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Letter

Highly Diastereoselective Preparation of Tertiary Alkyl Isonitriles by Stereoinvertive Nucleophilic Substitution at a Nonclassical Carbocation

Xu Chen and Ilan Marek*

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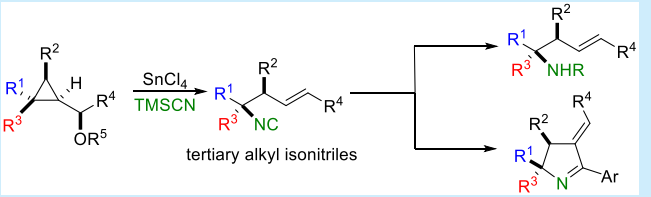
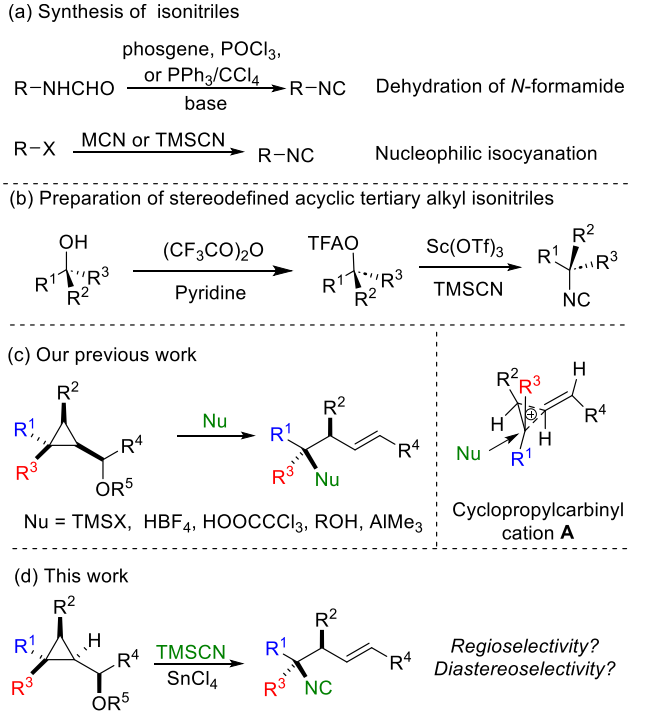
ABSTRACT: A highly efficient $SnCl_4$-catalyzed nucleophilic isocyanation of cyclopropyl ethers has been developed. The reaction proceeds at the quaternary carbon stereocenter of the cyclopropane with a complete inversion of configuration, providing a new avenue for the construction of synthetically challenging tertiary alkyl isonitriles with high diastereopurity. The diversity of the incorporated isocyanide group has been demonstrated by the transformation of tertiary alkyl isonitriles into the corresponding tertiary alkyl amines, amides, and cyclic ketoimines.



The isonitrile functional group is of major interest to the synthetic community due to its zwitterionic nature. It either reacts as a nucleophile or an electrophile or participates as a ligand in various metal-mediated chemical transformations. It has been particularly used in multicomponent reactions,[1−3] in insertion reactions,[4−9] in a radical cascade reaction,[5] in peptide synthesis,[10] as handles for bio-orthogonal functionalization of proteins,[11] and in the synthesis of polymers.[12] In addition, isonitriles, especially secondary and tertiary substituted alkyl isonitriles, are highly stable in plasma and against oxidative hepatic metabolism and have therefore attracted more attention from medicinal chemists.[13] The dehydration of *N*-formamide[1,14,15] and the nucleophilic isocyanation[16] using metal cyanide or TMSCN as an N-nucleophile are two typical methods for the preparation of isonitriles (Scheme 1a). However, dehydration of *N*-formamide usually derailed for the preparation of congested tertial alkyl isonitrile due to the low yield resulting from the dehydration process. Nucleophilic isocyanation[16] via a tertiary carbocation intermediate provides a complementary approach for tackling these issues, and several important methods have been developed for the synthesis of tertiary alkyl isonitriles.[17−23] Due to the steric hindrance of the tertiary alkyl electrophile and the difficulty in gaining stereocontrol over the tertiary carbon undergoing substitution,[24−32] methods for the synthesis of stereodefined tertiary alkyl isonitriles are limited,[20,21,33−39] with a notable exception for the $Sc(OTf)_3$-catalyzed stereoinvertive substitutions of tertiary alcohols under solvolytic conditions (Scheme 1b).[34−39] Therefore, the development of additional methods for the preparation of sterically hindered acyclic tertiary alkyl isonitriles possessing adjacent stereocenters with high diastereopurity is still highly desirable.

