then performed under solvent-free conditions (Table 3). Not surprisingly, no product was observed when the reaction was performed in the absence of catalyst

	i) Cu(OTI PhCN,	f) ₂ CH₂Cl₂	· 10 -	. 11	
ii) SOCl ₂ (1.5 equiv.)		
Entry	Cu(OTf) ₂ (equiv.)	PhCN (equiv.)	10 : 11	Yield [%]	
1	0	2.0	-	0 ^[a]	
2	0.05	2.0	14:1	29	
3	0.1	2.0	14.1	38	
4	0.2	2.0	15:1	71	
5	0.2	3.0	11:1	51	
6	0.2	4.0	9.5:1	81	
7	0.2	5.0	7.8:1	76	
8	0.4	2.0	ND	28	

^[a] No product was observed after 24 h.

(entry 1). However, after 7 days a very small amount of product was observed. Importantly, this product mixture gave little selectivity.^[21]

In terms of product yield, a catalyst loading of 20% appears to be optimal especially with 4 to 5 equivalents of nitrile (entries 6 and 7). However, these additional equivalents of nitrile also lowered the ratio of retention to inversion (10:11). Taking into account yield and stereoselectivity, we selected 20% Cu(OTf)₂ and 1.9 or 2.0 equivalents nitrile as optimal conditions for our generality studies.

From our initial experiments involving catalytic Cu(II), dialkyl sulfite **12** was observed as a minor byproduct in the amidation reaction of L-menthol (Scheme 2). This is expected to arise from the chlorosulfite.^[22] In separate experiments, we observed that $Cu(OTf)_2$ catalyzed the reaction of this alcohol with its chlorosulfite to give dialkyl sulfite **12**. In addition, dialkyl sulfite **12** was prepared and subjected to our reaction conditions but amide product **10** was observed only after long reaction times (>24 h). Based on these findings, we sought to minimize dialkyl sulfite formation by altering the sequence of reagent addition. Thus a 1M CH_2Cl_2 solution of nitrile, $Cu(OTf)_2$, and alcohol were added slowly to thionyl chloride. This approach was ultimately successful



Scheme 2. Dialkyl sulfite by-product formation.

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leading to the synthetically useful yields described in the previous section (Table 3).

Previous reports indicate that L-menthol is a problematic substrate in Ritter reactions owing to its propensity to undergo cation rearrangements.^[23] Thus we proceeded to perform a nitrile generality study with this substrate to further probe the limits of our catalytic reaction. Our studies revealed that both aliphatic and aromatic nitriles afford amides **13** in moderate to good yields with no detectable hydride shift products (Table 4). Importantly, the amide products were

Table 4. Nitrile generality study.



Entry	RCN	Product	Yield [%] ^a (e (1.2 equiv.)	quiv. RCN) (1.9 equiv.)
1	CN	13a	66	79
2	CN	13b	41	68
3	CI	13c	37	46
4	CN	13d	48	45
5	→_CN	13e	68	71
6	CH ₃ CN	13f	55	68
7	CI3CCN	13g	NR	NR

^[a] Isolated yields for 1.2 and 1.9 equiv, of nitrile.

formed with complete retention of configuration. Interestingly, the reaction tolerates a phenolic hydroxy group (entry 4). The primary limitation appears to be with reactions involving electron-deficient nitriles such as *p*-chlorobenzonitrile (entry 3) and especially trichloroacetonitrile (entry 7). For optimal yield, two equivalents of nitrile were used; however, in most cases, reasonable yields were also obtained with as little as 1.2 equivalents.

We next examined a range of saturated cyclic alcohols to explore substrate generality (Table 5). Very similar to the previously mentioned menthol example, we observed the formation of amide products with complete retention of configuration with a number of cyclic alcohols (entries 1 and 3–6). One exception was *cis*-2-methylcyclohexanol which underwent rapid chlorination and no amidation. However, other Table 5. Substrate generality study.

