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RESEARCH ARTICLE

Asymmetric Biomimetic Transamination for Preparation of Tetrafluoroethylene-Containing Amines: An Update

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Abstract

Recent advancements in the asymmetric [1,3]-proton shift reaction for the preparation of amino compounds possessing a tetrafluoroethylene moiety have been reported. We critically discuss the observed stereochemical outcomes with respect to the trifluoromethyl and perfluoroalkyl groups traditionally employed in this reaction. The methodological significance of these results is highlighted as well as noting a potential inaccuracy in the reported enantioselectivities due to the self-disproportionation of enantiomers (SDE) phenomenon.

Keywords: Biomimetic Transamination, [1,3]-Proton Shift Reactions, Asymmetric Synthesis, Fluorine Chemistry, Tetrafluoroethylene Moiety, Self-Disproportionation of Enantiomers (SDE) Phenomenon.

1. Introduction

The increasing prevalence of fluorine-containing, small molecule pharmaceuticals is a well justified phenomenon capitalizing on the distinctive steric, electrostatic, and chemical properties of fluorine [1]. Despite well founded health and environmental concerns [2], the integration of fluorine into bioactive molecules shows no signs of abating [3]. Fluorine-containing drugs are literally saving lives and contributing significantly to the standard of well-being in Western countries [4]. Nevertheless, projecting future trends, it is plausible to anticipate that well established substituents in drug design such as the trifluoromethyl *1* and pentafluoroethyl *2* groups (Figure 1) which degrade into persistent TFA and pentafluoropropionic acid, respectively [5], will likely face increased regulatory scrutiny [6]. On the other hand, fluorinated substituents such as tetrafluoroethylene *3–5* [7], which may biodegrade to fluoride and thus align with evolving environmental legislation, are likely to encounter more favorable regulatory prospects.

The properties and bioactivity of tetrafluoroethylene-containing compounds are generally not well known apart from reports on the applications of tetrafluoroethylene moieties of type *6* and **7** (Figure

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2) in the design of liquid crystals and fluorescent materials [8]. Additionally, compounds *8* and *9* have been reported to exhibit some insecticidal and herbicidal activity, respectively [9].

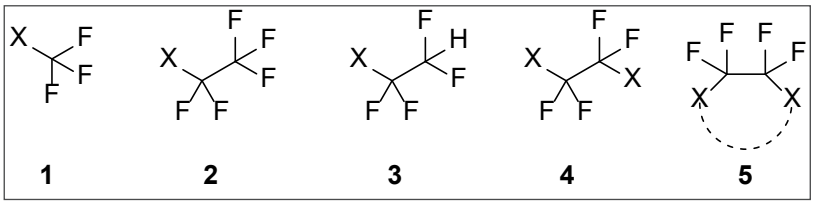


Figure 1. *Common fluorine-containing moieties: trifluoromethyl 1, pentafluoroethyl 2, tetrafluoroethyl 3, acyclic tetrafluoroethylene 4, and cyclic tetrafluoroethylene 5 groups.*

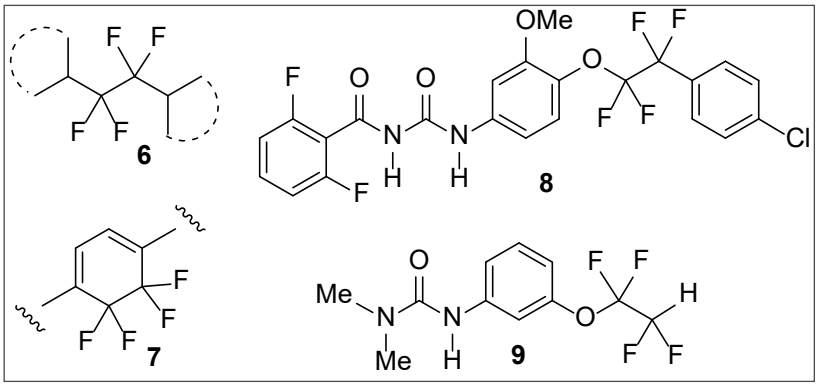
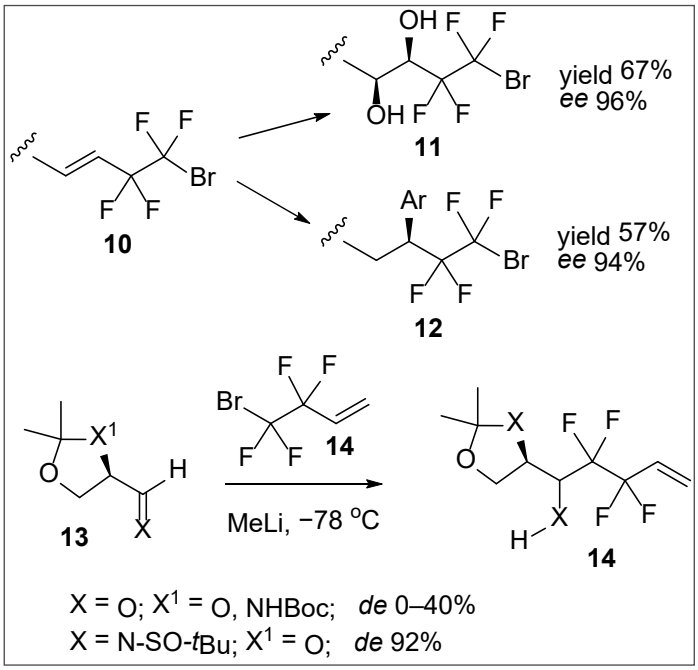


