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Direct Synthesis of α-Amino Nitriles from Sulfonamides via Base-Mediated C−H Cyanation

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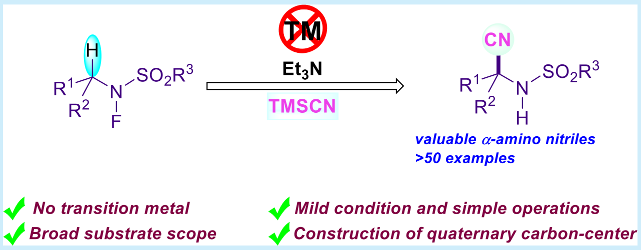
ABSTRACT: Herein, we disclose a transition-metal-free reaction system that enables α-cyanation of sulfonamides through C−H bond cleavage for the preparation of α-amino nitriles, including difficult-to-access all-alkyl α-tertiary scaffolds. More than 50 substrate examples prove a wide functional group tolerance. Additionally, its synthetic practicality is highlighted by gram-scalability and the late-stage modification of natural compounds. Mechanistic experiments suggest that this process involves in situ formation of an imine intermediate via base-promoted elimination of HF.



Direct C−H activation adjacent to nitrogen in amine derivatives for coupling transformations is an extremely effective and important approach in organic synthesis.[1,2] Remarkably, C_α−H cyanation of nitrogen-containing compounds has garnered tremendous attention because it can provide versatile α-amino nitriles, which play key roles in the synthesis of alkaloids, amino acids, heterocycles, and pharmaceuticals.[3−7] In this context, previous works has been developed mainly using stoichiometric oxidants,[8] biocatalysts,[9] or transition metal catalysts,[10] including Cu,[11] Fe,[12] Au,[13] Ru,[14] V,[15] W,[16] Co,[17] Ti,[18] and Ir[19] (Figure 1A). Notably, transition-metal-free C_α−H cyanation is essential and challenging.[20] For example, Lambert presented an example of using the tropylium ion as a promoter and KCN as a cyano source to achieve α-cyanation of amines in 2011.[21] In 2012, Seidel described a carboxylic acid catalyzed α-cyanation of amines with trimethylsilyl cyanide (TMSCN) in toluene at 200 °C.[22] In 2016, a nitroxyl-radical-catalyzed oxidative C_α−H cyanation of sulfonamides was reported by Moriyama.[23] In 2018, Stahl developed an electrochemical approach for C_α-cyanation of secondary piperidines to synthesize α-amino nitriles employing 9-azabicyclononane *N*-oxyl as a catalytic mediator.[24] However, the substrate scope of these methods is mainly focused on benzyl and cyclic amines,[25] thus hampering their synthetic applicability and industrial scale-up potential. Recently, our group reported a new reaction pattern for the cross-coupling of sulfonamides with arylimines through strain-release rearrangement. And an imine intermediate, which was generated through base-assisted HF elimination, was proposed according to control experiments and theoretical calculations.[26] Inspired by this progress, we speculated that if the imines formed in situ from sulfonamides would selectively proceed addition reaction with nucleophile, it would provide a great opportunity for α-functionalization. Herein, we describe a metal-free C_α−H cyanation of sulfonamides mediated by a weak base under mild conditions, affording a broad scope of α-amino nitriles, including the valuable α-quaternary carbon variants (Figure 1B).

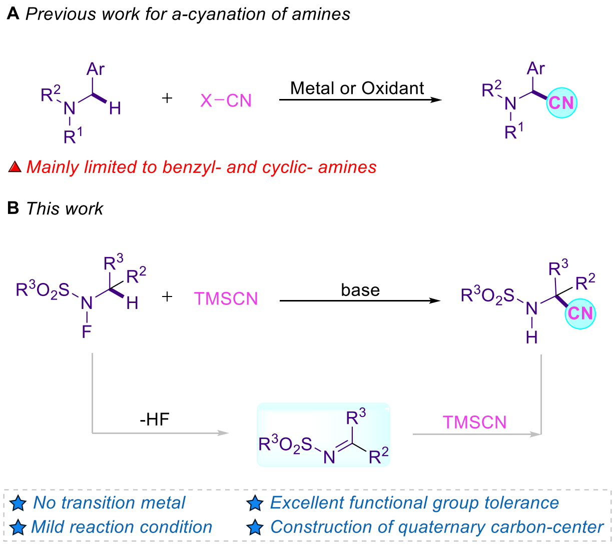


Figure 1. C_α−H cyanation of amine derivatives.

