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Letter

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Trisubstituted 2-Trifluoromethyl Pyrrolidines via Catalytic Asymmetric Michael Addition/Reductive Cyclization

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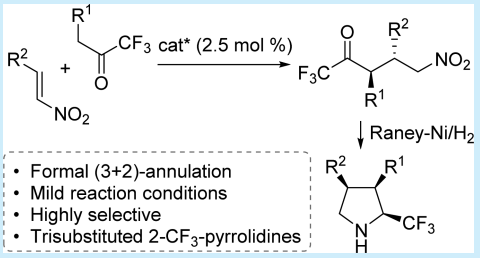
Supporting Information

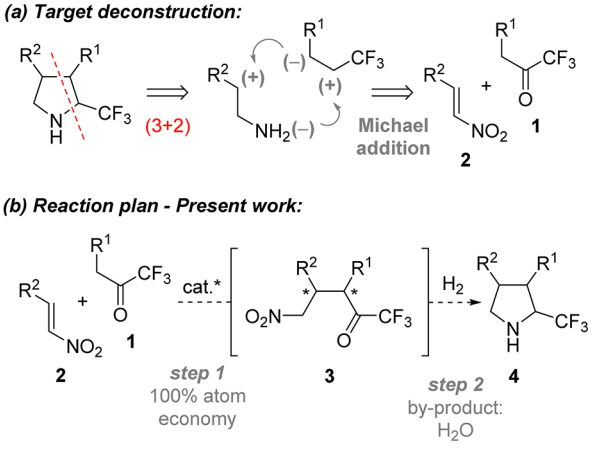
ABSTRACT: The stereoselective synthesis of trisubstituted 2-trifluoromethyl pyrrolidines by asymmetric Michael addition/hydrogenative cyclization is described. The direct organocatalytic addition of 1,1,1-trifluoromethylketones to nitroolefins proceeds under mild reaction conditions and low catalyst loadings to provide Michael adducts in high yield with excellent diastereo- and enantioselectivity. Catalytic hydrogenation of the Michael adducts stereoselectively generates 2-trifluoromethylated pyrrolidines bearing three contiguous stereocenters. A stereospecific route to epimeric 2-trifluoromethyl pyrrolidines from a common intermediate is described.



This letter describes a simple reaction platform for the enantio- and diastereoselective preparation of 2-trifluoromethyl pyrrolidines. Pyrrolidines are highly desirable building blocks due to their prevalence in the pharmaceutical and agrochemical industries.[1] Given the unique physicochemical properties engendered by the trifluoromethyl (CF_3) group,[2] considerable effort has been directed toward new methodologies for the preparation of CF_3-containing compounds.[3] A productive merger of these functionalities has led to interest in the development of methodologies for the construction of *N*-containing organofluorine compounds.[4] Consequently, methods toward the generation of optically active 2- and 3-trifluoromethylated pyrrolidines have garnered increasing attention in the literature. A common strategy for the synthesis of 3-trifluoromethylated proline derivatives utilizes the asymmetric 1,3-dipolar cycloaddition of azomethine ylides and CF_3-substituted alkenes.[5] A majority of the methods for the preparation of optically active 2-trifluoromethylated pyrrolidines rely on the use of chiral starting materials or auxiliaries.[6] A more attractive method to generate these 2-trifluoromethylated pyrrolidines would utilize *de novo* pyrrolidine syntheses to rapidly generate molecular complexity from simple starting materials via asymmetric catalysis.[7] Here, we report a formal (3 + 2)-annulation strategy for the preparation of trisubstituted 2-trifluoromethyl pyrrolidines via organocatalytic asymmetric Michael addition of 1,1,1-trifluoromethylketones to nitroolefins followed by diastereoselective reductive cyclization.

