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SHORT COMMUNICATION

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Direct and Stereoselective Alkylation of Nitro Derivatives with Activated Alcohols in Trifluoroethanol

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Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

Keywords: Alkylation / Nucleophilic substitution / Alcohols / Organocatalysis

Herein we disclose the simple, effective, and practical alkylation of nitroalkanes that takes place with benzylic, benzhydrylic, and propargylic alcohols in trifluoroethanol. A variety of different nitroalkanes bearing functional groups can be used in this S_N1-type reaction to afford the desired products in quantitative yields. Different chiral nitro derivatives were submitted to this highly diastereoselective alkylation reaction with selected benzhydrols. A new, effective, and chiral pyrrolidine organocatalyst was prepared by using this methodology.

Introduction

Deprotonated nitroalkanes are an important class of ambident anions that are widely used in organic synthesis.[1] Their application in diverse chemical transformations results in their frequent use in total synthesis.[2] Recently, nitro derivatives have also found applications in organocatalysis,[3] principally in Michael- and Henry-type reactions.[4] However, the simple alkylation of nitro derivatives is quite troublesome.[5] In fact, the intrinsic preference for attack of the oxygen atom of the nitronate anion is so large that irreversible S_N2 reactions with a variety of alkylating agents generally proceed in this manner.[6] As a consequence of the failure to achieve C-alkylation of nitronate anions by simple substitution reactions,[7] Seebach et al. developed a method for the α-alkylation of nitroalkanes that proceeds via doubly deprotonated nitroalkanes.[8] By using SOMO concepts, MacMillan recently developed the alkylation of nitronates.[9] Generally, in organocatalysis only a handful of C–C alkylation reactions occurring with nitro derivatives have been described.[10] However, Mayr reported S_N1-type reactions of stabilized benzhydrylium ions with nitro derivatives, in which C–C bonds are formed.[11] Good yields of the C-alkylation products were obtained when solid benzhydrylium tetrafluoroborate was added to solutions of the potassium nitronate in aqueous acetonitrile. The reactions with carbenium ions were used to establish the nucleophilicity parameters of nitronates. Recently, we established the possibility to generate stable carbenium ions from alcohols in alkylation reactions.[12] The possibility to directly use alcohols in the selective alkylation of nitro compounds is intriguing and has attracted our attention. In this communication, we report the facile and remarkable reaction of various nitro compounds with alcohols in CF_3CH_2OH. In addition, highly functionalized chiral compounds obtained by organocatalytic nitro-Michael reactions react with the selected alcohols with high selectivity.

Results and Discussion

Trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) are solvents with unique properties.[13] In particular, their high ionizing power and low nucleophilicity have made them the media in which to perform nucleophilic ring opening of oxiranes,[14] intramolecular electrophilic additions to C–C bonds,[15] and aromatic electrophilic substitution reactions.[16] These reactions are conducted in the absence of any other activating agents or Lewis acids. Recently, it was shown that HFIP could be employed as a medium and as an activator for a number of classical C–C bond-forming reactions by using carbonyl compounds and their acetals.[17]

We reasoned that the acidic properties and low nucleophilicity of TFE would work to our advantage in the formation of carbenium ions from benzhydrylic alcohols.[18] We selected alcohols **1a** and **1b**, positioned at –7 and –1.5 on the Mayr scale, respectively, for preliminary investigation (Table 1).[19] Nitro derivatives **2a**–**f** were shown to give excellent yields with alcohol **1a**. In all cases, no byproducts derived from *O*-alkylation were identified in the crude reac-

