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Cyanomethyl anion transfer reagents for diastereoselective Corey–Chaykovsky cyclopropanation reactions†

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A readily available and bench-stable cyanomethyl sulfonium salt was used in highly diastereoselective Corey–Chaykovsky cyclopropanation reactions of electron-poor olefins. This efficient method provides a rapid route to access densely functionalized cyclopropyl nitriles.

Cyclopropanes are a fascinating class of small molecules and possess unique properties that are reasoned by the conformational rigidity and distinctive spatial arrangement of substituents in this smallest-possible carbocycle.¹ Cyclopropyl nitriles are ubiquitous in pharmaceutical research, for example as Cathepsin C inhibitors (**1**, Fig. 1) or as NMDA receptor modulators (**2**).³ They are also valuable precursors for the synthesis of cyclopropyl methylamines,² as the reduction of the nitrile group readily furnishes cyclopropyl methylamines. These compounds in turn are privileged scaffolds in many biologically active compounds (**3–5**) and find applications in marketed drugs, *e.g.* Tasimelteon (**4**) or Levomilnacipran (**5**).^{3,4} The latter was approved in 2013 and is used for the treatment of depression (Fig. 1).

Despite tremendous research in the synthesis of ester or trifluoromethyl-substituted cyclopropane ring systems,^{1,5} synthetic methods of nitrile-substituted cyclopropanes are still scarce.⁶ Even today, the introduction of a “cyanomethylene” group remains a challenge to organic synthetic methodology⁷ and only normally proceeds either by transfer of a cyanomethyl carbene^{6a} or cyanomethyl radical.^{6b} From a synthetic perspective, traditional approaches are limited with respect to the use of either expensive catalysts or hazardous reagents. From a diversity point of view, they only allow the synthesis of *trans*-substituted nitrile-cyclopropanes with moderate diastereoselectivity. It is thus not surprising that current applications of nitrile cyclopropanes are almost exclusively on *trans*-substituted cyclopropanes.



Fig. 1 Applications of cyclopropyl nitriles and cyclopropyl methylamines.

We therefore became intrigued in exploring alternative reagents for the introduction of a cyanomethylene group^{6,8} and envisaged a Michael initiated ring closing reaction using a cyanomethylene anion transfer reagent (Scheme 1). In previous studies,⁹ it was already demonstrated that halogen-substituted acetonitrile provides an access to nitrile-cyclopropanes though with strict limitations to substrate scope, yield and stereoselectivity.

Inspired by these findings, we set out to explore the cyclopropanation reaction between nitro styrene, as a model substrate for electron-deficient olefins to prepare functionalized cyclopropanes, and halo-acetonitrile in the presence of different organic and inorganic bases (Table 1). Unfortunately, only the rapid decomposition of the halo-acetonitrile was observed under these basic reaction conditions. We subsequently evaluated different types of nucleophilic additives that could potentially form an intermediate onium salt, which is more acidic and should require less basic reaction conditions to proceed (Table 1, entries 3–9). Of all additives tested, only dimethyl sulfide gave some positive results and cyclopropane **7a** was isolated in 10% yield. The screening of different reaction conditions did not lead to an improvement of this transformation.

We thus decided to exchange the halogen moiety by a neutral leaving group and turned our attention to the preformed sulfonium salt **8** (Table 2) for Corey–Chaykovsky cyclopropanation reactions

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Scheme 1 Cyanomethyl anion transfer.

as a substitute of bromo acetonitrile.¹⁰ In 1966, Baizer described the synthesis of a cyanomethyl sulfonium salt for the first time,^{11a} which is being used today as a versatile coupling reagent in peptide synthesis.^{11,12} From a synthetic perspective, sulfonium salts are much less explored, *e.g.* in carbonyl homologation reactions^{11b,d} or in the synthesis of pyridine-2*H*-ones and isatines.^{11c,d} Jeckel and Gosselck reported the reaction with malonic acid derivatives in cyclopropanation reactions, though only two single examples are provided.^{11f} The deprotonation of a cyanomethyl sulfonium salt provides a sulfur ylide, whose nucleophilic and kinetic properties were well studied by Mayr and co-workers.¹³