A number of highly functionalized pyrrolidines have previously been accessed via asymmetric Michael addition/reductive cyclization protocols employing aldehydes,[8] aryl ketones,[9] α-keto ester/amides,[10] and β-keto esters[11] as two-carbon donor synthons with nitroolefins for the *de novo* synthesis of substituted pyrrolidines. We postulated that an analogous (3 + 2)-annulation approach could be utilized in the preparation of trisubstituted 2-trifluoromethyl pyrrolidines **4** (Scheme 1a). The realization of this approach would require the invention of a heretofore unknown catalytic, enantioselective Michael addition of 1,1,1-trifluoromethylketones **1** to nitroolefins **2** that would provide the requisite γ-nitro carbonyl intermediate **3**. An attractive feature of the projected experimental plan was the high level of atom efficiency associated with the catalytic addition/hydrogenative cyclization sequence (Scheme 1b).

Scheme 1. Strategy for the Synthesis of Highly Substituted 2-Trifluoromethylated Pyrrolidines



Despite significant interest in the synthetic utility of 1,1,1-trifluoromethylketones as electrophiles, their application as nucleophiles has gone relatively unexplored.[12] Yan et al. recently reported the formal (4 + 2)-cycloaddition of 4,4,4-trifluoroacetoacetates to β,γ-unsaturated-α-keto esters;[13] however, the direct catalytic asymmetric α-functionalization of simple 1,1,1-trifluoromethylketones is to the best of our knowledge unknown. While the electron-withdrawing nature of the CF_3 group engenders enhanced C−H acidity relative to

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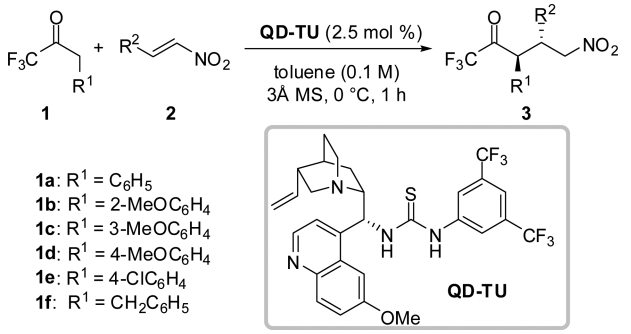
normal ketones, by corollary it also stabilizes the resultant enolate, rendering trifluoromethylketone enolates poorly nucleophilic.[12] We anticipated that application of a bifunctional catalyst bearing thiourea and tertiary amine moieties would provide a pseudointramolecular pathway to overcome this inherent barrier to reactivity.[14] We sought to harness the Brønsted acid/base ambifunctionality of these catalyst systems to develop the Michael addition of 1,1,1-trifluoromethylketones to nitroolefins.[15]

We began our studies by evaluating the feasibility of the Michael addition of 1,1,1-trifluoromethylketone **1a** to nitroolefin **2a**. Our experiments led to the use of bifunctional catalyst **QD-TU**,[16] affording the desired γ-nitro carbonyl **3aa** in quantitative yield with >20:1 dr and 95:5 er (Table 1, entry 1; see the Supporting Information (SI) for full optimization studies). A variety of reaction partners were next examined in the asymmetric Michael addition of 1,1,1-trifluoromethylketones **1** to nitroolefins **2** (Table 1). Electron-releasing and -withdrawing *ortho*-substituted aromatic nitroolefins were well tolerated, providing Michael adducts **3ab**−**3ae** as single diastereomers with excellent levels of enantioselectivity (entries 2−5). Less sterically encumbering substitution at the *meta*-position of the nitroolefin resulted in a slight drop in diastereo- and enantiocontrol providing **3af** in 98% yield with 19:1 dr and 93.5:6.5 er (entry 6). Examination of electron-releasing and -withdrawing *para*-substituents on the aromatic nitroolefin revealed significant electronic effects with respect to the diastereo- and enantioselectivity of the reaction (entries 7−11). Whereas electron-withdrawing groups (Br, NO_2, CN) provided Michael adducts **3ag**−**3ai** with high levels of selectivity, electron-releasing groups (Me and OMe) provided **3aj** and **3ak**, respectively, in diminished diastereo- and enantioselectivity. This electronic effect was also observed in the reaction of electron-rich heteroaromatic 2-thienyl- and 3-*N*-Ts-indoyl-substituted nitroolefins **2l** and **2m**, which afforded their respective Michael adducts **3al** and **3am** in diminished enantioselectivity (entries 12 and 13). Despite noticeably reduced reactivity, alkenyl and aliphatic nitroolefins were also found to be competent reaction partners providing **3an** and **3ao** in moderate conversion, but with high diastereo- and enantiocontrol (entries 14 and 15).