	ROH	i) Cu(OTf) ₂ (PhCN (1.9 CH ₂ Cl ₂ (1 ii) SOCl ₂ , r.t	(20%) 9 equiv.) M) ., 2–12 h	R	H N Ph
Entr	y	ROH	Pi	roduct	Yield [%] ^[a]
1	D	ОН		10	71
2	Ľ	OH		-	0 ^[p]
3		/ // ОН		14	69
4		ОН Н		15	21 ^[c]
5	\mathcal{L}	ОН		16	64
6	\checkmark	ОН		17	67
7 8 9 10 11	5		n = 1 n = 2 n = 3 n = 4 n = 8	18a 18b 18c 18d 18e	53 51 70 74 27
12	A			19	73
13	A	ОН		20	41
14	Ph	∼∕он		-	NR

^[a] For entries 1 and 3–6, yields are for isolated amide products which were obtained as single diastereomers with retention of configuration at the carbinol carbon center.

- ^[b] Only chlorination and minor elimination products observed.
- ^[c] Chlorination with retention of configuration (5:1) was the major by-product.

methyl cyclohexanol isomers (entries 5 and 6) also gave the expected stereoretentive amide product in reasonable yields although a small amount of hydride shift product was observed in each case.

The case of (-)-borneol (entry 3) presents an interesting opportunity to compare the present method with previously reported Ritter modifications. In our case, (-)-borneol was converted to amide product **14** in 69% yield with complete retention of configuration (*endo* product). This outcome stands in contrast with virtually all reported Ritter reactions involving this substrate.^[24] Using a recently developed iodine-catalyzed Ritter reaction performed at a 120 °C, (-)-borneol led to an amide product whose relative stereochemistry was clearly demonstrated by X-ray crystal structure analysis to be the inversion product.^[25] Ritter reactions of bornyl and isobornyl chloride in the presence of SbCl₅ in acetonitrile have been shown to give the same *exo*-amide product^[26] suggesting a common carbocation intermediate and a preference for *exo*-attack.^[27] In the case of isoborneol (entry 4), the present method gave only the stereoretentive amide (*exo*-product) product **15** albeit in low yield (21%). However, the main by-product is the chloride but, here as well, we observe a preference for stereoretention (i.e., isobornyl chloride).

A variety of ring sizes also afforded good product yields under the present conditions (entries 7–10). Interestingly, poor yields of amide were observed with cyclododecanol which gave almost exclusive elimination product (entry 11). Carbocations involving similar macrocyclic substrates are known to form transannular μ -hydrido bridges.^[28] Perhaps these non-classical carbocation intermediates alter the course of the present amidation reaction with this large ring substrate. As in our previous studies,^[12] tertiary and primary alcohols gave little or no yields in this reaction except in the case of 1-adamantanol (entry 13).

The high degree of stereoretention in the present reaction argues against a classical S_N1 mechanism involving a planar cation. In such systems, stereocenters nearby the planar carbocation center should influence facial preference in nucleophilic attack. Such a mechanism explains previously reported Ritter reactions of borneol and isoborneol which led to product mixtures favoring the *exo*-product. Based on our recent extensive computational study of a related system,^[17] we argue that cyclic carbocations in the present reaction retain their configuration due to stabilization by hyperconjugation.^[15] In this scenario, the copper(II) catalyst chelates to both chlorosulfite and the nitrile coupling partner to give complex **A** (Scheme 3). This chelation to chlorosulfite increases its leaving group abili



Scheme 3. Proposed mechanism and intermediates for the observed amidation reaction.

ty leading to rapid cation formation under mild conditions. This configurationally "frozen" carbocation is then trapped by nitrile delivered to the front face in ion pair **B** to form a nitrilium salt which is converted to amide upon aqueous work-up.

