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ENANTIOSELECTIVE CATALYSIS FOR THE SYNTHESIS OF 1-SUBSTITUTED-2,2,2-TRIFLUOROETHYLAMINES (review).

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1-Substituted-2,2,2-trifluoroethylamines have emerged as structurally distinct and pharmacologically potent motifs in modern drug design, contributing to enhanced metabolic stability, target selectivity, and bioactivity across various therapeutic classes. This review provides a comprehensive account of their catalytic enantioselective synthesis, encompassing chiral auxiliary-based methods and a wide array of asymmetric catalytic strategies — including hydrogenation, [1,3]-proton shift reactions, nucleophilic additions, and cycloadditions. Emphasis is placed on the stereochemical outcomes achieved with ruthenium, palladium, phosphoric acid, borane, and squaramide-based catalysts, many of which routinely deliver an enantiomeric excess (ee) exceeding 90–99%. Despite these advances, the phenomenon of self-disproportionation of enantiomers (SDE) remains critically underreported, casting doubt on the veracity of ee values in the literature. This review highlights the pronounced SDE behavior of fluorinated amines and underscores the need for rigorous stereochemical validation. By integrating synthetic innovation with epistemic scrutiny, this work aims to guide future research toward more reliable, efficient, and stereochemically sound methodologies for the synthesis of fluorinated amine derivatives.

Keywords: fluorinated amines, catalytic enantioselective synthesis, medicinal chemistry, self-disproportionation of enantiomers, epistemic scrutiny.

INTRODUCTION.

Amino compounds, such as amines and amino acids, are foundational to both natural biochemistry and modern drug design [1–4]. Amines are ubiquitous in nature — from neurotransmitters such as dopamine and serotonin to alkaloids in plants and signaling molecules in animals. Their basicity, hydrogen-bonding capacity, and structural versatility make them essential for molecular recognition and biological activity. Amino acids, the building blocks of proteins, are a specialized class of amines that orchestrate nearly every cellular function, from enzymatic catalysis to structural support and immune signaling. Beyond their role in protein biosynthesis, amino acids serve as precursors for hormones, metabolic intermediates, and redox regulators. Most endogenous amines in biological systems are derived from amino acids through enzymatic decarboxylation or other transformations [5].

In drug design, amino compounds are prized for their ability to engage biological targets through ionic and hydrogen-bonding interactions. Many small-molecule drugs incorporate primary, secondary, or tertiary amines, as well as amino acids and derivatives such as 2-hydroxyamines and 1,2-diamines, to enhance solubility, receptor binding, and pharmacokinetics [6–9]. Amino acid derivatives, including peptidomimetics and β-amino acids, offer tunable scaffolds for modulating bioavailability and selectivity. The strategic incorporation of amine and amino acid motifs continues to drive innovation in medicinal chemistry, enabling the design of therapeutics that mimic, modulate, or disrupt biological processes with precision [10–13].

Besides natural and tailor-made amino compounds, modern drug design is characterized by strategic fluorination to achieve enhanced pharmacokinetic profiles, metabolic stability, and target selectivity [14–16]. The introduction of fluorine atoms or fluorinated groups into bioactive molecules profoundly influences their physicochemical properties — modulating lipophilicity, acidity, and membrane permeability [17]. The high electronegativity of fluorine and its small size allow it to mimic hydrogen while altering electronic distribution, often improving binding affinity through dipolar interactions or conformational control. In metabolic terms, C–F bonds resist oxidative degradation, extending drug half-life and reducing off-target effects [18, 19]. Fluorination can also block metabolic hotspots or redirect biotransformation pathways, contributing to safer and more efficacious therapeutics [20, 21]. Notably, fluorinated motifs such as trifluoromethyl, difluoromethylene, and aryl fluorides [22–24] are now commonplace in approved drugs across oncology, neurology, and infectious diseases. The precision with which fluorine modulates molecular behavior makes it indispensable in lead optimization, enabling medicinal chemists to fine-tune activity and ADME properties without compromising scaffold integrity. As synthetic methodologies advance [25–38], the role of fluorine continues to expand, driving innovation at the interface of chemistry and biology.