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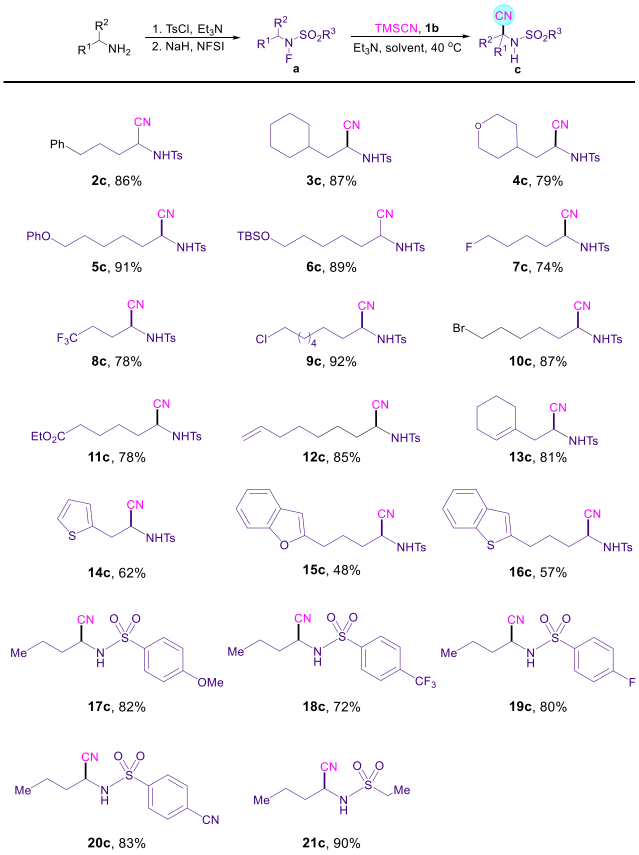
We initiated our C_α−H cyanation studies by monitoring the reactivity of *N*-fluorotosylamides **1a** derived from amines with TMSCN (**1b**) (see the Supporting Information for details). The results showed that 1.5 equiv of triethylamine (Et_3N) exhibited the best activity in toluene. To demonstrate the generality of this approach, a variety of amides were evaluated under the optimized reaction conditions (Scheme 1). The primary amine derivatives **2a**−**16a** bearing different functional groups on the carbon chain proceeded smoothly. For example, substrates possessing phenyl (**2a**), cycloalkyl (**3a**), ether group (**4a** and **5a**), and TBS-protected hydroxyl (**6a**) were well tolerated. Additionally, this cyanation process was not affected by halo substituents such as F (**7c**), CF_3, (**8c**), Cl (**9c**), and Br (**10c**) on the substrates, highlighting its potential in combination with subsequent cross-coupling transformations. Amide derivatives with ester group and alkenyl motif were also compatible with our standard conditions and successfully converted to the desired *α*-amino nitriles (**11c**−**13c**). Interestingly, common heterocyclic cores (**14c**−**16c**) were found to successfully undergo C_α−H cyanation. Notably, this reaction was competent for electron-donating, electron-neutral, and electron-withdrawing arylsulfonamide derivatives (**17c**−**20c**). Excitingly, ethanesulfonamides effectively reacted with TMSCN, giving products **21c** in 90% yield.