Conclusions

We have previously disclosed a stereoretentive Ritter reaction involving chlorosulfites conveniently formed *in situ*. However, this earlier work entailed large excess of TiF_4 and the use of the nitrile coupling partner as a cosolvent. In the present work, we have dramatically increased the atom economy of this stereoselective reaction through a systematic evaluation of various metal catalysts and reaction conditions. As a result of these improvements, it is now possible to directly convert non-activated cyclic secondary alcohols directly to the corresponding amide with a high degree of retention of configuration.

Experimental Section

General Information

All reaction mixtures were purified using flash silica gel 40– 63µ. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous potassium permanganate solution staining. ¹H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Coupling constants were reported in Hz and ¹³C NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer. Chemical shifts are reported in ppm, with solvent resonance employed as the internal standard. High-resolution mass spectra were obtained from University of Florida Mass Spectrometry Laboratory. All reagents were used without any further purification. Solvents were dried with activated molecular sieves.

General Titanium(IV) Fluoride Procedure

To a solution of alcohol (1.0 equiv.) in dichloromethane (1.0M) at 0 °C 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 TiF₄ (10 equiv.) suspension in dichloromethane (4.0M) and allowed to stir at room temperature until complete dissolution (~15 min). Since TiF₄ is fairly moisture sensitive, it was quickly transferred to a reaction vessel under argon and then weighed. The amount of each remaining reagent was then based on the weight of the TiF₄. The titanium/nitrile solution was then cooled to 0 °C and to it was added the previously prepared chlorosulfite transferring by cannula under argon pressure. The chlorosulfite containing vessel was further washed with an amount of TiF₄ 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 twice with dichloromethane. All organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum.

General Copper(II) Triflate Procedure

Nitrile (1.9 mmol) and copper(II) triflate (0.15 mmol) were added with stirring to an oven-dried vial under an argon atmosphere containing anhydrous dichloromethane (1 mL). Alcohol (1.0 mmol) was then added and the mixture was stirred at room temperature (15–22 °C) until a homogenous mixture is observed. This solution was then transferred (over >45 min) through cannula to an oven-dried flask containing thionyl chloride (1.7 mmol) under argon at room temperature. Headspace gases were replaced with argon several times in the first 1 hour. The reaction was monitored for the disappearance of alcohol by TLC using an aqueous potassium permanganate staining solution. After completion, the reaction mixture was cooled, diluted and poured into cooled aqueous KOH solution (20% w:v; 25 mL) and stirred for several hours. The aqueous layer was then extracted several times with dichloromethane followed by drying and evaporation. The crude mixture was purified using silica chromatography (in EtOAc/hexanes).

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References

- [1] C. A. G. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827.
- [2] a) E. Valeur, M. Bradley, *Chem. Soc. Rev.* 2009, *38*, 606; b) V. R. Pattabiraman, J. W. Bode, *Nature* 2011, *480*, 471.
- [3] a) E. Saxon, C. R. Bertozzi, *Science* 2000, 287, 2007;
 b) F. Damkaci, P. DeShong, *J. Am. Chem. Soc.* 2003, 125, 4408.
- [4] A. Jeffery, G. L. Milligan, J. Am. Chem. Soc. 1991, 113, 8965.
- [5] H. Masaharu, O. Yasushi, S. Satoshi, I. Yasutaka, J. Org. Chem. 2008, 73, 2894.
- [6] a) L. U. Nordstrøm, H. Vogt, R. Madsen, J. Am. Chem. Soc. 2008, 130, 17672; b) W.-J. Yoo, C.-J. Li, J. Am. Chem. Soc. 2006, 128, 13064.
- [7] a) I. E. Marko, A. Makhalifa, *Tetrahedron Lett.* 1990, 31, 7237; b) K. Ishihara, T. Yano, Org. Lett. 2004, 6, 1983; c) K. R. Reddy, C. U. Maheswari, M. Venkateshwar, M. L. Kantam, Eur. J. Org. Chem. 2008, 3619.
- [8] a) L. K. Reddy, *Tetrahedron Lett.* 2003, 44, 1453; b) E.
 Callens, A. J. Burton, A. G. M. Barrett, *Tetrahedron Lett.* 2006, 47, 8699.