Figure 2. *Tetrafluoroethylene-containing compounds 6–9 possessing useful properties.*

Synthetic approaches for preparing compounds with a tetrafluoroethylene moiety are quite scarce, limited primarily to the elaboration of the double bond in substrates of type *10* or the addition of Li–CF_2CF_2– species to C=O or C=N bonds (Scheme 1).

Sharpless dihydroxylation of the double bond in substrates *10,* conducted under standard conditions, affords diols *11* with excellent enantioselectivity, albeit only in moderate yields [10]. Similarly, enantioselective conjugate addition of aryl boronic acid to the C=C bond in *10* in the presence of a rhodium/BINAP catalyst provides compounds *12* also with high enantioselectivity, but again albeit only in 57% yield [11]. It should be noted that low-to-moderate chemical yields coupled with high-to-excellent enantioselectivities can often be an indication of erroneously recorded stereochemical outcomes due to workers' oversight of the self-disproportionation of enantiomers (SDE) phenomenon [12]. Thus, unless SDE tests [13] are conducted, as required by some journals [14], the true enantioselectivity of these reactions remains unconfirmed and other workers attempting to replicate such results should be aware of this fact.



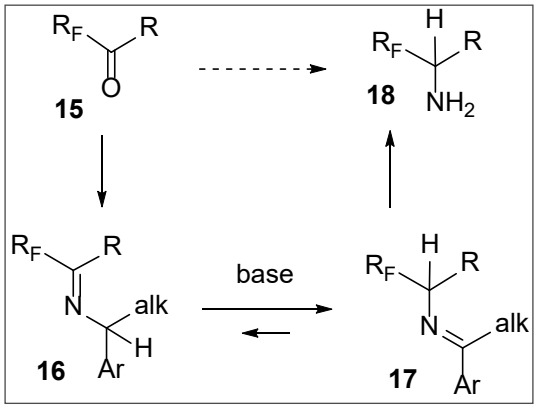
Scheme 1. *Examples of asymmetric synthesis of tetrafluoroethylene compounds.*

Diastereoselective addition reactions of Li–CF_2CF_2– species to the C=O and C=N bonds of chiral derivatives *13* are conducted under very restrictive and operationally inconvenient conditions and only yield addition products *14* with moderate yields (61–76%) and variable diastereoselectivity [15].

Considering the high potential interest in tetrafluoroethylene-containing derivatives and the rather limited synthetic access to these compounds, it was exciting to see the report from Prof. Tsutomu Konno's laboratory on the asymmetric synthesis of tetrafluoroethylenated amines via the [1,3]-proton shift reaction [16]. In this brief review, we highlight the practical significance and methodological advances of the reported results while at the same time noting potential inaccuracies in the reported enantioselectivities due to the SDE phenomenon.

1.1 [1,3]-Proton shift reaction

The [1,3]-proton shift reaction refers to the azomethine–azomethine isomerization via base-catalyzed [1,3]-proton transfer, as seen in the transformation of *16* to *17* (Scheme 2) [17]. This isomerization is a crucial step in the broader, overall biomimetic reductive amination [18] of various carbonyl compounds *15* to amines *18* and amino acids [19].

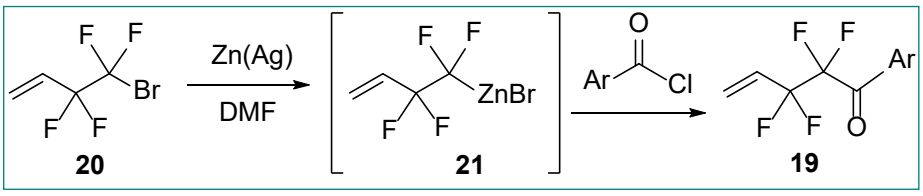


Scheme 2. *Azomethine–azomethine isomerization via base-catalyzed [1,3]-proton transfer as a key step in biomimetic reductive amination.*