We next turned our attention to examining electronic and structural variations of the 1,1,1-trifluoromethylketone donor **1** by placing methoxy groups at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring. Although sterically demanding *ortho*-substituted **1b** required longer reaction times (3 h) to achieve full conversion, **3bg** was obtained in 97% yield with >20:1 dr and 96:4 er (entry 16). Less sterically encumbered electron-releasing nucleophiles **1c** and **1d** proceeded efficiently under the standard reaction conditions to provide **3cg** and **3dg**, respectively, in excellent yield and diastereoselectivity, but with reduced enantioselectivity (entries 17 and 18). This electronic effect was confirmed by utilizing electron-withdrawing *para*-substituted **1e** as the nucleophile, which provided **3eg** in 95% yield with 17:1 dr and 93:7 er (entry 19). It is worth noting that subjecting **3eg**, which possesses enhanced C−H acidity, to silica gel chromatography resulted in erosion of diastereoselectivity from 17:1 to 2:1 dr presumably due to facile epimerization via enol formation. Lastly, we employed aliphatic 1,1,1-trifluoromethylketone **1f** in the Michael addition to nitroolefin **2a** to provide **3ea** in 73% yield with >20:1 dr and 97:3 er, although the reaction required a higher catalyst loading and longer reaction times to achieve acceptable conversion (entry 20). The majority of adducts are crystalline solids. A single recrystallization of **3ai** provided a useful upgrade in the enantiomeric composition (to 99.5:0.5 er).

Having developed a highly diastereo- and enantioselective Michael addition to access γ-nitro trifluoromethyl ketones **3** (Table 1), we sought to exploit this functional array toward the synthesis of 3,4-diaryl-2-trifluoromethyl pyrrolidines **4** (Scheme 2). Subjecting the crude products obtained via Michael addition to Raney-Ni hydrogenation conditions resulted in the clean formation of the desired pyrrolidines with excellent levels of diastereocontrol (>20:1 in all cases) bearing an all *cis*-relationship as determined by NOESY analysis. Attempts employing a one-pot protocol were promising; however, the molecular sieves from step 1 were found to be detrimental to the hydrogenation step, resulting in only moderate conversions.

Table 1. Scope of Michael Addition of 1,1,1-Trifluoromethylketones 1 to Nitroolefins 2[a]



entry	1	2	3	yield (%)[b]	dr[c]	er[d]
1	**1a**	C_6H_5	**3aa**	98	>20:1	95:5
2	**1a**	2-BrC_6H_4	**3ab**	95	>20:1	96.5:3.5
3	**1a**	2-$NO_2C_6H_4$	**3ac**	94	>20:1	97.5:2.5
4	**1a**	2-$CF_3C_6H_4$	**3ad**	96	>20:1	96.5:3.5[e]
5	**1a**	2-$OMeC_6H_4$	**3ae**	98	>20:1	94:6
6	**1a**	3-ClC_6H_4	**3af**	98	19:1	93.5:6.5
7	**1a**	4-BrC_6H_4	**3ag**	99	>20:1	95.5:4.5
8	**1a**	4-$NO_2C_6H_4$	**3ah**	99	7:1	95.5:4.5
9	**1a**	4-CNC_6H_4	**3ai**	96	>20:1	96:4
10	**1a**	4-MeC_6H_4	**3aj**	96	8:1	93:7
11	**1a**	4-$OMeC_6H_4$	**3ak**	91	6:1	86.5:13.5
12	**1a**	2-thienyl	**3al**	97	16:1	91.5:8.5
13[f]	**1a**	3-*N*-Ts-indoyl	**3am**	92	>20:1	87.5:12.5
14	**1a**	$CH{=}CHC_6H_5$	**3an**	62 (65)[g]	>20:1	87:13
15	**1a**	cyclohexyl	**3ao**	42 (43)[g]	>20:1	94:6
16	**1b**	4-BrC_6H_4	**3bg**	97	>20:1	96:4
17	**1c**	4-BrC_6H_4	**3cg**	96	>20:1	88:12
18	**1d**	4-BrC_6H_4	**3dg**	97	>20:1	87:13
19	**1e**	4-BrC_6H_4	**3eg**	95	>20:1	93:7
20[h]	**1f**	C_6H_5	**3fa**	73 (82)[g]	>20:1	97:3

