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A Simple Method for Asymmetric Trifluoromethylation of *N*-Acyl Oxazolidinones via Ru-Catalyzed Radical Addition to Zirconium Enolates

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Abstract

A Ru-catalyzed direct thermal trifluoromethylation and perfluoroalkylation of *N*-acyloxazolidinones has been developed. The reaction is experimentally simple and requires inexpensive reagents while providing good yields of products with good levels of stereocontrol. Preliminary studies have shown notable compatibility with functional groups, aromatics, and certain heteroaromatic substituents. The described method provides a useful alternative for the synthesis of fluorinated materials in an experimentally convenient manner.

The growing appreciation of unique physical and chemical properties of fluorinated organic compounds has resulted in their increasingly broad application in medicine, materials sciences, agrochemicals, and many other areas of research.¹ In order to enable future advances in the discovery and application of fluorinated materials, practical methods for efficient and selective fluorination are needed. Within this general context,^{1a,2} stereoselective introduction of the trifluoromethyl and other perfluoroalkyl groups at the α -position of carbonyl compounds has remained an ongoing challenge, with several notable developments reported in the past few years. Following early studies in diastereoselective radical trifluoromethylation of lithium enolates employing the iodotrifluoromethane–Et₃B/O₂ system for CF₃ radical generation,³ a number of elegant alternatives based on electrophilic,⁴ radical,⁵ or photoredox organocatalytic strategies⁶ have been developed.⁷ These methods collectively constitute important advances toward highly selective α -fluoroalkylation of a diverse range of carbonyl compounds and highlight novel patterns of reactivity. On the other hand, issues of practicality related to experimental simplicity, cost of reagents, and energy efficiency (use of cryogenic conditions or high temperatures) remain persistent, stimulating continued progress in this area.

Recently, we demonstrated that an experimentally simple, high-yielding diastereoselective α -trichloromethylation of titanium enolates can be achieved (eq 1).⁸ The process is based on a Ru-catalyzed redox formation of the trichloromethyl radical from BrCCl₃ followed by its addition to catalytically generated titanium enolates derived from chiral *N*-acyl

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Supporting Information

Detailed experimental procedures, characterization data, copies of ¹H, ¹³C, and ¹⁹F NMR spectra, and X-ray crystallography data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

oxazolidinones. This type of radical addition may be facilitated by the putative biradical character of titanium enolates.⁹ Overall, the process allows for a direct, one-step chloroalkylation of *N*-acyl oxazolidinones, and its utility in the synthesis of natural products with CCl₃-substituted stereogenic centers has been highlighted.^{8c,10} Although direct extension of this type of reactivity to fluoroalkylation reactions has proven to be highly challenging, we have succeeded in reaching this goal by enlisting in situ generated zirconium enolates (eq 1). The development of this protocol highlighting operational simplicity in the direct α -fluoroalkylation of *N*-acyl oxazolidinones is described herein.¹¹

(1)

Early attempts to extend the chloroalkylation reaction of titanium enolates to fluoroalkylations concentrated on screening a range of transition metal catalysts, including those that have been previously used in Kharasch-type additions of iodoperfluoroalkanes to olefins. Typical examples include [Ph₃P]₃RuCl₂,¹² Ru₃(CO)₁₂,¹³ Fe₃(CO)₁₂,¹³ and Co₂(CO)₈;¹³ however, in no instance any amount of fluoroalkylation product was detected. After exhausting our options with titanium enolates, we explored other metal halides potentially capable of effecting soft enolizations (SmBr₃, BiCl₃, InCl₃, Yb(OTf)₃, VOCl₃, VCl₃, VCl₄, ZrCl₄, HfCl₄).¹⁴ In contrast to our expectations, it was the group IVa metal halides, ZrCl₄ and HfCl₄,¹⁵ that proved to be uniquely competent in the fluoroalkylation reactions.

Once these metal halides had been identified, a number of transition metal redox catalysts for the generation of perfluoroalkyl radicals were examined (Table 1). Among these, ruthenium catalysts emerged as the most promising (entries 7–11), with Ru[Ph₃P]₃Cl₂, the catalyst used in the original chloroalkylation of titanium enolates, being the most effective. The ruthenium-catalyzed perfluoropropylation of *N*-acyl oxazolidinone **1**, which served as a benchmark reaction, was characterized by a clean transformation to **2** using only a moderate excess (5 equiv) of *n*-C₃F₇I (entry 11). The side products were comprised of only the α,β -unsaturated imide as a result of HF elimination from **2** (12%) and the cleaved oxazolidinone auxiliary (11%),¹⁶ which together accounted for the majority of the remaining mass balance. Similar outcomes were observed with hafnium enolates derived in situ from hafnium tetrachloride and Et₃N (entry 12).

The scope of perfluoroalkylating agent was investigated next (Table 2).¹⁷ No byproduct resulting from α,β -elimination of hydrogen fluoride was observed in any trifluoromethylation reactions (entry 1; also see Table 3). We did observe partial (9–17%) formation of an α,β -unsaturated byproduct (**A**) with primary perfluoroalkyl- and perfluorobenzyl-substituted products (entries 2, 3, 5, and 6). As in the trifluoromethylation reaction, no HF elimination was detected when the 2-perfluoropropyl group was introduced (entry 4).