Fluorine-containing amino compounds represent a powerful class of molecular tools in contemporary drug design. Incorporation of fluorine into amine-bearing scaffolds — such as trifluoroethylamines, difluoromethylamines, and fluorinated anilines — can modulate basicity, enhance metabolic stability, and improve target engagement through altered hydrogen-bonding profiles and dipolar inte-

ractions. Fluorinated amino acids, including α-trifluoromethylated and β-fluorinated analogs, offer conformational rigidity and proteolytic resistance, making them valuable in peptidomimetics and protein–protein interaction inhibitors [39–41]. These modifications often lead to improved pharmacokinetic properties, such as increased membrane permeability and reduced clearance. Strategically placed fluorine atoms can also influence stereoelectronic effects, guiding molecular recognition and selectivity. As synthetic access to fluorinated building blocks expands, their integration into drug candidates enables fine-tuning of bioactivity without compromising scaffold integrity. Fluorine-containing amines and amino acids thus serve as versatile elements in lead optimization, bridging structural innovation with functional precision across therapeutic areas [42–44].

Building on our long-standing interest in the asymmetric synthesis of fluorine-containing amines [45–48] and amino acids [49–54], we have focused this review on the catalytic enantioselective synthesis of 1-substituted-2,2,2-trifluoroethylamines — a structurally distinct class of compounds with growing relevance in modern drug design. The article encompasses: (i) an overview of marketed pharmaceuticals and bioactive molecules featuring the 2,2,2-trifluoroethylamine motif; (ii) a detailed account of catalytic asymmetric methodologies for their synthesis; and (iii) a discussion of the self-disproportionation of enantiomers (SDE) phenomenon [55], which is particularly pertinent to fluorinated amines and their derivatives.

We anticipate that this compilation will serve not only as a practical reference for researchers working with fluorine-containing amino compounds, but also as a conceptual springboard for innovation in synthetic and medicinal chemistry. In particular, it aims to support those exploring the strategic role of fluorine in the design and optimization of pharmaceutical agents.

Recent advances in 2,2,2-trifluoroethylamine-containing pharmaceuticals.

In recent years, the incorporation of 2,2,2-trifluoroethylamine residues into bioactive compounds has garnered significant attention for its ability to modulate biological activity, pharmacokinetics, and other drug-like properties. These efforts have culminated in the approval of two drugs approved by the US-American Food and Drug Administration (FDA) and the identification of two additional compounds that have served as indispensable structural leads in drug development.

The most recent FDA-approved drug in this class is Vorasidenib **1** (Fig. 1), marketed under the brand name Voranigo. Developed by Servier Pharmaceuticals, Vorasidenib is a brain-penetrant, dual inhibitor of mutant isocitrate dehydrogenase-1 (IDH1) and IDH2. It received FDA approval on August 6, 2024, becoming the first systemic therapy for Grade 2 astrocytoma or oligodendroglioma harboring a susceptible IDH1 or IDH2 mutation.

The drug emerged from efforts to target metabolic vulnerabilities in gliomas, where IDH mutations lead to the accumulation of 2-hydroxyglutarate (2-HG) — an oncometabolite that disrupts cellular differentiation and promotes tumorigenesis. Vorasidenib works by selectively inhibiting mutant IDH enzymes, thereby reducing 2-HG levels and slowing tumor progression. Its efficacy was demonstrated in the Phase III INDIGO trial, where it

significantly extended progression-free survival and delayed the need for further intervention.

Interestingly, although racemic Vorasidenib exhibits comparable nanomolar-level bioactivity, the enantiomer with *R,R* absolute configuration demonstrates approximately ten-fold greater potency in cellular assays [56].

The therapeutic profile of Vorasidenib is notable for its oral bioavailability, central nervous system penetration, and targeted mechanism, making it particularly suited for low-grade gliomas post-surgery. It is administered once daily, with dosing adjusted for pediatric patients based on body weight [57–60].

While the full particularities have not been publicly disclosed in detail, fluorinated motifs—such as trifluoroethylamine or related groups — are often employed in IDH inhibitors to enhance lipophilicity, metabolic stability, and binding affinity to the mutant enzyme pocket. The electron-withdrawing properties of fluorine can fine-tune the pharmacodynamics and improve central nervous system (CNS) penetration, which is critical for brain tumor therapeutics. In general, Vorasidenib represents a paradigm shift in glioma treatment, combining precision oncology with strategic fluorine chemistry to address a previously underserved patient population.