[a]Reactions were performed with **1** (0.21 mmol) and **2** (0.20 mmol) and proceeded to full conversion as adjudged by TLC. [b]Isolated yield. The diastereomers were not separable, and this represents the combined yield. [c]The diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude product. [d]The enantiomeric ratio was determined by HPLC or SFC analysis on a chiral stationary phase. [e]The enantiomeric ratio was determined following reduction of **3ad** with $NaBH_4$ (see the SI). [f]The reaction was performed at 0 °C for 3 h. [g]Number in parentheses is conversion of nitroolefin as determined by ^1H NMR spectroscopic analysis of the crude product. [h]The reaction was performed employing **QD-TU** (10 mol %) at 0 °C for 12 h.

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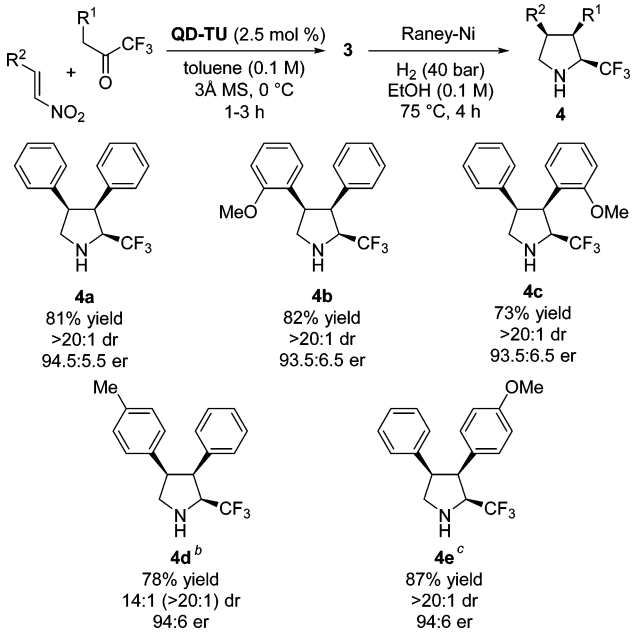
Scheme 2. Synthesis of Enantioenriched 2-Trifluoromethyl Pyrrolidines[a]

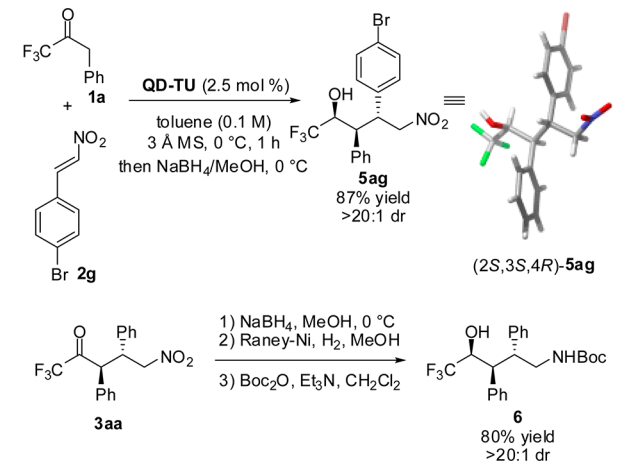


[a]Reactions were performed as described in Table 1. The yield is for both diastereomers. The diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude product. The enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. [b] Number in parentheses is dr following column chromatography. [c] The Michael addition was performed at −10 °C for 1 h.