A variety of *N*-acyl oxazolidinones can be successfully trifluoromethylated using the simple protocol developed in the course of this investigation (Table 3). We found that reagents can be mixed all at once in any order at room temperature with no influence on the isolated yield of the desired product. Therefore, the reaction setup can be guided solely by experimental convenience rather than by other factors intrinsic to the reaction. *N*-Acyl oxazolidinones obtained from unfunctionalized alkanolic acids undergo efficient and diastereoselective

trifluoromethylations, with yields increasing for β -branched substrates (entries 1–4). These are clean transformations, where unreacted starting material is the major byproduct as indicated by yields based on recovered starting materials (entries 2–4), while auxiliary cleavage (25%) was observed for the reaction in entry 1. The presence of aryl and benzyl ethers is well-tolerated (entries 5, 6), as is the presence of functionalized β -aryl substitution, although the extent of chiral auxiliary detachment was higher (31–34% for entries 7, 8). Substitution with a phenyl group at the α -position resulted in a clean reaction (82% yield brsm, entry 9), albeit at a reduced conversion under the standard conditions (59%). Diastereoselective alkylations controlled by the oxazolidinone stereochemistry can be performed with substrates that have a stereogenic center at the β -position in the *N*-acyl substituent (entries 10, 11). More functionalized heterocyclic substituents such as benzofurans and benzoxazoles are also compatible with the reaction conditions (entries 12, 13).

The proposed mechanism of the reaction based on the related Ru-catalyzed trichloromethylation is depicted in Scheme 1.^{8a,10} NMR spectroscopic studies of the enolate formation using *N*-propionyl oxazolidinone **1**, zirconium tetrachloride, triethylamine, and CDCl₃ revealed that a rapid, clean, and essentially complete enolization producing enolate **4** occurs at room temperature. We succeeded in obtaining a single-crystal X-ray structure of a complex between the substrate and ZrCl₄ revealing a nearly perfectly planar arrangement of atoms in the six-membered cyclic chelate **6** which is in all respects similar to the corresponding titanium complex (not shown). Therefore, we surmise that the geometric structures of the zirconium (**4**) and titanium enolates are similar, and it is the dissimilarities in their electronic structure that are responsible for differences in their reactivity in the ruthenium-catalyzed fluoroalkylation reaction. Once **4** is formed, it undergoes an addition reaction with the trifluoromethyl radical generated by a redox process from iodotrifluoromethane and the ruthenium(II) catalyst. The addition product is probably better represented by resonance form **5b** rather than carbon-centered form **5a**, and a potential biradical character of **4** may facilitate the addition of the CF₃ radical. The ruthenium catalyst is recovered by a single electron transfer from intermediate **5b** to Ru(III) species.

Additional insight into the course of the perfluoroalkylation was acquired from the following experiments. First, when the catalyst loading in the perfluoropropylation of **1** was increased from 7 to 30 mol %, the rate of the process was notably enhanced. The reaction was complete in 4 rather than 16 h, showing a substantially reduced level of side reactions and giving the expected product in 86% isolated yield. Similar, albeit somewhat lower efficiency was observed when the amount of *n*-C₃F₇I was increased from 5 to 15 equiv. Taken together, these observations suggest that the generation of the perfluoroalkyl radical is the rate-limiting step of the process. Second, monitoring the course of the reaction performed in CD₂Cl₂ by ¹H and ¹⁹F NMR spectroscopy revealed that another major pathway of reactivity for *n*-C₃F₇-I is reduction to *n*-C₃F₇-H, which presumably occurs by oxidation of triethylamine. Overall, these key observations are expected to aid in developing more efficient perfluoroalkylation processes based on radical additions to transition metal enolates.

Conversion of the reaction products to broadly useful fluorinated building blocks for organic synthesis is illustrated by examples in Scheme 2 that include hydrolytic and reductive removal of the chiral auxiliary. Trifluoromethyl-substituted derivative **7** and perfluoropropyl derivative **8**¹⁸ could be readily hydrolyzed with a LiOH–H₂O₂ reagent system to the corresponding carboxylic acids with a high level of retention of stereochemical integrity. While reductions of these compounds with sodium borohydride in aqueous THF were sluggish, removal of the oxazolidinone could be readily achieved by treatment with lithium aluminum hydride. For substrate **5**, virtually complete preservation of stereochemistry was

observed, while only a minor erosion of stereochemistry was noted for the perfluoropropyl-substituted substrate. Notably, these transformations are characterized by very good yields and nearly quantitative recovery of the chiral auxiliary.