We examined different bases and solvents for the cyclopropanation reaction (Table 2) and in all cases we could isolate the desired cyclopropane as a single diastereoisomer, which was identified as the *trans*-isomer **7a** (referring to the relative stereochemistry of the nitro and nitrile moiety) as determined by NOE spectroscopy.¹⁴ The aryl group is arranged in *cis* stereochemistry to the nitrile group. Only in the case of TBAT (tetrabutylammonium triphenyl difluorosilicate, entry 7) we could observe a trace amount of a second isomer, which was identified as the all-*cis* isomer as shown by NOE experiments. The concentration had a significant effect on the yield (entries 2, 12 and 13) and the combination of sodium carbonate, DCM solvent and a concentration of 0.1 M proved to be the best conditions for the Corey–Chaykovsky cyclopropanation reaction, which proceeded in excellent yield and diastereoselectivity. The *cis* stereochemistry of the nitrile group and the aromatic ring is remarkable and highlights differences in reactivity and complementarity of the carbene^{5a} and radical reactivity^{5b} versus the Corey–Chaykovsky reactivity^{8a,10} as now both diastereoisomers can be accessed

Table 2 Optimization of reaction conditions

| # ^a | Base | Solvent | Concentration (M) | Yield (%) (7a) |
|-----------------|-------------------------------------|-------------------|-------------------|----------------|
| 1 | Li ₂ CO ₃ | DCM | 0.2 | Traces |
| 2 | Na ₂ CO ₃ | DCM | 0.2 | 76 |
| 3 | K ₂ CO ₃ | DCM | 0.2 | 63 |
| 4 | Cs ₂ CO ₃ | DCM | 0.2 | 60 |
| 5 | NEt ₃ | DCM | 0.2 | 64 |
| 6 | CsF | DCM | 0.2 | 73 |
| 7 | TBAT | DCM | 0.2 | 43 |
| 8 | Na ₂ CO ₃ | EtOAc | 0.2 | 53 |
| 9 | Na ₂ CO ₃ | THF | 0.2 | 55 |
| 10 | Na ₂ CO ₃ | 1,4-Dioxane | 0.2 | 72 |
| 11 | Na ₂ CO ₃ | CHCl ₃ | 0.2 | 62 |
| 12 | Na ₂ CO ₃ | DCM | 0.8 | 60 |
| 13 | Na₂CO₃ | DCM | 0.1 | 93 |
| 14 ^b | Na ₂ CO ₃ | DCM | 0.1 | 43 |

^a Reaction conditions: **6a** (0.2 mmol), 2 eq. **8** and 1.5 eq. of Na₂CO₃ were stirred in 2 mL of DCM for 12 h at rt. Yields refer to isolated products as single diastereoisomer. ^b Reaction with *Z*-nitro styrene.

with a high degree of stereo control. We also investigated *Z*-nitro styrene and obtained a single product, which turned out to be the same diastereoisomer as for the *E*-nitro olefin, albeit in reduced yield.

In further experiments, we studied different nitro olefins to evaluate the applicability of this transformation. Different electron-withdrawing and electron-donating substituents in *ortho*-, *meta*- or *para*-position were well-tolerated and the desired cyclopropanes were isolated as a single diastereoisomer with good to high yields (Scheme 2, entries **7b–7l**). Similarly, heterocycles, such as thiophene (**7p**), furane (**7o**) or pyridine (**7n**) and other carbocycles (**7m**) were tolerated and the corresponding nitro olefins reacted smoothly to afford the cyclopropanation products. Notably, an aliphatic substrate was converted to the desired cyclopropane (**7q**) in good isolated yield. In the case of β -methyl-*trans*- β -nitro styrene, the cyclopropane was obtained only in low yield, albeit as a single diastereoisomer (**7r**). On the other hand, α -methyl-*trans*- β -nitro styrene did not

Table 1 Initial investigations on the cyanomethyl anion transfer reaction

| # ^a | X | Base | Additives | Yield (7a) |
|----------------|--------|--|-------------------|------------|
| 1 | Br, Cl | NEt ₃ , DBU, TBAT, TBAF | — | No rct. |
| 2 | Br, Cl | Li ₂ CO ₃ , Na ₂ CO ₃ , K ₂ CO ₃ , Cs ₂ CO ₃ , CsF, NaOEt, KOH | — | No rct. |
| 3 | Br | K ₂ CO ₃ | Me ₂ S | 10% |
| 4 | Br | Na ₂ CO ₃ | Me ₂ S | Traces |
| 5 | Br | CsF | Me ₂ S | No rct. |
| 6 | Br | NEt ₃ | Me ₂ S | No rct. |
| 7 | Br | K ₂ CO ₃ | PhSMe | No rct. |
| 8 | Br | K ₂ CO ₃ | Ph ₂ S | No rct. |
| 9 | Br | K ₂ CO ₃ | DMAP | No rct. |

^a Reaction conditions: **6a** (0.2 mmol), 2 eq. halo acetonitrile and 1.5 eq. of base were stirred in 2 mL of DCM for 12 h at rt. Yields refer to isolated products as single diastereoisomer.