Scheme 1. Preparation of Isonitriles



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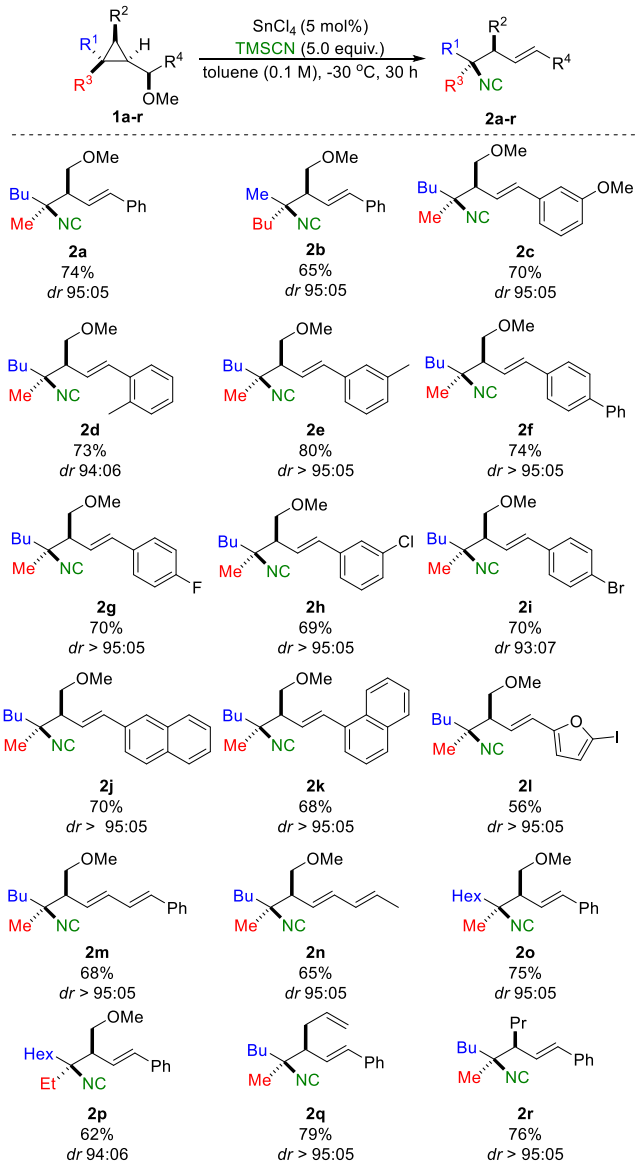
Recently, we[40−43] and others[44−46] have reported several strategies for controlling the stereochemistry of the S_N1 reaction at nonclassical carbocations, utilizing the exergonic ring opening of stereodefined cyclopropyl carbinol derivatives bearing quaternary carbon stereocenters, with a complete inversion of configuration (Scheme 1c). Recent theoretical calculations confirmed that nonclassical cyclopropylcarbinyl cation **A** is a stable intermediate that undergoes nucleophilic substitution at the most substituted quaternary carbon center in a stereoinvertive manner,[47] representing a new avenue for the construction of various challenging acyclic structures with stereodefined adjacent tertiary and quaternary carbon stereocenters. Inspired by these results, we envisioned that an efficient method for the preparation of acyclic tertiary alkyl isonitriles with high diastereopurity could originate from a judicious combination of an isonitrile precursor with a Lewis acid (Scheme 1d). Our study began with a screening a series of Lewis acids with TMSCN in DCM for the selective nucleophilic substitution of cyclopropyl carbinol ether **1a**[42] (for all of the details, see the Supporting Information).