In closing, we report an experimentally simple asymmetric fluoroalkylation reaction of *N*-acyl oxazolidinones based on the unique radical reactivity of group IVa metal enolates. For titanium enolates, the biradical character has been supported by computational and spectroscopic studies that provide an intriguing conceptual basis for reaction development. From a practical perspective, the reaction requires inexpensive reagents, which can be mixed in any order, and mild heating over the course of a few hours delivers fluoroalkylation products directly in good yields and high diastereoselectivities. Ongoing studies are directed at the development of a more active catalytic system, catalytic generation of the metal enolate, and defining a more detailed picture for the mechanism of the reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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  15. ZrCl₄: \$0.38/g (\$0.09/mmol, Sigma-Aldrich); HfCl₄: \$1.09/g (\$0.35/mmol, Strem).
  16. Control experiments in the absence of the Ru catalyst revealed that the free auxiliary is produced concomitantly with the enolate acylation byproduct through Claisen-type self-condensation of the substrate. The extent of the competitive self-condensation is substrate-dependent.
  17. The assigned relative configuration is supported by X-ray crystallographic studies for the product shown in entry 4. See Supporting Information.
  18. Efficiently prepared according to the standard conditions for perfluoroalkylations described herein. See Supporting Information for details.

Scheme 1.
Proposed Mechanism of the Ru-Catalyzed Trifluoromethylation Reaction

Scheme 2.

Preparation of Versatile Enantioenriched Fluorinated Building Blocks by Hydrolytic and Reductive Removal of the Chiral Auxiliary^a

^aThe chiral auxiliary is recovered in nearly quantitative yield in all reactions.

Table 1

Identification of Transition Metal Catalysts Suitable for Fluoroalkylation of Zirconium and Hafnium Enolates^a

entry	MCl ₄	metal catalyst (5–7 mol %)	conversion ^b (%)	2 (%) ^b
1	ZrCl ₄	Fe ₃ (CO) ₁₂	17	0
2		Co ₂ (CO) ₈	26	0
3		Ru ₃ (CO) ₁₂	37	0
4		FeBr ₂	31	0
5		Cu(OEP) ^f	33	0
6		[Rh(cod)Cl] ₂	30	0
7		[(<i>p</i> -cymene)RuCl ₂] ₂	46	22
8		[(C ₆ H ₆)RuCl ₂] ₂	61	28
9		IndRu[Ph ₃ P] ₂ Cl•CH ₂ Cl ₂	49	19
10		Cp*Ru[Ph ₃ P] ₂ Cl	87	59 ^c
11 ^e		Ru[Ph ₃ P] ₃ Cl ₂ ^g	97	74 ^d
12 ^e	HfCl ₄	Ru[Ph ₃ P] ₃ Cl ₂ ^g	>98	57

^aStandard conditions: **1** (0.50 mmol), ZrCl₄ (1.05 equiv), Et₃N (2.0 equiv), *n*-C₄F₉I (5.0 equiv), CH₂Cl₂ (~0.1 M), mixed and stirred at 45 °C for 24 h.

^bDetermined by the 500 MHz NMR analysis of the crude mixture of products.

^cIn addition, 18% of α,β -unsaturated byproduct resulting from HF elimination has also been observed.

^dIn addition, 12% of α,β -unsaturated byproduct resulting from HF elimination has also been observed.

^e*n*-C₃F₇I (5.0 equiv) was used.

^fOEP = 2,3,7,8,12,13,17,18-octaethyl-21*H*,23*H*-porphyrine.

^g7 mol % of the metal catalyst was used.

Table 2

Scope of Perfluoroalkylating Agent^a

1	2	3
74% yield^b dr 9:1	74% yield (12%) dr 24:1	71% yield, (16%) dr 24:1
4	5	6
75% yield 91 % brsm^c dr >98:2	63% yield, (17%) dr >98:2	73% yield, (9%) dr >98:2

^aYields of isolated products are reported. The numbers in parentheses are yields of the corresponding α,β -unsaturated byproduct A, when observed. Diastereomer ratios were determined by 500 MHz ^1H NMR analysis. ^b15 mol % of $[\text{Ph}_3\text{P}]_3\text{RuCl}_2$ were used. ^cbrsm = based on recovered starting material.

Table 3 Scope of *N*-Acyl Oxazolidinones in the Trifluoromethylation Reaction^a

1 71% yield dr 9.4:1	2 79% yield (89% brsm) dr >98:2	3 76% yield (96% brsm) dr >98:2
4 70% yield (100% brsm) dr >98:2	5 75% yield (84% brsm) dr 9:1	6 51% yield (59% brsm) dr 9:1
7 63% yield (69% brsm) dr 9:1	8 60% yield (66% brsm) dr 9:1	9 48% yield (82% brsm) dr 9:1
10 49% yield (89% brsm) dr 6.4:1	11 53% yield (86% brsm) dr 10:1	
12 34% yield (69% brsm) dr 9:1	13 49% yield (88% brsm) dr 9:1	

^aYields of isolated products are reported. At least two experiments were carried out to confirm reproducibility. The numbers in parentheses are yields based on recovered starting material (brsm). Diastereomer ratios were determined by 500 MHz ¹H NMR analysis of the crude mixture of products.