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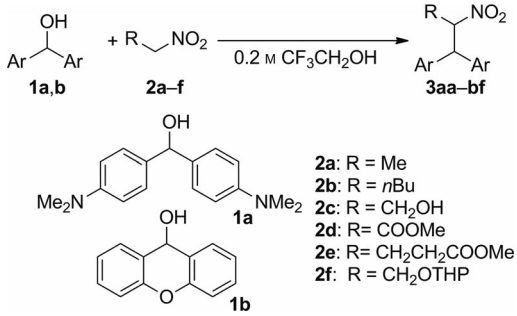
tion mixture. The reactions are very convenient; they are performed in air at room temperature and generate water as the only byproduct.[20] In the case of alcohol **1b**, a more electrophilic carbenium ion is produced, and a base additive was necessary to perform the reaction. We screened various organic and inorganic bases and found that the addition of DMAP was necessary to perform the reaction. Notably, the addition of Brønsted acids and bases to the reaction of nitromethane (5–10 equiv.) with alcohol **1a** gave no reaction. The carbenium ion was isolated as its tetrafluoroborate salt, but this species was not reactive to nitroethane when the reaction was performed in the presence of DABCO. With all acid and base combinations examined, this highlights the simple conditions that we have found. The reaction tolerates the presence of many functional groups, and unprotected primary alcohols can also be present.

Table 1. Addition of alcohols **1a**,**b** to various nitro derivatives **2a**–**f** in TFE.[a]

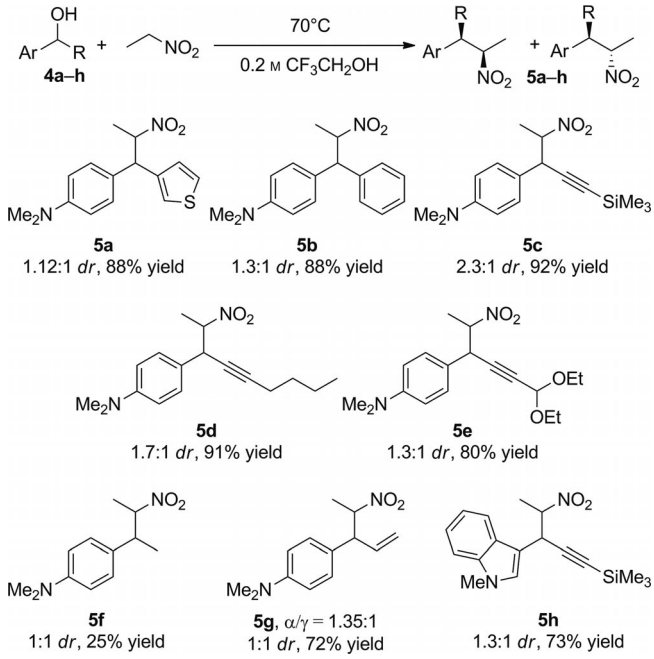


Entry	Time [h]	RCH_2NO_2	Product	Yield[b]
1	16	**2a**	**3aa**	99
2	20	**2b**	**3ab**	99
3	20	**2c**	**3ac**	99
4	3	**2d**	**3ad**	99
5	20	**2e**	**3ae**	95
6	70	**2f**	**3af**	99
7[c]	70	**2a**	**3ba**	99
8[c]	23	**2b**	**3bb**	99
9[c]	20	**2c**	**3bc**	62
10[c]	48	**2c**	**3bc**	99
11[c]	48	**2d**	**3bd**	99
12[c]	20	**2e**	**3be**	60
14[c]	48	**2e**	**3be**	99
15[c]	20	**2f**	**3bf**	65

[a] The reactions were performed at 25 °C with **1a**,**b** (0.1 mmol) and nitro derivative **2a**–**f** (3 equiv.), and the reactions were run until completion, as determined by TLC (16–24 h). [b] Yield after chromatographic purification. [c] The reaction was performed at 25 °C with **1b** (1 mmol) and nitro derivative **2a**–**f** (3 equiv.) in the presence of DMAP (0.2 equiv.) as a catalyst.

Because many stabilized carbenium ions can be generated within the useful limits of the Mayr scale, as established with the model substrates, we found that other benzhydrylic, benzylic, and propargylic alcohols reacted under the reaction conditions at 70 °C (Scheme 1).