Another notable drug incorporating a 2,2,2-trifluoroethylamine residue is Pirtobrutinib **2** (Fig. 1), marketed as Jaypirca. Developed by Loxo Oncology, a subsidiary of Eli Lilly and Company, Pirtobrutinib is a next-generation, non-covalent inhibitor of Bruton's tyrosine kinase (BTK). It received accelerated FDA approval on January 27, 2023, for the treatment of relapsed or refractory mantle cell lymphoma (MCL) following at least two prior lines of systemic therapy, including a BTK inhibitor. A subsequent approval in December 2023 expanded its indication to chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) in patients previously treated with both a BTK and a Bcl-2 inhibitor [61, 62].

The therapeutic profile of Pirtobrutinib is distinguished by its reversible binding to BTK, unlike earlier covalent inhibitors such as Ibrutinib. This allows it to re-establish BTK inhibition in patients who have developed resistance to covalent BTK inhibitors. It is administered orally at 200 mg once daily, offering a convenient and targeted approach to B-cell malignancies.

Mechanistically, Pirtobrutinib binds to the ATP-binding site of BTK, blocking downstream signaling that promotes B-cell proliferation and survival. Its non-covalent interaction enables sustained inhibition even in the presence of BTK mutations that impair covalent binding [63–65].

While the full details are proprietary, fluorinated motifs—particularly trifluoroethylamine or trifluoromethyl groups — are commonly employed in kinase inhibitors to enhance lipophilicity, metabolic stability, and selectivity. In Pirtobrutinib, fluorine likely contributes to CNS penetration, binding affinity, and pharmacokinetic optimization, reinforcing its efficacy in hematologic malignancies. Pirtobrutinib represents a significant advance in precision oncology, offering renewed therapeutic options for patients with limited alternatives.

Another notable fluorinated drug is Inavolisib **3** (Fig. 1), a PI3Kα-selective inhibitor developed by Genentech, a member of the Roche Group. The approved molecule incorporates a 2,2-difluoroethylamine residue. Interestingly, a related drug candidate—compound **4**, fea-

turing a 2,2,2-trifluoroethylamine fragment—played a pivotal role in optimizing the pharmacological profile of Inavolisib. Substitution with a trifluoromethyl group in compound **4** yielded a α isoform of phosphatidylinositol 3-kinase (PI3Kα) IC_{50} of 0.095 nM and a PI3Kδ/PI3Kα selectivity ratio of 171, indicating reduced isoform selectivity. In contrast, Inavolisib, bearing a difluoromethyl group, achieved a PI3Kα IC_{50} of 0.034 nM and a PI3Kδ/PI3Kα ratio of 361, demonstrating markedly enhanced selectivity for the α isoform.

Marketed under the brand name Itovebi, Inavolisib received FDA approval in May 2024 for use in combination with Fulvestrant ± Palbociclib in patients with hormone receptor-positive (HR+), HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer who have progressed following prior endocrine therapy. The therapeutic profile of Inavolisib is defined by its high selectivity for the PI3Kα, a frequently mutated oncogenic driver in breast cancer [66]. Unlike earlier pan-PI3K inhibitors, Inavolisib exhibits improved tolerability and reduced off-target toxicity, owing in part to its rational design and physicochemical optimization [67–70].

Mechanistically, Inavolisib binds to the ATP-binding pocket of PI3Kα, inhibiting downstream protein kinase B and mammalian target of rapamycin (AKT/mTOR) signaling and promoting degradation of mutant p110α protein. This dual action not only suppresses tumor cell proliferation but also enhances sensitivity to endocrine therapy, particularly in tumors harboring PIK3CA mutations [70–73].

Structurally, Inavolisib incorporates a difluoroethylamine, a fluorinated motif that contributes to its metabolic stability, target selectivity, and oral bioavailability. The role of fluorine in modulating lipophilicity and binding kinetics is well-established in kinase inhibitor design, and in Inavolisib, it likely enhances CNS penetration and pharmacokinetic performance.

Administered orally at 30 mg once daily, Inavolisib offers a convenient and targeted approach to overcoming endocrine resistance in breast cancer. Common adverse effects include hyperglycemia, rash, diarrhea, and stomatitis, consistent with PI3K pathway inhibition [74–76].

Inavolisib represents a refined evolution in PI3K-targeted therapy, balancing potency with precision and reaffirming the value of fluorinated scaffolds in modern oncology.