Scheme 2 Substrate scope of nitro olefins and unsaturated carbonyl compounds. Reaction conditions: Michael acceptor (0.2 mmol), 2 eq. **8** and 1.5 eq. of Na_2CO_3 were stirred in 2 mL of DCM for 12 h at rt. Yields refer to isolated products as single diastereoisomer; ^a 6.7 mmol scale; ^b using 1.75 eq. Cs_2CO_3 in 2 mL 1,4-dioxane; ^c 6.2 mmol scale.

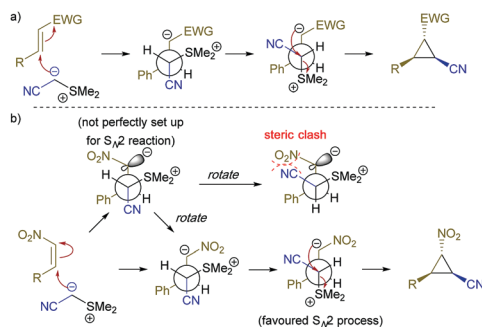
provide the desired cyclopropanation product; both these results can be attributed to steric hindrance of the methyl group at the nitro olefin. In a scale-up of this cyclopropanation reaction we could demonstrate that the desired cyclopropane **7a** can be obtained on gram-scale (1.04 g **7a**, 82%, 6.7 mmol reaction scale).

To further expand the scope and applicability of this cyclopropanation reaction, we examined different unsaturated carbonyl compounds. Interestingly, typical Michael acceptors, such as cinnamic aldehyde, nitrile or ethyl ester did not provide the desired reaction products. Only in the case of benzylidene malodinitrile the cyclopropanation product (**9**) could be isolated, though with poor yield. We next turned our attention to terminal α,β -unsaturated ketones. In our model reaction, we were delighted to observe that the desired cyclopropane **10a** could be isolated as a single diastereoisomer, irrespective of solvent and base, which is also the *trans*-isomer as shown by NOE spectroscopy.¹⁴ The substitution pattern on the aromatic rings of other analogous substrates (Scheme 2, entry **10b–10f**) had little influence on the cyclopropanation reaction. Similarly, sulfur-containing heterocycles (**10i**), carbocycles (**10g**) and aliphatic substrates (**10j**) reacted smoothly under the present conditions. β -Substituted unsaturated ketones or benzyl acrylate gave significantly diminished yields (**10k–m**), which might be attributed to steric hindrance due to the substituent in the β -position.

In all cases the *trans* configured product was obtained exclusively as a single diastereoisomer.¹⁴

Finally, we decided to study applications of this protocol in the synthesis of a key precursor of Levomilnacipran (**5**). For this purpose, we investigated the reaction of 2-phenyl acrylic acid ester with our sulfonium salt. To our delight, this ester reacted smoothly to form the desired cyclopropane **11** in excellent yield, albeit in moderate diastereoselectivity. Unfortunately, even after extensive screening of solvents and bases the diastereoselectivity of this transformation could only be improved to a 6 : 1 ratio.¹⁴ This can be rationalized by the lack of steric discrimination between the ester and phenyl groups. In a gram-scale experiment we were able to demonstrate the scalability of this transformation (1.11 g **11**, 89%, 6.2 mmol reaction scale). The stereochemistry of the major product was confirmed to be *trans* by comparison with literature data.¹⁵

The stereochemistry of this cyclopropanation reaction is consistent with previous observations^{8a} in Corey–Chaykovsky cyclopropanation reactions and can be rationalized by the mechanism depicted in Scheme 3a. We believe the cyclopropanation of *Z*-nitro styrene involved a re-orientation process when the nitro group on the carbanion intermediate rotated to avoid steric clash with the cyano group (see step 2 of mechanism depicted in Scheme 3b) to prepare for the $\text{S}_{\text{N}}2$ cyclopropanation, hence forming the same product as the *E*-isomer.



Scheme 3 Proposed mechanism for the for the cyclopropanation reaction, (a) reaction with electron poor olefins, (b) reaction with Z-nitro olefin.

In summary, we have developed a novel and robust protocol for the highly diastereoselective synthesis of nitrile-substituted cyclopropanes. We could demonstrate applications of a (cyano-methyl) dimethyl sulfonium salt in cyclopropanation reactions of electron-poor olefins and showcase their potential as a surrogate for hazardous diazoacetone nitrile carbene precursor. This protocol features a broad functional group tolerance, including a diverse set of heterocyclic- and aliphatic substituted electron-poor olefins. Moreover, this approach can be readily applied to the synthesis of a key synthetic precursor of Levomilnacipran.

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Conflicts of interest

There are no conflicts to declare.

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