Asymmetric phenyldimethylaminobenzhydrylic substrates substituted with aryl or heteroaryl groups are reactive under the reaction conditions and give the products in high yields but with poor diastereoselectivities. Moderate



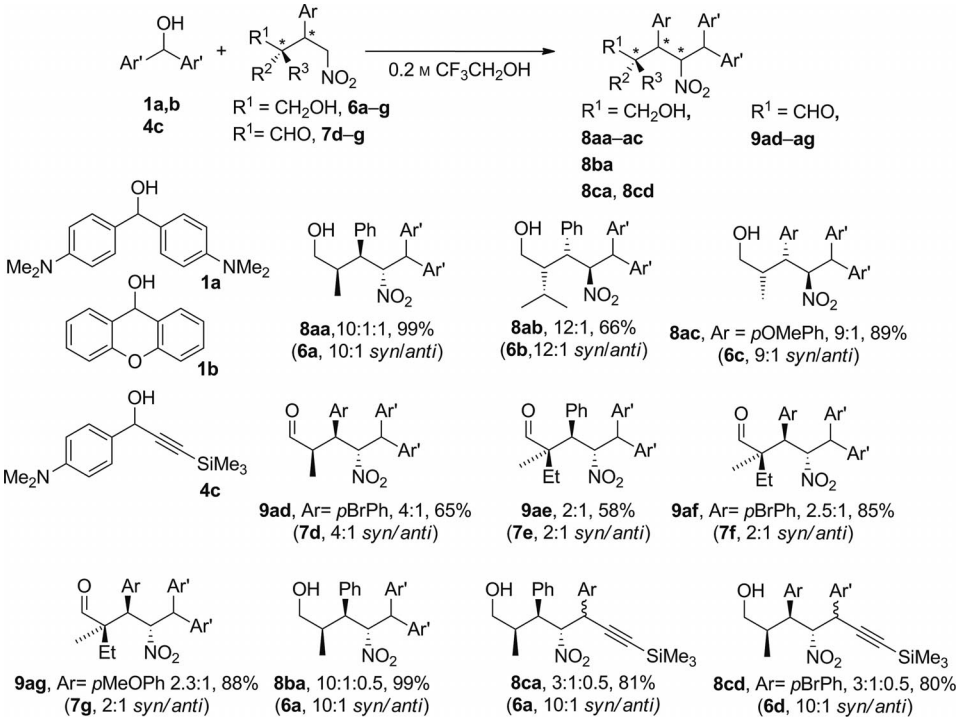
Scheme 1. Reaction of alcohols **4a**–**h** with nitroethane in trifluoroethanol.

levels of simple diastereoselection were recorded with alkynyl derivatives. The presence of the *p*NMe_2 substituent as an activating group was important for the formation of the desired product in good yield, but it is not mandatory, as other alcohols able to form stabilized carbenium ions in the range of –7 and –1 on the Mayr scale could be used.[21] For example, indolylalkynyl substrates can form carbenium ions that are quite stable,[22] and they are suitable substrates for this reaction. In addition, the presence of the activating *p*NMe_2 moiety is not a limitation for the chemistry, as it is possible to take advantage of its presence to introduce further functional groups, for example, by nickel-[23] or palladium-catalyzed[24] reactions. Other alcohols, such as 1,3-diphenylprop-2-en-1-ol, were reactive as well, but the formation of ether byproducts, obtained by the attack of the alcohol to the carbenium ion, were the predominant products in these cases. Also, different benzylic substrates (i.e., Ar = *p*NMe_2Ph, R = *n*Bu) were reactive under the reaction conditions, but the formation of alkenes as byproducts, through elimination of water, was predominant.