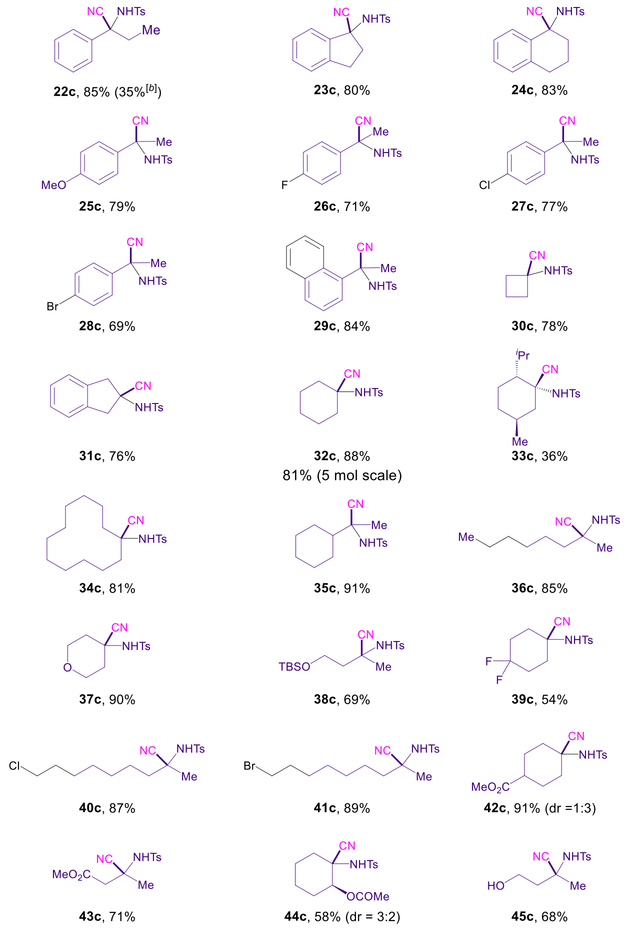
Scheme 1. Substrate Scope for Primary Amides[a]



[a]Reaction conditions: A mixture of *N*-fluorotosylamides **a** (0.20 mmol), TMSCN **1b** (0.30 mmol), and Et_3N (0.3 mmol) in toluene (1 mL) was stirred for 24 h at 40 °C under Ar, isolated yield after chromatography.

Next, the transformation was assessed with various secondary amides under modified conditions (Scheme 2). A wide range of benzylamine substrates provided the corresponding products **22c**−**28c** with good yields. Naphthylamides were favorably coupled with TMSCN to afford the products **29c** in 84% yield. A series of carbon chain amides were also tolerated in this system, affording the various *α*-amino nitriles in 36%−88% yield (**30c**−**45c**). The reaction could also be applied in gram-scale synthesis, obtaining **32c** with 81% yields on a 5 mol scale. When **33a** is used as the substrate, the *α*-cyanation product was obtained in 36% yield while retaining its enantiopurity. Surprisingly, **45a** converted into products **45c** with hydroxyl group in 68% yield under standard conditions, and this process involved the hydrolysis of methyl esters. More importantly, this methodology enables the late-stage derivatization of complex molecules (**46c**−**53c**). The structure of **50c** was characterized by X-ray crystallographic analysis (Scheme 3).

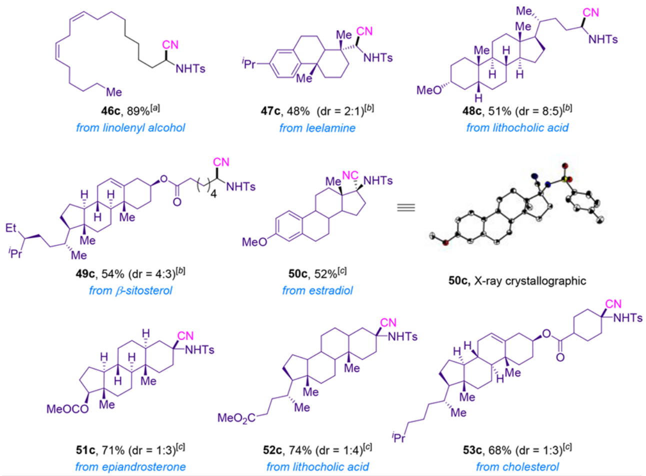
Scheme 2. Substrate Scope for Secondary Amides[a]



[a]Reaction conditions: A mixture of *N*-fluorotosylamides **a** (0.20 mmol), TMSCN **1b** (0.50 mmol), and Et_3N (0.3 mmol) in MeCN (1 mL) was stirred for 24 h at 60 °C under Ar, isolated yield after chromatography. [b]A mixture of *N*-fluorotosylamides **a** (0.20 mmol), TMSCN **1b** (0.30 mmol), and Et_3N (0.3 mmol) in toluene (1 mL) was stirred for 24 h at 40 °C under Ar, isolated yield after chromatography.