Finally, we would like to mention Odanacatib **5** (MK-0822) featuring 2,2,2-trifluoroethylamine residue. It was a promising investigational drug developed by Merck & Co., discovered at Merck Frosst in Montreal in the early 2000s. It was designed as a selective inhibitor of cathepsin K (CTSK), a cysteine protease critical for osteoclastic bone resorption. By targeting CTSK, Odanacatib aimed to treat osteoporosis and bone metastases by reducing bone degradation while preserving bone formation — an advantage over traditional bisphosphonates.

Merck advanced Odanacatib into Phase III clinical trials, and by 2014, the company announced plans to seek FDA approval based on strong efficacy and a favorable safety profile. However, in 2016, Merck discontinued its development after post-trial analysis revealed an increased risk of stroke, halting its regulatory submission [77, 78].

The fluorinated motif, 2,2,2-trifluoroethylamine, plays a pivotal role in enhancing metabolic stability, lipophilicity, and target

binding affinity. The CF_3 group contributes strong electron-withdrawing effects, which modulate the basicity of the adjacent amine and improve pharmacokinetic properties. Additionally, the trifluoroethylamine unit helps fine-tune the interaction of the molecule with the cathepsin K active site, contributing to its selectivity and potency. Furthermore, Odanacatib features residues of fluoroleucine and nitrile of aminocyclopropane carboxylic acid, underscoring the role of tailor-made amino acids in modern drug design [79–81].

Though never approved, Odanacatib remains a notable example of how fluorinated amine motifs can be leveraged in drug design to achieve precise biological effects and favorable drug-like properties.

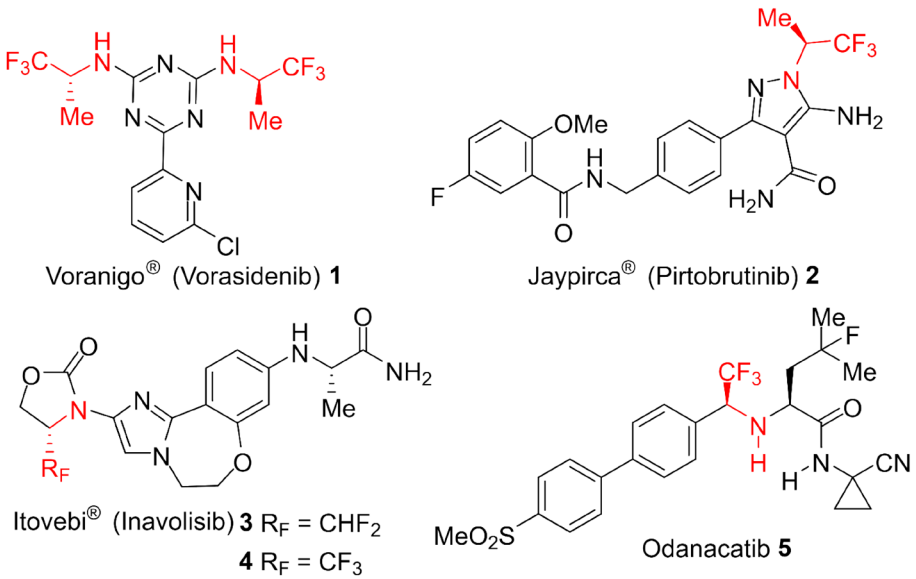


Fig. 1. Representative examples of fluorinated drug scaffolds containing the CF_3–$CH(NR_2)$ moiety.

Brief Overview of Chiral Auxiliary-Based Approaches for the Synthesis of the 2,2,2-Trifluoroethylamine Moiety.

Considering the critical role of enantiomeric purity in the development of chiral pharmaceuticals [82–84], chiral auxiliary-assisted asymmetric synthesis of 2,2,2-trifluoroethylamines has garnered significant attention. Most research in this area centers on the use of chiral derivatives of industrially available trifluoroacetaldimines **6** and **7** (Fig. 2). *p*-Toluenesulfinimine **6**, derived from Davis' *p*-toluenesulfinamide [85–88], is a cost-effective, readily accessible, and operationally reliable reagent. It exhibits high reactivity toward nucleophilic additions, furnishing 1-substituted 2,2,2-trifluoroethylamines **8** in chemical yields and diastereoselectivities exceeding 90% [89–92]. Ellman's *tert*-butanesulfinamide-derived imine **7** has proven even more prolific, inspiring a substantial body of research [93–102]. It enables the synthesis of target trifluoroethylamines **8** with excellent yields (>95%) and virtually complete diastereoselective control (>98%) [103–109].