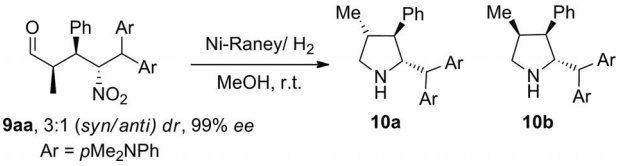
Organocatalytic Michael- and Henry-type reactions give simple stereoselective access to useful densely functionalized building blocks. Nitro derivatives obtained through organocatalytic reactions have found increasing applications in total synthesis. The organocatalyzed Michael addition of functionalized aldehydes to nitroalkenes is the key step in the total synthesis of Tamiflu and ABT 341.[25] Therefore, we wondered if such enantioenriched and accessible building blocks could be employed in our nitro alkylation reaction performed in TFE. We were pleased to discover that the reaction was possible, and it was also highly diastereoselective. Compounds **6a**–**c** and **7d** were obtained through standard organocatalytic procedures described by

Hayashi[26] with high *ee* values (10:1 to 12:1 *syn*/*anti*).[27] Flash chromatography purification of these compounds, performed by our group, resulted in decreased diastereomeric ratios in comparison to the results obtained by Hayashi.[28] When the aldehyde was reduced to the corresponding alcohol prior to chromatography, the *dr* values obtained were in line with those in Hayashi's paper. Nevertheless, in both cases, the inseparable mixtures of diastereoisomers were used in the nitro alkylation reaction to evaluate the diastereoisomeric stereoselectivity of the reaction.

By employing Hayashi's protocol, enantiomeric excess values up to 99% were obtained, and just two stereoisomers of the four possible isomers were present in the mixtures (*syn* and *anti* diastereoisomers of the nitro-Michael reaction). In the alkylation reaction performed in TFE over 20–70 h, alcohols that were not able to form the carbenium ion were recovered unconsumed after the reaction, and they do not need to be protected. Four diastereoisomers can be formed by this alkylation reaction performed in TFE: *syn*–*syn*, *syn*–*anti*, *anti*–*syn*, and *anti*–*anti*. In all the substrates investigated, we found [in the limits of NMR spectroscopy, GC–MS, and HPLC–MS (ESI)] the predominant presence of two favored diastereoisomers. Starting from a mixture with 10:1 *dr*, it was possible to recognize the presence of another diastereoisomer as a minor component in the crude reaction mixture (for **8aa** and **8ba**, Scheme 2). The reaction was highly diastereoselective, and the stereogenic center formed in the alkylation reaction was obtained with high stereocontrol (up to 9–10:1 *anti*/*syn*). The variation in the ratio between the starting and final diastereoisomers is inferred by the different reactivities of the *syn* (major diastereoisomer) and *anti* (minor diastereoisomer) forms of the starting material. In fact, the reaction of **7e** (2:1 *syn*/*anti*) with **1a** in TFE at 0 °C was not complete after 24 h, and the observed ratio of **9ae** was 4:1 *syn*/*anti*. In contrast, when **7f** (2:1 *syn*/*anti*) was treated with **1a** in TFE at –20 °C for 18 d, the *dr* of the final mixture (50% conversion) was 4:1. Substrates **7e**–**g** were obtained with a thiourea catalyst by following the protocol established by Jacobsen.[29] As reported by Jacobsen, the *dr* obtained in this reaction is moderate. However, more hindered substrates undergo alkylation in TFE in a diastereoselective reaction. No evidence for the presence of the other two diastereoisomers was obtained by ^{1}H NMR spectroscopy or HPLC–MS (ESI). The reaction was also possible with alcohol **4c**, but a mixture of diastereoisomers was obtained. The reaction of a chiral nitro derivative with alcohols **1a**, **1b**, and **4c** is another example of a diastereoselective S_N1-type reaction. Quite recently, Bach exploited diastereoselective alkylations[30] by using S_N1-type reactions[31] in which chiral carbenium ions are formed and treated with various nucleophiles. The relative *anti* configuration of the newly formed stereogenic center was established by NOE correlation with 400- and 600-MHz NMR spectrometers on a cyclic product obtained after reduction of the nitro group (Scheme 3, see Supporting Information for full details). The reaction of **7a** (3:1 *syn*/*anti*, 99% *ee*) in TFE gave corresponding product **9aa**, which was purified by chromatography and treated with Ni-Raney in MeOH at 20 °C in the presence of H_2. Corresponding pyrrolidine **10a** was isolated in 60% yield with high enantiomeric excess after chromatographic purification.