To probe the mechanism of this cyanation reaction, we conducted several control experiments. First, the standard

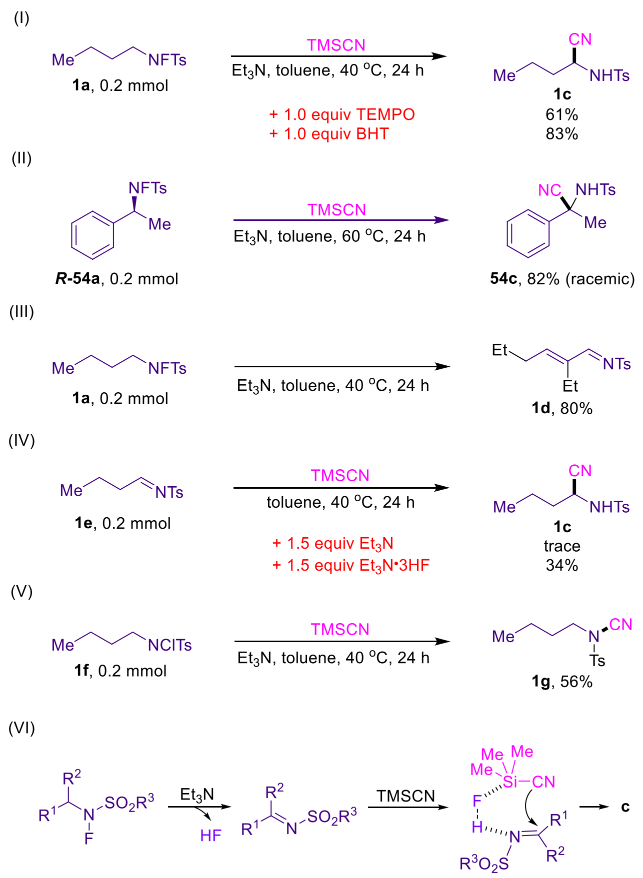
Scheme 3. Late-Stage Functionalizations



[a] Reaction conditions: A mixture of *N*-fluorotosylamides **a** (0.20 mmol), TMSCN **1b** (0.30 mmol), and Et_3N (0.3 mmol) in toluene (1 mL) was stirred for 24 h at 40 °C under Ar, isolated yield after chromatography. [b] A mixture of *N*-fluorotosylamides **a** (0.20 mmol), TMSCN **1b** (0.50 mmol), and Et_3N (0.3 mmol) in MeCN (1 mL) was stirred for 24 h at 60 °C under Ar, isolated yield after chromatography. [c] Using 2.5 equiv of TMSCN, the reaction was carried out in MeCN (1 mL) for 24 h at 80 °C.

reaction was carried out in the presence of 1.0 equiv of TEMPO or BHT (Scheme 4I). These radical inhibitors did not hinder the smooth progress of the transformation. Subsequently, when *R*-**54a** (99% ee) was allowed to react with TMSCN under standard conditions, racemic product **54c** was observed in 82% yield (Scheme 4II). When removing cyano reagents from standard conditions, *α*,*β*-unsaturated imines **1d** was generated from the self-coupling of **1a** (Scheme 4III). On the basis of these investigations, we have hypothesized that the imine species may be an intermediate in the process. To further confirm this conclusion, imine **1e** was applied to our conditions (Scheme 4IV). And we indeed detected the corresponding product with 34% using $Et_3N·3HF$ as base. In addition, when employing *N*-chloro amide **1f** instead of **1a**, no *α*-amino nitrile was detected, and **1g** was isolated with 56% yield (Scheme 4V). These observations show that the fluorine atom was an important driving force for this C−H cyanation. In view of the above results and previous works,[26,27] we propose a possible experimental mechanism (Scheme 4VI). An imine intermediate was generated from *N*-fluorotosylamide through a base-assisted HF elimination. Subsequently, this imine was attacked by TMSCN, which was simultaneously activated by the formed HF species, offering the corresponding product. To further confirm the practicality of this method, a facile deprotection process of *α*-amino nitriles bearing mesitylenesulfonyl group (**55c**) was shown in Scheme S19 (Supporting Information).

Scheme 4. Mechanistic Experiments



In summary, we have developed an effective and metal-free system, which is capable of achieving *α*-C−H bonds dehydrocyanation of aliphatic amides under mild condition, providing a broad scope of *α*-amino nitriles with an all-carbon quaternary stereocenter. We also illustrated that sulfonamides derived from complex molecules can be applied to carry out C_α−H cyanations with good yields. Given how widespread the cyano group are in chemicals, we anticipate that this methodology will simplify the synthesis elaboration of *α*-amino nitriles for research in chemistry, medicine, and biology, and open up new frontiers in metal-free C−H functionalization of amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01232.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 2059493 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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