In addition to bis(phenyl) pyrrolidine **4a**, *ortho*- and *para*-substituents were tolerated at both the 3- and 4-positions of the pyrrolidine providing products **4b**–**4e** in high yield and enantioselectivity. No erosion in diastereo- or enantiomeric composition was observed during the hydrogenation, indicating that neither epimerization nor retro-Michael pathways are operative during the reaction.

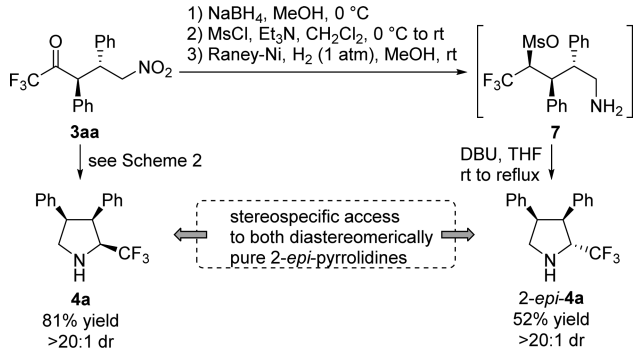
In addition to providing expedient access to new classes of enriched 2-trifluoromethyl pyrrolidines, the obtained Michael adducts **3** are also amenable to a number of other secondary transformations (Scheme 3). Employing a modified workup to the Michael addition of **1a** to **2g** by addition of $NaBH_4$/MeOH mixture results in the highly diastereoselective reduction of the carbonyl to provide **5ag** in 87% yield. An X-ray diffraction study of alcohol **5** was performed to assign the relative and absolute stereochemistries as (2*S*,3*S*,4*R*).[17] By analogy, the Michael adducts were assigned as (3*S*,4*R*)-**3** and the pyrrolidines as (2*S*,3*S*,4*R*)-**4**. Next, sequential carbonyl/nitro reduction was employed to provide the Boc-protected amino alcohol **6** bearing three contiguous stereocenters in 80% overall yield from **3aa** as a single diastereomer.

Scheme 3. Secondary Transformations of Michael Adducts and Determination of Relative and Absolute Stereochemistries



The high *syn*-selectivity observed in the $NaBH_4$ reduction of Michael adducts **3aa** and **3ag** (Scheme 3) led us to pursue a unified strategy to access both C(2)-epimers of 2-trifluoromethylated pyrrolidine **4a**. We envisioned stereospecific intramolecular S_N2-displacement of an alcohol derivative by the terminal amine would provide 2-*epi*-**4a** (Scheme 4).

Scheme 4. Access to Diastereomerically Pure Epimeric 2-Trifluoromethylated Pyrrolidines



Reduction of the alcohol with $NaBH_4$, conversion of the free alcohol to its derived mesylate, and hydrogenation of the nitro group provided the unstable primary amine intermediate **7**. The latter was immediately treated with DBU to induce cyclization to diastereomerically pure 2-*epi*-**4a** in 52% yield over the four steps.

In conclusion, we have developed a formal (3 + 2)-annulation strategy for the highly selective synthesis of trisubstituted 2-trifluoromethyl pyrrolidines via asymmetric Michael addition/reductive cyclization. A direct catalytic Michael addition of 1,1,1-trifluoromethylketones to nitroolefins was developed, providing access to 3,4-disubstituted-5-nitro-1,1,1-trifluoromethylketones with excellent levels of diastereo- and enantioselectivity. The obtained Michael adducts were then utilized in a diastereoselective reductive cyclization to afford functionalized 3,4-disubstituted-2-trifluoromethyl pyrrolidines bearing three contiguous stereocenters. We also demonstrated that C(2)-epimeric 2-trifluoromethyl pyrroldines can be accessed from a common intermediate with excellent diastereocontrol utilizing an intramolecular S_N2-displacement.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of the products, and CIF data for CCDC 979177. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) CCDC 979177 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure in Scheme 3-D were generated with CYL*view*: Legault, C. Y. CYL*view*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.