Scheme 2. Highly diastereoselective addition of enantioenriched nitro derivatives **6a**–**g** and **7d**–**g** to alcohols **1a**, **1b**, and **4c**. Conversions were determined by ^{1}H NMR spectroscopy.



Scheme 3. Cyclization of derivative **9aa** by Ni-Raney in MeOH.

Although the precise role of TFE in the diastereoselective reaction is not clear at the present time,[32] we can suggest a model for the formation of the major stereoisomer. We assume that the steric hindrance of the carbenium ion, generated by the action of TFE, is attacked by the nitro derivative while avoiding steric interaction with the aryl groups on the α-carbon atom (Figure 1).

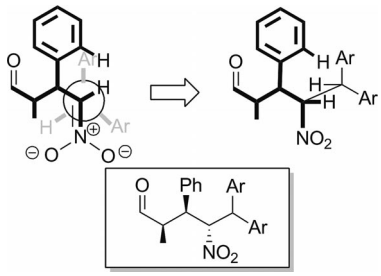
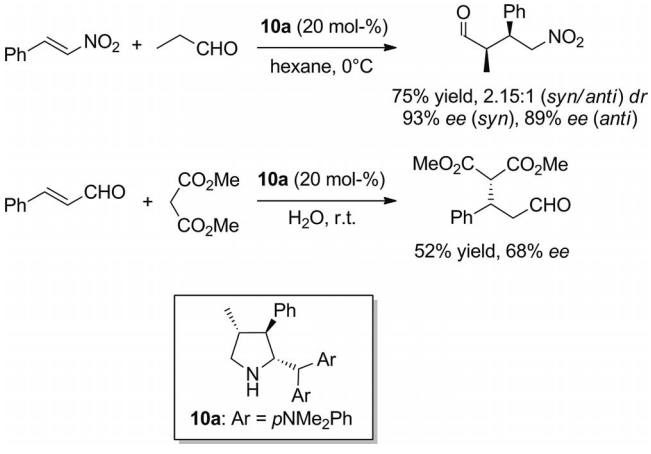


Figure 1. Stereochemical model for the addition of chiral nitro derivatives to benzhydrylic alcohols.

It is worthy to note that the cyclization procedure gives simple access to α-substituted pyrrolidines that might serve as potential organocatalysts. To shown the potentially of newly synthesized catalysts **10a**,[33] we have explored its use in standard organocatalytic reactions (Scheme 4).



Scheme 4. Organocatalytic reactions performed in the presence of pyrrolidine catalyst **10a**.

Conclusions

In conclusion, we have described the first addition of nitro derivatives to alcohols. The reaction tolerates a range of functional groups and was performed in TFE as the reaction solvent. Acyclic chiral nitro derivatives undergo alkylation of the carbenium ions formed from the alcohols in a highly diastereoselective fashion. Hindered secondary amines can be prepared from these adducts in a straightforward manner to give access to functionalized, useful organocatalytic chiral pyrrolidines. A family of new pyrrolidines bearing stereogenic centers and functional groups can be readily accessed by this methodology.[34]

Experimental Section

General Procedure: To a solution of the nitro derivative (3–5 equiv.) dissolved in TFE (0.2 mL) was added the alcohol (0.1 mmol). The mixture was stirred at room temperature in a capped vial until the reaction was complete. After addition of water and evaporation of TFE under reduced pressure, the aqueous phase was extracted with Et_2O (2× 5 mL). The collected organic layers were dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography.

Supporting Information (see footnote on the first page of this article): Full experimental procedures, characterization data, ^1H NMR and ^{13}C NMR spectra, LC–MS data, and HPLC traces.

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