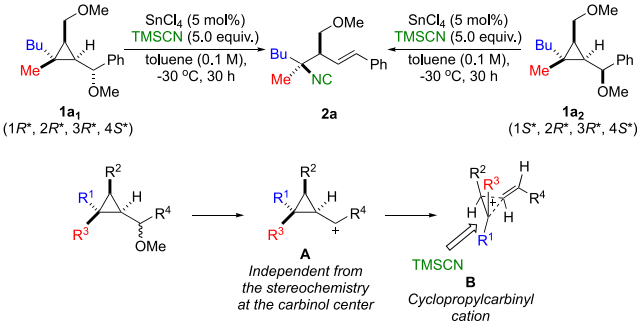
After a systematic survey, we found that the use of 5 mol % $SnCl_4$ in toluene at −30 °C for 30 h was the optimal condition for providing isonitrile **2a** in 74% yield with an excellent diastereomeric ratio [dr 95:05 (Scheme 2)] and a complete inversion of configuration, which was later confirmed by transforming isonitrile **2i** into previously reported amide **4a**[42] as shown in Scheme 4. With a suitable condition in hand, a variety of cyclopropyl carbinol derivatives were investigated (Scheme 2). The opposite diastereomer, **2b**, could be easily prepared via simple permutation of the two substituents at the quaternary carbon stereocenter of **1b**. A variety of cyclopropyl carbinol derivatives **1** containing aryl groups (R^4) possessing either electron-donating or -withdrawing groups, such as methyl, fluoro, bromo, methoxy, and phenyl groups, were transformed into the corresponding tertiary alkyl isonitriles (**2a**−**2k**) in good yields with excellent diastereoselectivities (dr from 93:07 to >95:05). A heterocycle such as furan was suitable for this transformation as **2l** was obtained in excellent diastereoselectivity (dr >95:05). The nature of substituent R^4 is not restricted to an aromatic ring as the presence of a diene did not alter the outcome of this transformation (Scheme 2, **2m** and **2n**). It is also important to note that $R^2 = CH_2OMe$ is not mandatory for a selective ring opening of **1**, as the R^2 substituent could also be an allyl or a propyl group without changing the stereochemical outcome of the reaction (Scheme 2, **2q** and **2r**). It is noteworthy that this approach represents a nice complement to the previous notable method for the construction of highly congested tertiary alkyl isonitriles[34] via stereoinvertive substitution at tertiary trifluoroacetate under solvolytic conditions, where moderate diastereoselectivities were observed for highly branched acyclic tertiary trifluoroacetates.

To gain some additional mechanistic insight into the reaction mechanism, the two diastereomers at the carbinol center of **1a** were independently prepared and both (1*R**,2*R**,3*R**,4*S**)-$\mathbf{1a_1}$ and (1*S**,2*R**,3*R**,4*S**)-$\mathbf{1a_2}$ were treated under our reaction condition (Scheme 3). The result shows that in both cases, the same *E*-isomer of **2a** was obtained, suggesting that the nucleophilic substitution is independent of the initial stereochemistry at the carbinol center. Therefore, the reaction primarily starts with the formation of a cyclopropyl cation **A** that is transformed into cyclopropylcarbinyl cation **B**. A scale-up reaction of **1a** (2.0 mmol) was also carried out to afford **2a** in 70% isolated yield (386 mg) with the same level of diastereoselectivity (dr 95:05). The positive charge located at the quaternary carbon stereocenter is more stabilized and therefore reacts with the nucleophile (TMSCN) to provide isonitrile **2** with a complete inversion of configuration.[47]

