Perhaloalkylation

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Perhaloalkylation of Metal Enolates—Unconventional and Versatile**

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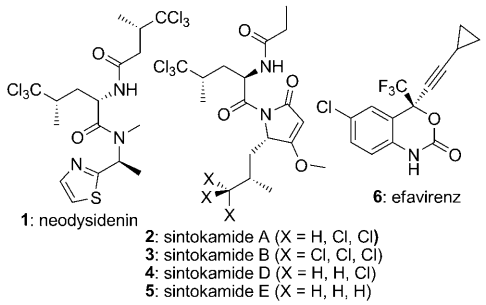
electron transfer · enols · perhaloalkylation · radical reactions · valence tautomerism

Dedicated to Professor Henning Hopf on the occasion of his 70th birthday

Halogenated natural products,[1] especially those with di- and trichloromethyl groups (**1**–**5**),[2,3] have recently come to the focus of interest of organic and medicinal chemists as well as biologists (Scheme 1). Trifluoromethyl-containing compounds do not occur in nature, but are common among

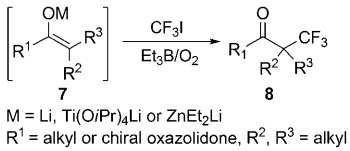


Scheme 1. Natural products and drugs containing perhaloalkyl groups.

pharmaceuticals (such as **6**) and agrochemicals.[4] Considerable progress has been made recently in the transition-metal-catalyzed coupling of CF_3 groups to C_{sp} and C_{sp2} systems.[5] For the synthesis of simple aliphatic trifluoromethyl compounds a number of methodologies based on nucleophilic and electrophilic trifluoromethylation reagents have been developed.[6] They are, however, not generally suitable for the α-trifluoromethylation of carbonyl compounds. The arsenal of methods for the introduction of other di- or perhalomethyl groups to organic molecules is even more limited and traditionally restricted to the Kharasch addition.[7]

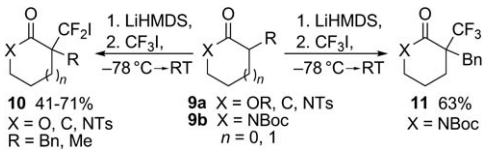
So far only modest progress has been made in the direct α-perhaloalkylation of carbonyl compounds. Recently, organocatalytic photoredox catalysis was reported as a breakthrough for α-trifluoromethylation, but this strategy is not applicable for most C-H acidic compounds as it is inherently restricted to aldehydes.[8]

The addition of perhaloalkyl radicals to metal enolates as radical acceptors represents a conceptually more versatile approach. Iseki et al.[9] and Mikami et al.[10] were the first to report the use of lithium, titanate, and zincate enolates **7** of imides and ketones in radical α-trifluoromethylation and perfluoroalkylation reactions (Scheme 2). Remarkably, lithium enolates reacted extremely fast with the CF_3· radical relative to the titanate and zincate enolates, and the former reactions could be carried out catalytically with the Et_3B radical initiator.



Scheme 2. Radical α-trifluoroalkylation reactions of metal enolates.

Very recently, Mikami and co-workers have provided intriguing evidence that with CF_3I it is possible to switch between the trifluoromethylation and the difluoroiodomethylation of enolates (Scheme 3).[11] When lithium enolates of esters, aryl ketones, and *N*-tosyl lactams **9a** reacted with CF_3I, α-difluoroiodomethyl carbonyl compounds **10** resulted through selective C–F bond cleavage in the presence of the weaker C–I bond. On the other hand, *N*-Boc lactam **9b** gave α-trifluoromethyl lactam **11** exclusively. Presumably, enolates derived from **9a** attack CF_3I by a polar pathway based on C–F activations in which the fluoride ion is the leaving group, while more electron-rich **9b** is a better single-electron donor



Scheme 3. C–F versus C–I activation in perhalomethylation reactions of lithium enolates. Bn = benzyl, Boc = *tert*-butoxycarbonyl, LiHMDS = lithium hexamethyldisilazide, Ts = 4-toluenesulfonyl.

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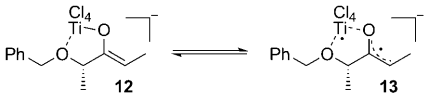
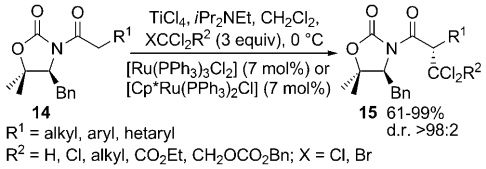
and thus reacts through a single-electron transfer (SET) mechanism.

Theoretical studies in concert with physical methods provide extremely valuable information on the nature of reactive species, which can be applied in the design of new reactivity patterns. Moreira et al. showed based on NMR, EPR, and computational studies that titanate enolates generated from $TiCl_4$/α-alkoxy ketone complexes and tertiary amines display considerable biradical character.[12] These enolates must thus be considered unconventional valence-tautomeric tetrachlorotitanate(IV) enolate/tetrachlorotitanate(III) α-carbonyl radical pairs **12**/**13** (Scheme 4).



