Diastereoselective Ritter reactions of chiral secondary benzylic alcohols†

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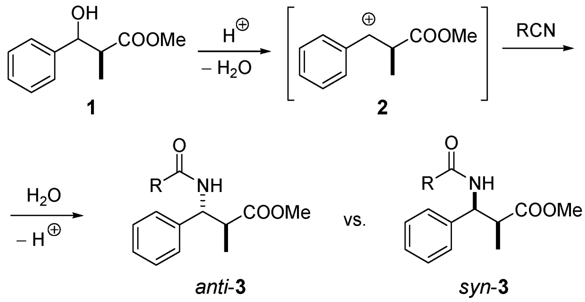
An acid-catalysed Ritter reaction of chiral secondary benzylic alcohols enables diastereoselective access to chiral amides, which represent *inter alia* valuable intermediates for the synthesis of chiral 1,2-diamines and β-amino acids.

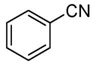
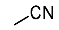
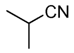
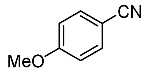
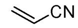
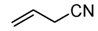
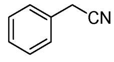
The introduction of an amino group into an organic molecule proceeds typically *via* an S_N2-type displacement of a suitable leaving group by an appropriate strong nitrogen nucleophile.[1] The reaction is stereospecific and—if applicable—the question of facial diastereoselectivity must be addressed when establishing the stereogenic center at the leaving group. An alternative reaction mode for the creation of a C–N bond is the acid-catalysed Ritter reaction, *i.e.* the reaction of nitriles as weak nitrogen nucleophiles with suitable electrophile precursors.[2] Carbenium ions have been invoked as intermediates in this S_N1-type reaction.[3] The facial diastereoselectivity of this process, however, has not yet been studied.[4] We have now investigated the reaction of the title compounds, which serve as precursors for chiral benzylic cations. Suitable conditions for the Ritter reaction were established and the reactions were shown to proceed with remarkable diastereoselectivities.

Initial studies were conducted with the β-hydroxyester **1**,[5] which was expected to react *via* the cation **2** to give the corresponding amides **3** (Scheme 1). Before studying the facial diastereoselectivity of the reaction we searched for suitable reaction conditions. The Brønsted acid $HBF_4{\cdot}OEt_2$, commonly used for the substitution of benzylic alcohols by carbon nucleophiles,[6] failed to deliver a defined product. After extensive experimentation we found that trifluoromethanesulfonic acid (HOTf) in dichloromethane is an excellent catalyst for the desired transformation, delivering the respective amides in high yields (Table 1). In contrast to many Ritter reactions, the nitrile was not required to be used as the solvent. Consequently, solid nitriles such as *p*-methoxybenzonitrile could also be used as reagent (entry 4). The facial diastereoselectivity of the reactions was high with the *anti*-product *anti*-**3** being predominantly formed. It was shown that the reactions proceed under kinetic product control and that they are stereoconvergent, *i.e.* independent of the relative configuration of the substrate (see ESI†). The diastereomeric ratio of the products **3** varied between 91/9 for the relatively slim nucleophile allyl cyanide (entry 6) and 98/2 for the relatively bulky nucleophile isobutyronitrile (entry 3). Yields are remarkably high given that aromatic and olefinic nitriles (entries 1, 4–7) offer also other nucleophilic positions, at which reactions with cation **2** could occur. The product configuration was determined for product **3a** by comparison of the analytical data of either diastereoisomer with known data for *anti*-**3a**.[7] The relative configuration is in line with a previously suggested model,[6e] which is based on the preferred conformation of cations such as **2** and which predicts nucleophilic attack from the less congested diastereotopic face (*vide infra*). The *para*-fluoro analog of benzylic alcohol **1** reacted similarly with benzonitrile delivering the substitution product in 80% yield and with a d.r. = 93/7.



Scheme 1 Acid-catalysed diastereoselective reaction of β-hydroxyester **1** with various nitriles to give amides **3** (*cf.* Table 1).