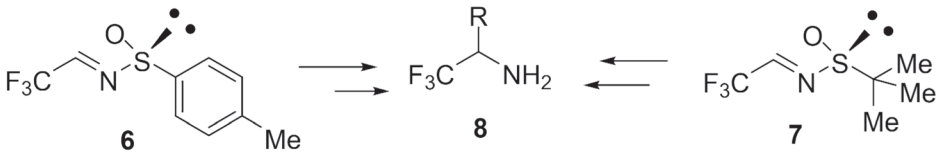


Fig. 2. Chiral auxiliary-based approaches to trifluoroethylamines.

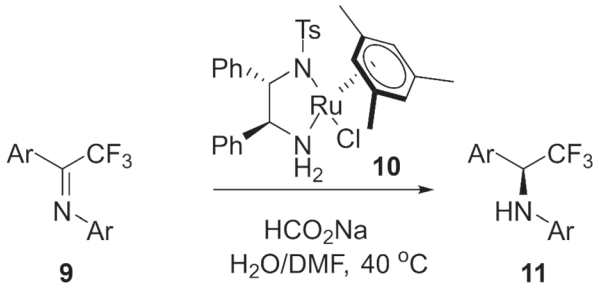
Enzymatic resolution of racemic 2,2,2-trifluoroethylamines **8** remains relatively underexplored. Nonetheless, the use of penicillin acylase (penicillin amidase, EC 3.5.1.11) [110] offers a practical and efficient route to both enantiomers, delivering products of exceptionally high enantiomeric purity (>99% ee) [111–113].

Catalytic enantioselective Approaches for the Synthesis of the 2,2,2-Trifluoroethylamine Moiety

Reduction of C=N Bond.

Catalytic enantioselective hydrogenation of imines is a well-established methodology, supported by a rich arsenal of chiral catalysts, optimized reaction conditions, and broad substrate scope. Its application to the reduction of fluorinated imines is generally straightforward, albeit with occasional complications. The key distinction of fluorine-containing imines lies in their heightened reactivity, which can influence both selectivity and reaction kinetics. Nonetheless, the enantioselective reduction of fluoroimines remains a robust and extensively studied domain of synthetic chemistry [114].

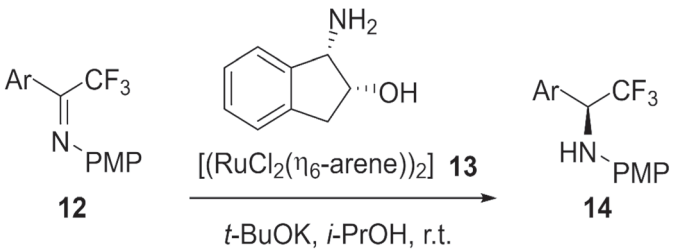
A representative example is the work by Wu *et al*. (Scheme 1) [115], who achieved the enantioselective transformation of α-trifluoromethylimines **9** into α-trifluoromethylamines **11** via asymmetric transfer hydrogenation. The reaction employed a ruthenium catalyst **10** (2 mol%) derived from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine, with sodium formate serving as the hydrogen source and a water–dimethylformamide mixture as the cosolvent. Conducted at 40 °C, the process afforded the desired amines in excellent chemical yields (>90%) and high enantioselectivity (>95% ee), highlighting the efficiency and practicality of this catalytic system.



Scheme 1. Hydrogenation of *N*-aryl aryl/CF_3-ketimines using Ru(II) catalyst **10**.

Dai and Cahard (Scheme 2) [116] reported the in situ generation of catalyst **13** (2 mol%), derived from dichloro(*para*-cymene)ruthenium(II) dimer [$(RuCl_2(\eta^6\text{-arene}))_2$] and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol, in the presence of isopropyl alcohol. This protocol

enables the formation of a bifunctional chiral catalyst directly in the reaction medium, which efficiently promotes the asymmetric transfer hydrogenation of trifluoromethyl ketimines **12**, affording the corresponding amines **14** in excellent yields (>95%) and high enantioselectivities (up to 93% ee). The reactions are performed under ambient temperature conditions in the presence of a base (*t*-BuOK), highlighting the operational simplicity and stereochemical efficiency of this catalytic system.