Of particular interest is the asymmetric version of this reaction, which can be conducted using a chiral base [20] – and is thus enantioselectively catalyzed – or a chiral amine to form the requisite Schiff base *16* [21] – and thus utilizes a stoichiometric amount of chiral auxiliary – starting from ketone *15*. Base-catalyzed, azomethine–azomethine isomerization [22] is a reversible process and therefore it is only of synthetic value when the equilibrium between *16* and *17* is strongly shifted towards *17,* e.g. when *17* is present in greater than 95%, to ultimately lead to the amine *18*. Consequently, all of the parameters such as reaction conditions [23] and the nature of the substituents [24] play a critical role in the overall synthetic success. In this regard, the recent reports from Prof. Konno's laboratory on the use of tetrafluoroethylene-containing substrates represent a significant methodological advancement and represents a convenient access route to the corresponding amino compounds possessing valuable properties and potential bioactivity [16].

2. Asymmetric Synthesis of Tetrafluoroethylenated Amines via [1,3]-Proton Shift

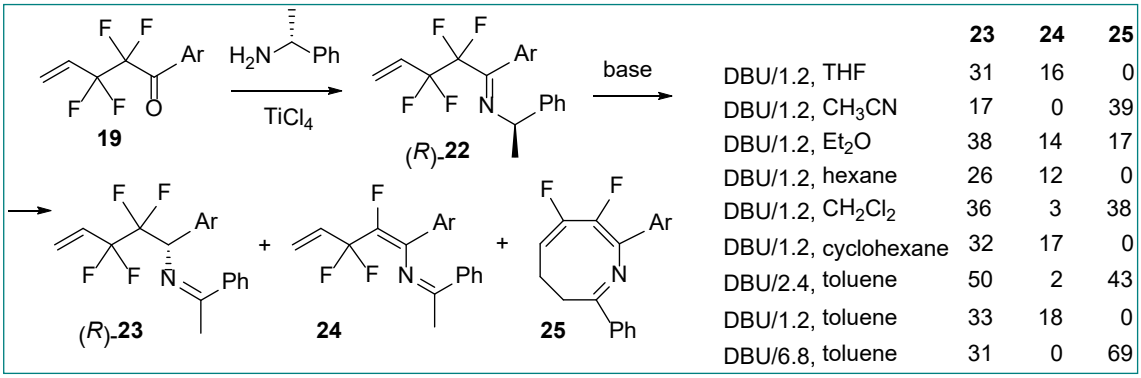
Starting tetrafluoroethylenated ketones *19* (Scheme 3) were prepared in a single step using commercially available 3,3,4,4-tetrafluoro-1-butene (*20*). These were then converted to organometallic species *21* followed by reaction with acyl chloride to afford the target ketones *20* [25].



Scheme 3. *Synthesis of starting tetrafluoroethylenated ketones 19.*

The reaction of ketones *19* with enantiomerically pure 1-phenylethylamine (Scheme 4) were conducted under mild conditions at ambient temperature in diethyl ether using $TiCl_4$ as a dehydrating agent [26]. The procedure yielded the corresponding imines *22* in moderate-to-excellent isolated yields (60–96%).

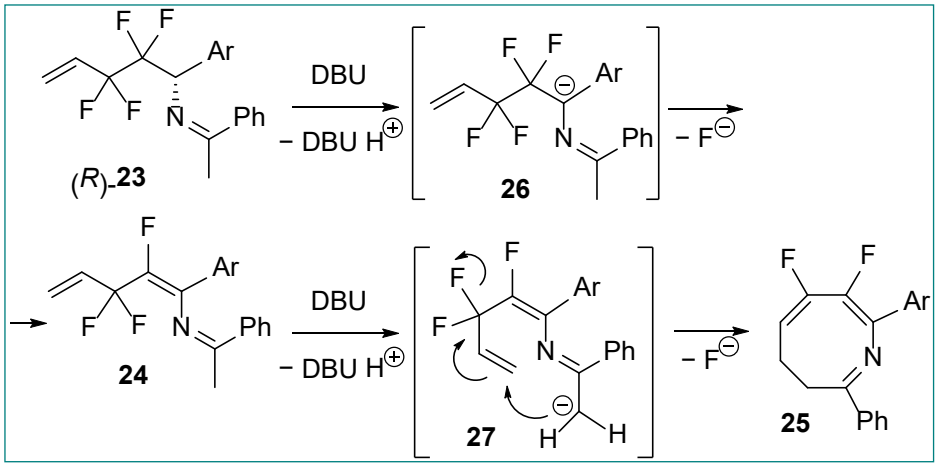
The [1,3]-proton shift reactions of the tetrafluoroethylenated imines *22* revealed rather unexpected results. The azomethine–azomethine isomerizations conducted in the presence of a strong base such as DBU gave rise to three major products *23–25*. Product *(R)-23* was the intended and expected compound while the dehydrofluorinated derivative *24* could be anticipated based on literature results [17, 20, 21, 23, 24]. However, the double dehydrofluorinated entity *25* was an entirely unexpected surprise.