Table 1 HOTf-promoted Ritter reaction of alcohol **1** with various nitriles to give the corresponding amides **3**

Entry	RCN[a]	Product	t^a/h	d.r.[b]	Yield[c] [%]
1		*anti*-**3a**	1.5	94/6	86
2		*anti*-**3b**	1.5	93/7	88
3		*anti*-**3c**	3	98/2	84
4		*anti*-**3d**	1.5	92/8	87
5		*anti*-**3e**	3.5	92/8	94
6		*anti*-**3f**	4.5	91/9	87
7		*anti*-**3g**	4	94/6	96

[a] All reactions were conducted for the indicated period of time *t* at a substrate concentration of 0.25 mM in dichloromethane using 4 equiv. of the corresponding nitrile RCN and 1.25 equiv. of trifluoromethanesulfonic acid at 0 °C. [b] The diastereomeric ratio (*anti*/*syn*) of the crude product was determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

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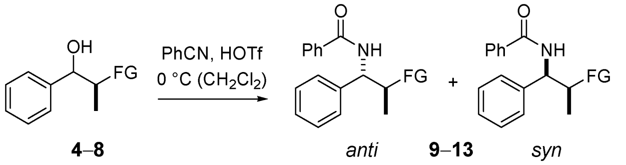
† Electronic supplementary information (ESI) available: Procedures for the preparation of **3a–g**, **6**, **7**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16** and **18a–d** and their NMR data. See DOI: 10.1039/b901937e

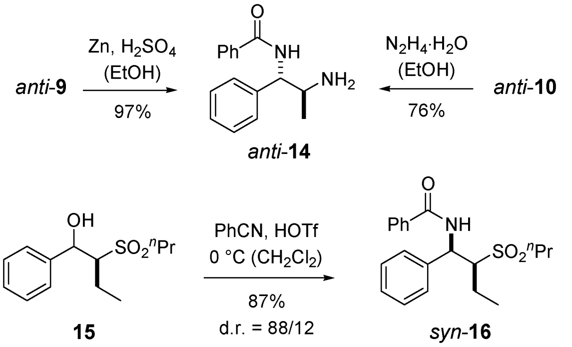
Table 2 HOTf-promoted Ritter reaction of alcohols **4–8** with benzonitrile to give the corresponding amides **9–13**



Entry	FG	Subst.	Product	t[a]/h	d.r.[b]	Yield[c] [%]
1	NO_2	**4**	*anti*-**9**	4.5	90/10	85
2	NPhth	**5**	*anti*-**10**	3	75/25	78
3	$PO(OEt)_2$	**6**	*syn*-**11**	5	8/92	90
4	SO_2Et	**7**	*syn*-**12**	3.5	4/96	92
5	^{t}Bu	**8**	**13**	5	—	—

[a] All reactions were conducted for the indicated period of time t at a substrate concentration of 0.25 mM in dichloromethane using 4 equiv. of benzonitrile and 1.25 equiv. of trifluoromethanesulfonic acid at 0 °C. [b] The diastereomeric ratio (*anti*/*syn*) of the crude product was determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