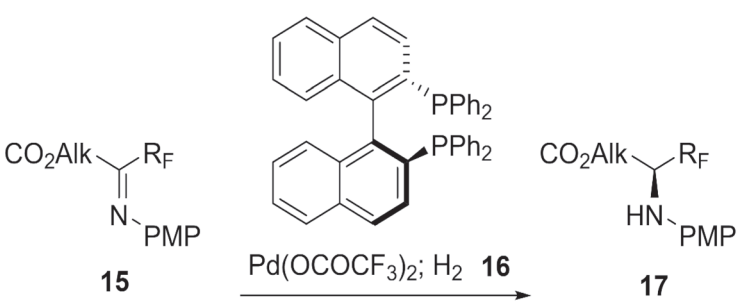


Scheme 2. Hydrogenation of *N*-PMP aryl/CF_3-ketimines using Ru(II) catalyst **13**.

While the methods outlined in Schemes 1 and 2 yield excellent results for trifluoromethyl and aryl imines, their application to alkyl ketimines proves ineffective, often resulting in low reactivity and/or poor enantioselectivity. This diminished performance may be attributed to imine–enamine tautomerism via a 1,3-proton shift reaction (*vide infra*) [117], and/or the presence of a mixture of *Z*/*E* imine geometric isomers.

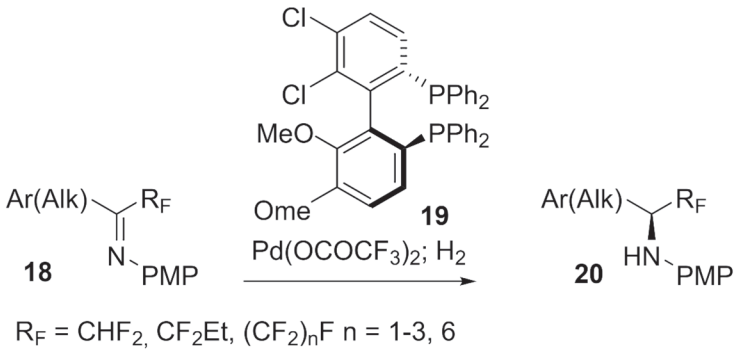
Abe *et al*. (Scheme 3) [118] demonstrated that under hydrogen pressure, a catalytic system comprising palladium(II) trifluoroacetate and 2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl (BINAP) **16** (2 mol%) effectively promotes the asymmetric hydrogenation of α-fluorinated iminoesters **15**, yielding highly enantioenriched β-fluorinated α-amino esters **17**. Both yield and enantioselectivity were significantly enhanced by employing fluorinated alcohols — notably 2,2,2-trifluoroethanol, which enabled enantioselectivities of up to 91% ee.

It is noteworthy that imines derived from trifluoropyruvic acid, serving as versatile synthons for the general synthesis of α-trifluoromethyl amino acids, were first introduced in 1986 by the Kukhar – Yagupolskii group [119–122].



Scheme 3. Hydrogenation of fluoroalkyl-substituted α-iminoesters.

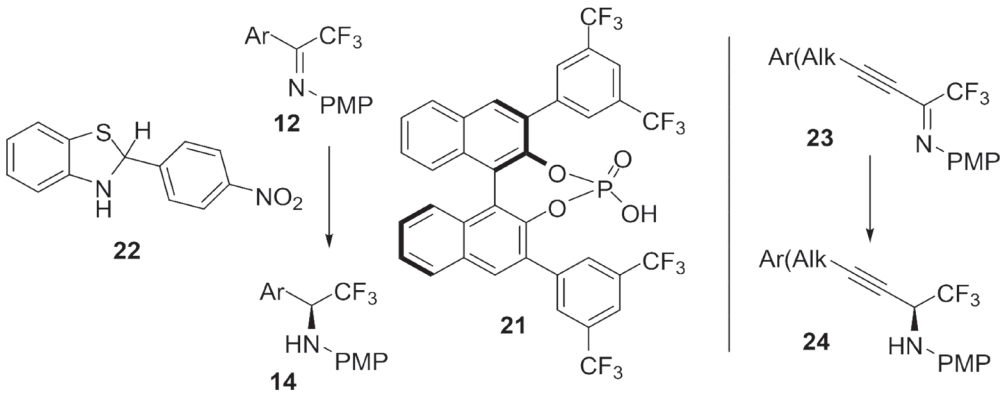
Chen *et al.* (Scheme 4) [123] demonstrated that the use of Cl-MeO-BIPHEP **19** (2 mol %) as a catalyst effectively generalizes the previously discussed approach to the hydrogenation of aryl- and alkyl-substituted imines **18**, affording the corresponding amines **20** in excellent chemical yields (>95%) and with enantioselectivities of up to 94% ee. Notably, the presence of 2,2,2-trifluoroethanol was found to be crucial for achieving high stereochemical fidelity.