Scheme 2. Catalytic Nucleophilic Isocyanation



Scheme 3. Mechanistic Insight



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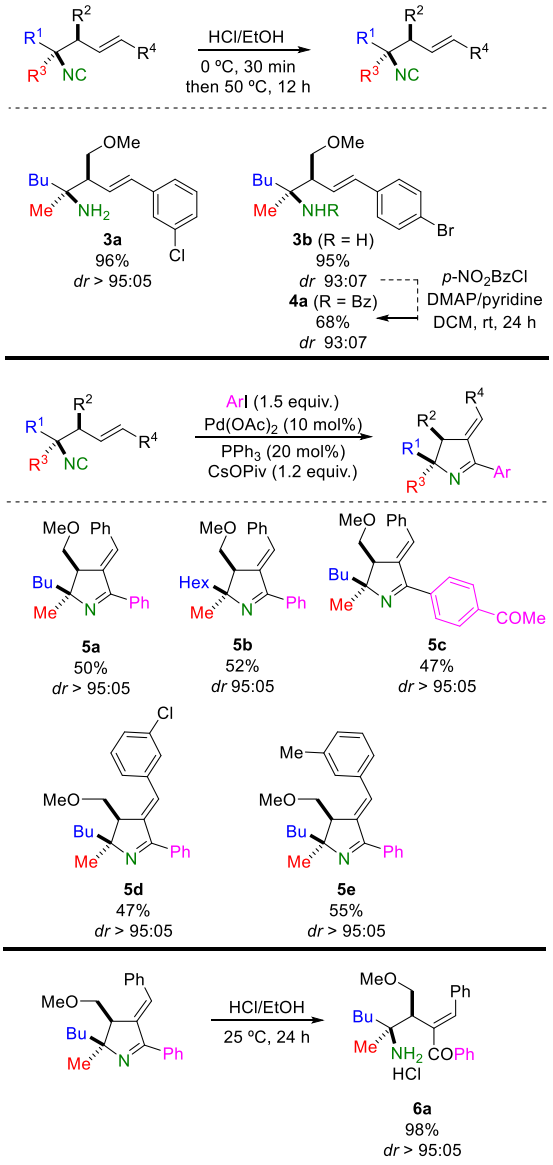
Scheme 4. Transformation of Isonitriles into Amines, Amides, and Cyclic Ketoimines



Importantly, this procedure also enables the conversion of cyclopropyl ethers to the corresponding amines and their derivatives. For instance, **2h** and **2i** could easily be transformed into tertiary alkyl amine **3a** and **3b**, respectively.[34] Amine **3b** could eventually be protected to afford the previously reported amide **4a** (NHBz).[42] Additionally, isonitriles could be readily converted into stereodefined polysubstituted cyclic ketoimines **5a**−**5e** by an intramolecular imidoylative Heck reaction.[48] The stereochemistry of the formed exocyclic double bond was determined by correlation with literature precedent[48] and by NMR analysis of the NOE spectra. The obtained cyclic imine **5a** then could be hydrolyzed to acyclic amine **6a** under mild reaction conditions, illustrating a potential extension of this chemistry to a more complex molecular structure.

In conclusion, we have developed a highly efficient method for the synthesis of tertiary alkyl isonitriles via a stereoinvertive nucleophilic substitution at a quaternary carbon stereocenter of cyclopropane, through the formation of a cyclopropylcarbinyl cation. A series of tertiary alkyl isonitriles were obtained in high yields with excellent diastereopurity. The latter could be readily transformed into the corresponding synthetically challenging tertiary alkyl amines, amides, and cyclic imines, which demonstrate the diversity of tertiary alkyl isonitrile functionalities in organic synthesis. Furthermore, this approach represents an additional example of the relatively rare catalytic nucleophilic isocyanation using TMSCN as the source of isocyanide for the stereoselective nucleophilic substitution at a nonclassical carbocation.[49]

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00583.

General procedures, product characterization, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ilan Marek − *Schulich Faculty of Chemistry and Resnick Sustainability Center for Catalysis, Technion - Israel Institute of Technology, Haifa 3200009, Israel;* orcid.org/0000-0001-9154-2320; Email: chilanm@technion.ac.il

Author

Xu Chen − *Schulich Faculty of Chemistry and Resnick Sustainability Center for Catalysis, Technion - Israel Institute of Technology, Haifa 3200009, Israel*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c00583

Notes

The authors declare no competing financial interest.

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