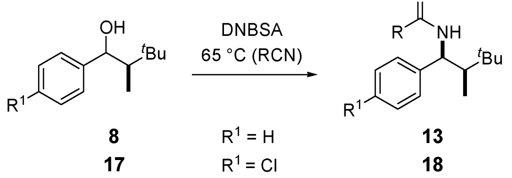
The acidic conditions established for the Ritter reaction of substrate **1** could be successfully applied to other chiral secondary benzylic alcohols (Table 2). Benzonitrile was employed as a representative nucleophile in these transformations. The reaction with nitro compound **4**[8] (entry 1) proceeded cleanly to give product **9**, the major diastereoisomer of which turned out to be product *anti*-**9**. The major product of the reaction of the phthaloyl (Phth)-protected amino alcohol **5**[9] was also the *anti*-isomer *anti*-**10** (entry 2). The configuration assignment rests on amine *anti*-**14**, which was obtained from both major diastereoisomers *anti*-**9** and *anti*-**10** (Scheme 2) and the dibenzoyl derivative of which has been reported[10] (see ESI†). The preference for *anti*-product formation with nitro compound **4** was further suggested by earlier precedents, in which a benzylic carbocation was formed by addition of a nitryl cation to an olefin and was subsequently trapped by a nitrile, although this process was not fully stereoconvergent.[11] In addition, the stereochemical outcome of the reactions **1** → **3** and **4** → **9** is in line with previous studies on Friedel–Crafts type reactions of secondary benzylic alcohols.[6] Apparently, chiral carbocations such as **2** adopt a preferred conformation in which one diastereotopic face is shielded by the methyl group and one by the functional group FG.[6e] If the size of the methyl group is larger than FG, *anti*-products are preferred. If the FG is larger than methyl the *syn*-products prevail. The high yielding transformations of phosphonate **6** and sulfone **7** delivered the corresponding products in almost diastereomerically pure form. The *syn*-configuration was assigned to these diastereoisomers based on analogy to previous work. The assignment was further supported by the reaction of compound **15** with benzonitrile which delivered product **16** with significantly lower diastereoselectivity than that with which **12** was formed from **7**. According to the previously mentioned model, replacement of the methyl group by an ethyl group should indeed lead to a decrease in selectivity if the *syn*-product was preferred (FG > alkyl).

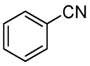
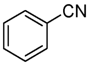
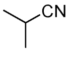
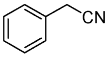


Scheme 2 Configuration proof of compounds **9**, **10**, **12**: conversion of **9** and **10** to *anti*-**14** and Ritter reaction of sulfone **15** to give product **16**.

Disappointingly, the *tert*-butyl-substituted alcohol **8** did not react with benzonitrile under the given reaction conditions (Table 2, entry 5). Severe decomposition occurred, which appeared to be caused by the strong Brønsted acid. Milder reaction conditions were studied and it was found that dinitrobenzenesulfonic acid (DNBSA)—as recently described by Sanz *et al.*[3m]—was an excellent catalyst for *tert*-butyl substrates. Substoichiometric amounts of DNBSA (0.2 equiv.) were sufficient to guarantee full conversion in the desired reaction. Both the parent benzyl alcohol **8** and its *para*-chloro derivative **17** could be successfully employed in the Ritter reaction (Table 3). Again, high diastereoselectivities were observed in the respective products. Benzonitrile delivered products **13** and **18a** in a diastereomeric ratio of 87/13 and 92/8 (entries 1, 2). Other nitriles reacted equally well producing amides **18b–18d** in very good yields and with significant diastereoselectivity. The *syn*-configuration was assigned to the major products based on analogy. Indeed, the relevant

Table 3 DNBSA-catalysed Ritter reaction of alcohols **8**, **17** with various nitriles RCN to give the corresponding amides **13**, **18**



Entry	RCN[a]	R^1	Product	t[a]/h	d.r.[b] (*syn*/*anti*)	Yield[c] [%]
1		H	*syn*-**13**	2	87/13	69
2		Cl	*syn*-**18a**	2	92/8	84
3		Cl	*syn*-**18b**	2	91/9	78
4		Cl	*syn*-**18c**	26	88/12	95
5		Cl	*syn*-**18d**	23	88/12	86

[a] All reactions were conducted for the indicated period of time t at a substrate concentration of 0.25 mM in the corresponding nitrile RCN as solvent and 0.2 equiv. of DNBSA at 65 °C. [b] The diastereomeric ratio (*syn*/*anti*) of the crude product was determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

benzylic cation derived from compound **8** has been intensively studied by NMR spectroscopy.[6c]

In summary, we have found a new route for the stereoselective formation of chiral benzylic amines from the corresponding alcohols by an $\mathrm{S_N}1$-type displacement reaction with the stereogenic center in the α-position to the carbocation center acting as a useful controlling device. Since benzylic alcohols such as **1** and **4–8** are readily available in enantiomerically pure form, the route enables access to a plethora of useful chiral diamines and β-amino esters, sulfones and phosphonates. Further studies including applications of this method to natural product synthesis are currently in progress in our laboratories.

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