Scheme 4. Valence tautomerism of titanate enolates.

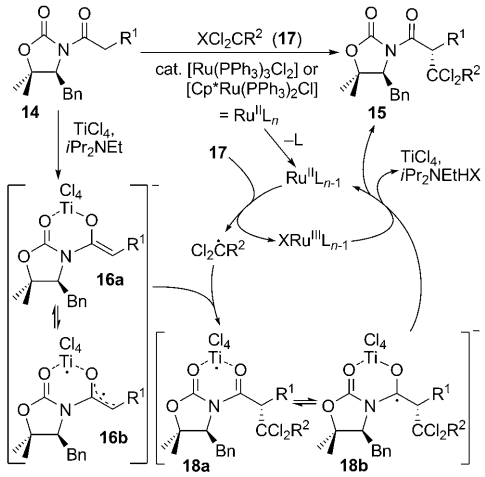
Zakarian and co-workers applied this finding now very elegantly by combining it with the ruthenium-catalyzed Kharasch addition.[2,3] Enolates derived from oxazolidinones **14** undergo highly diastereoselective catalytic trichloroalkylation reactions giving **15** (Scheme 5). The chemoselectivity of the method is very good, since derivatives bearing indole or alkene functionalities, which are good radical acceptors on their own, did not react competitively. Even bromodichloromethane and other less reactive haloalkylating agents, such as di- and trichloroacetates, gave good results, when Simal's catalyst [Cp*Ru(PPh_3)$_2$Cl] was applied.



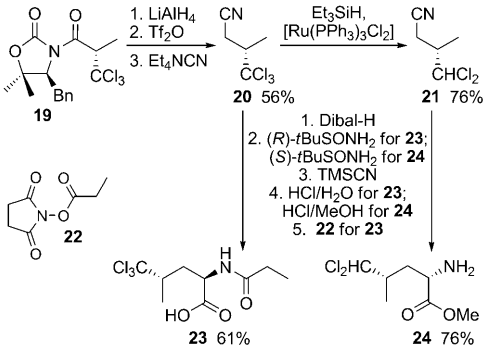
Scheme 5. Asymmetric ruthenium-catalyzed chloroalkylation reactions of titanate enolates. Cp* = C_5Me_5.

The reactions can be explained by a Ru-catalyzed reductive generation of transient haloalkyl radicals from **17**, which couple selectively to the persistent biradical valence-tautomeric pair **16a/b** (Scheme 6). The resulting valence-tautomeric titanate ketyl pair **18a/b** transfers an electron to the coformed Ru^{III} halide, regenerating the catalyst and forming products **15**.

The power of this methodology was demonstrated in total syntheses of the trichloroleucine-derived marine natural products neodysidenin (**1**)[2] and sintokamides A (**2**), B (**3**), and E (**5**).[3] All natural products were synthesized from the starting imide **19**, which was obtained as described above (Scheme 7). Central was the conversion of **19** to nitrile **20** in three steps. This was converted in a few steps into the di- and trichloroleucine derivatives **23** and **24**. The construction of the enantiomeric amino functions was accomplished easily by a Strecker reaction with Ellman's *tert*-butanesulfinamides.



Scheme 6. Mechanistic rationale for Zakarian's chloroalkylation.

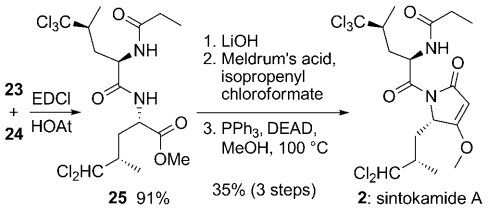


Scheme 7. Synthesis of sintokamide A intermediates from a common precursor. Dibal-H = diisobutylaluminum hydride, TMS = trimethylsilyl.

Standard coupling of the amino acid derivatives **23** and **24** gave access to dipeptide **25**. The tetramic acid unit of sintokamide A (**2**) was installed as the last step by a condensation reaction of dipeptide **25** with Meldrum's acid (Scheme 8).

The studies highlighted here provide important mechanistic insight and synthetic applications with the following implications for advanced organic chemistry:

1) High-yielding, chemoselective perhaloalkylation reactions of enolates leading to a variety of products are now available. The enolate counterions play a crucial role in steering the course of the reactions by differentially mediating electron transfer.



Scheme 8. Completion of the total synthesis of sintokamide A (**2**). DEAD = diethyl azodicarboxylate, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOAt = 1-hydroxy-7-azabenzotriazole.

2) Titanate enolates are substrates in which the persistent radical effect (PRE)[13,14] in the form of a valence-tautomeric biradical species operates; this can be applied in asymmetric reactions with transient radicals.
3) The electronic structure of enolates determines the outcome of perhaloalkylations significantly and can result in the switching between polar and SET pathways in haloalkylations. This is manifested in selective fluoride activation over the much more common iodide activation.

In summary, fundamentally new reactivity patterns for enolates in polar and radical reactions have been demonstrated, which will trigger new developments and applications in this field. Future aims must consist of rendering these reactions catalytic in the enolate and devising enantioselective variants without recourse to chiral auxiliaries.

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