	23	24	25
DBU/1.2, THF	31	16	0
DBU/1.2, CH_3CN	17	0	39
DBU/1.2, Et_2O	38	14	17
DBU/1.2, hexane	26	12	0
DBU/1.2, CH_2Cl_2	36	3	38
DBU/1.2, cyclohexane	32	17	0
DBU/2.4, toluene	50	2	43
DBU/1.2, toluene	33	18	0
DBU/6.8, toluene	31	0	69

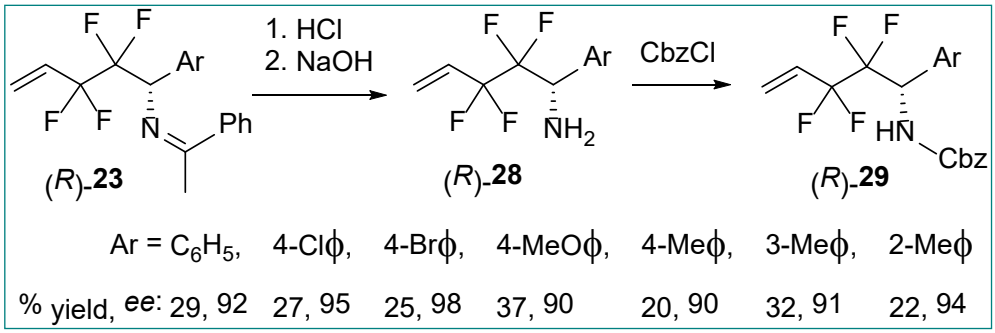
Scheme 4. *[1,3]-Proton shift reaction of imines 22 with the resulting relative amounts of the products 23–25.*

It was demonstrated that the reaction solvent and the amount of DBU can profoundly affect the relative ratio of products *23–25*. Analysis of the reaction outcomes conducted under various conditions led to the conclusion that imine *23* is the first reaction product, giving rise to intermediate triene *24* via the reaction anionic intermediate *26*. This intermediate then undergoes base-catalyzed cyclization to produce *25* via the reaction anionic intermediate *27*. The cyclic product *25* is likely the final and only product if the reaction is allowed to proceed to completion. The step-by-step sequence of the corresponding reactions and plausible mechanistic details are illustrated in Scheme 5.



Scheme 5. *Mechanism of dehydrofluorinated product formation.*

The [1,3]-proton shift products *23* (Scheme 6) were treated with 2*N* HCl aqueous solution in diethyl ether for 2 hours followed by neutralization with 2*N* NaOH aqueous solution to yield the corresponding free amines *28*. Subsequent treatment of the amines *28* with CbzCl and pyridine in dichloromethane afforded the corresponding protected derivatives *29* which were isolated in high enantiomeric purity and in reasonable yields.



Scheme 6. *Preparation of the protected target amines 29 from Schiff bases 23.*

The SDE is a ubiquitous, general phenomenon that has been observed and reported for practically all types of chiral compounds under all known physicochemical phase transitions, including achiral gas chromatography [27]. Typical laboratory purification methods such as achiral column chromatography [28] and sublimation [29] are particularly prone to the SDE phenomenon. Moreover, it has been well established that fluorine is one of the most forceful SDE-phoric groups as a large magnitude of the SDE is often observed for fluorinated compounds when a fluorine atom(s) is(are) located in close proximity to the stereogenic center [30]. Therefore, it should be considered an unfortunate oversight by the authors [16] that they did not perform the now requisite SDE tests [14] relative to their applied purification methods to confirm and validate the reported stereochemical outcome of this novel and fascinating [1,3]-proton shift reaction.

3. Conclusion

As reported by Prof. Konno's group, the [1,3]-proton shift reaction can be successfully extended to the asymmetric synthesis of amines containing a tetrafluoroethylene moiety. However, the corresponding DBU-catalyzed, azomethine–azomethine isomerization of the tetrafluoroethylene-containing imines is complicated by sequential dehydrofluorination leading to the formation of unsaturated byproducts. But by and large the target tetrafluoroethylene imines can be isolated with high enantiomeric purity in moderate yields. However, the true enantioselectivity of these reactions remains unconfirmed in the absence of SDE tests due to the potential for the SDE phenomenon to be in effect during routine purification steps and other workers attempting to replicate the reported results should be aware of this oversight. Nevertheless, the overall procedure provides a simple access to a previously unknown type of compound with potentially interesting biological activity.

Notes

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The authors declare no conflict of interest.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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