Scheme 4. Hydrogenation of alkyl- and aryl-substituted CF_3-imines.

It is important to recognize that while certain perfluorinated compounds have valuable applications in life sciences and materials chemistry, many members of this class — collectively known as per- and polyfluoroalkyl substances (PFAS) — pose significant environmental risks due to their persistence and bioaccumulative potential [124–126]. Consequently, the synthesis and use of such substances should be subject to strict regulatory oversight and pursued only when no suitable alternatives are available.

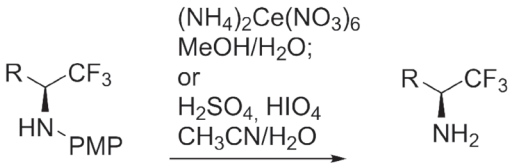
Henseler *et al.* (Scheme 5) [127] reported the metal-free synthesis of optically active α-CF_3 amines **14** under mild catalytic conditions. The reactions were carried out in refluxing dichloromethane for 24 hours, employing chiral phosphoric acid **21** (10 mol %) as the catalyst and benzothiazoline **22** (1.2 equiv.) as the reducing agent. The method afforded the desired amines in yields ranging from 70% to 90%, with enantioselectivities exceeding 95% ee.



Scheme 5. Hydrogenation of aryl-substituted CF_3-imines using chiral phosphoric acid **21**.

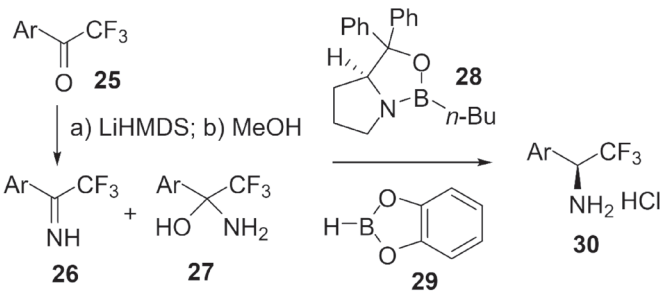
Chen *et al*. (Scheme 5) [128] applied the same catalytic protocol to the reduction of trifluoromethyl alkynyl ketimines **23**, affording the corresponding amines **24** with yields and enantioselectivities reaching up to 98% and 98% ee, respectively. Notably, the alkyne moiety remained intact, with no reduction of the triple bond observed under the reaction conditions.

In the methods discussed above for hydrogenation of trifluoromethyl-substituted imines, application of *N*-PMP is a common feature of the starting compounds. Stereoelectronic properties of the PNP group provides for proper reactivity of the C=N bond and its more stable geometric configuration. Furthermore, this group can be conveniently removed under the standard conditions shown in Scheme 6. Its cleavage via oxidative hydrolysis — commonly using harsh oxidants such as ceric ammonium nitrate (CAN), as illustrated in Scheme 6 — enables access to the free amine. Alternative strategies for PMP deprotection similarly rely on strongly acidic and oxidizing conditions to unveil the primary amine functionality. The conditions outlined in Scheme 6 preserve the enantiomeric integrity of the compounds and afford consistently high yields (>70%).



Scheme 6. Deprotection of PMP group.