- [9] a) A. Toshimitsu, C. Hirosawa, K. Tamao, *Tetrahedron* 1994, 50, 8997; b) T. J. Blacklock, P. Sohar, J. W. Butcher, T. Lamanec, E. J. Grabowski, *J. Org. Chem.* 1993, 58, 1672; c) K. Van Emelen, T. De Wit, G. J. Hoornaert, F. Compernolle, *Org. Lett.* 2000, 2, 3083; d) S. Davies, R. F. Newton, J. M. J. Williams, *Tetrahedron Lett.* 1989, 30, 2967.
- [10] P. Rubenbauer, T. Bach, Chem. Commun. 2009, 2130.
- [11] A. Guérinot, S. Reymond, J. Cossy, Eur. J. Org. Chem. 2012, 19.
- [12] D. Mondal, L. Bellucci, S. D. Lepore, Eur. J. Org. Chem. 2011, 7057.
- [13] a) C. Fraschetti, F. R. Novara, A. Filippi, M. Speranza, N. A. Trout, W. Adcock, E. Marcantoni, G. Renzi, G. Roselli, M. Marcolini, J. Org. Chem. 2009, 74, 5135; b) A. V. Igor, M. Mariappan, J. Org. Chem. 2004, 69, 9011.
- [14] a) A. Rauk, T. S. Sorensen, C. Maerker, J. W. Carneiro, M. De, S. Sieber, P. v. R. Schleyer, J. Am. Chem. Soc. 1996, 118, 3761; b) R. P. Kirchen, K. Ranganayakulu, T. S. Sorensen, J. Am. Chem. Soc. 1987, 109, 7811.
- [15] A. Rauk, T. S. Sorensen, P. v. R. Schleyer, J. Chem. Soc. Perkin Trans. 2 2001, 869.
- [16] S. D. Lepore, D. Mondal, S. Y. Li, A. K. Bhunia, *Angew. Chem.* 2008, 120, 7621; *Angew. Chem. Int. Ed.* 2008, 47, 7511.

- [17] D. Mondal, S. Y. Li, L. Bellucci, T. Laino, A. Tafi, S. Guccione, S. D. Lepore, J. Org. Chem. 2013, 78, 2118.
- [18] N. Ortega, A. Feher-Voelger, M. Brovetto, J. I. Padrón, V. S. Martín, T. Martín, Adv. Synth. Catal. 2011, 353, 963.
- [19] E. Callens, J. A. Burton, A. G. M. Barrett, *Tetrahedron Lett.* 2006, 47, 8699.
- [20] R. S. Mann, K. C. Yao, Ind. Eng. Chem. Prod. Res. Dev. 1969, 8, 331.
- [21] L-Menthol was also allowed to react in the absence of copper for 7 days. The reaction yielded the amide in 24% yield with a 3:1 ret: inv ratio.
- [22] a) P. D. Bartlett, H. F. Herbrandson, J. Am. Chem. Soc.
 1952, 74, 5971; b) H. F. van Woerden, Chem. Rev. 1963, 63, 557.
- [23] P. B. Shrestha-Dawadi, J. Jochims, Synthesis 1993, 4262.
- [24] R. M. Carman, K. L. Greenfield, Aust. J. Chem. 1984, 37, 1785.
- [25] K. Yoshio, U. Atsushi, H. Kahoka, Y. Yu, M. Takashi, S. Masami, F. Tsutomu, J. Oleo Sci. 2010, 59, 607.
- [26] N. Kitagawa, M. Nojima, N. Tokura, J. Chem. Soc. Perkin Trans. 1 1975, 2369.
- [27] H. C. Brown, J. H. Kawakami, K.-T. Liu, J. Am. Chem. Soc. 1973, 95, 2209.
- [28] R. P. Kirchen, T. S. Sorensen, J. Am. Chem. Soc. 1979, 101, 3240.