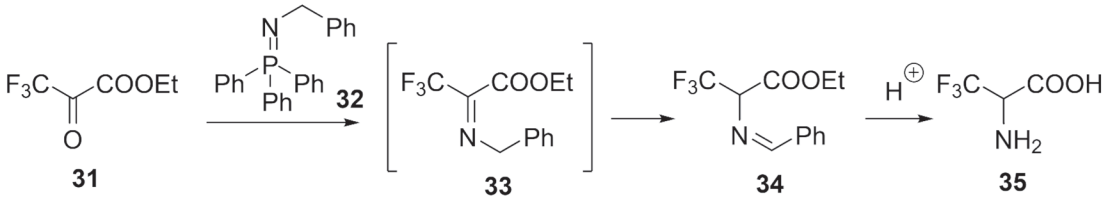
Gosselin *et al*. (Scheme 7) [129] developed a catalytic enantioselective strategy for the direct synthesis of trifluoromethylated amines **30**. The sequence begins with the addition of lithium bis(trimethylsilyl)amide to trifluoromethyl/aryl ketones **25**, generating (*E*)-*N*-TMS-ketimines. Subsequent treatment with methanol induces solvolysis of the N–Si bond, yielding bench-stable, isolable N–H imines **26** as *Z*/*E* isomer mixtures, along with a side product, aminoalcohol **27**. These three-component mixtures are then subjected to enantioselective reduction using catalyst **28** (2 mol%) and catecholborane **29** as the reducing agent, affording the desired CF_3-amines **30** in 72–95% yields and with enantioselectivities ranging from 75% to 98% ee. The reactions are conducted in toluene at –15 °C for 18 hours, and upon completion, the mixtures are quenched with 2.0 M HCl in diethyl ether, furnishing the products as hydrophilic acid salts.



Scheme 7. Chiral borane-catalyzed reductions of NH imines.

[1,3]-Proton Shift Reaction.

The discovery of biomimetic reductive amination of fluorinated carbonyl compounds dates back to 1986 [119, 130], when the Kukhar – Yagupolskii group attempted a Staudinger reaction between keto-ester **31** (Scheme 8) and phosphazene **32**. Unexpectedly, the reaction yielded Schiff base **34** as the sole product. It is reasonable to assume that the intended intermediate **33** underwent irreversible in situ isomerization to imine **34**, which was subsequently hydrolyzed with ease, affording trifluoroalanine **35** in high yield.

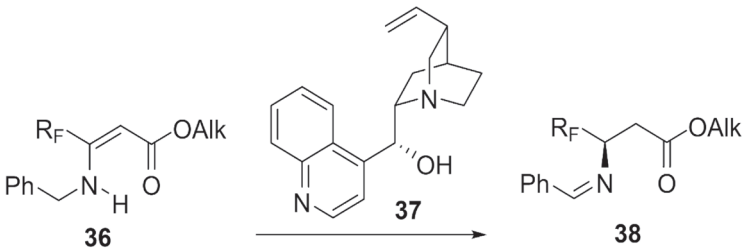


Scheme 8. Staudinger reaction followed by the irreversible [1,3]-proton shift.

The [1,3]-proton shift reaction has emerged as a synthetically versatile and broadly applicable transformation [131], enabling the efficient and practical conversion of various fluorinated carbonyl substrates — including CF_3-aldehydes [132, 133], CF_3-ketones [134, 135], as well as α-[136] and β-ketoacids [137, 138] — into their corresponding biologically relevant amino derivatives under a wide range of reaction conditions [139–141]. Notably, the reaction can proceed through two consecutive [1,3]-proton shift steps, further expanding its synthetic utility and enabling access to more complex molecular architectures [142, 143]. While the transformation is typically base-catalyzed [144], it can also occur under thermal conditions [145], underscoring its operational flexibility.

Moreover, the use of chiral phenylethylamine introduces a stereochemical dimension to the process, allowing for asymmetric [1,3]-proton shift transfer and affording enantiomerically enriched CF_3-amino compounds with enantiomeric excesses reaching up to 90% ee [146–149].

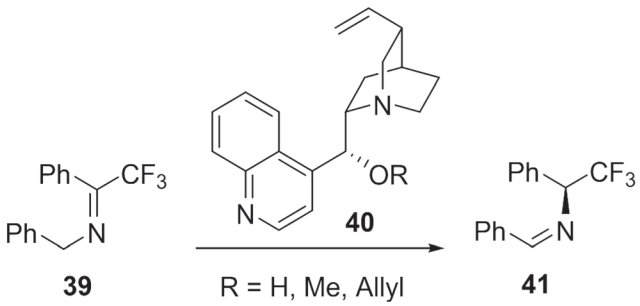
The first catalytic enantioselective [1,3]-proton shift reaction, reported in 1994, is illustrated in Scheme 9 [150]. In this pioneering study, *N*-benzylenamines **36**, prepared from β-polyfluoroalkyl-β-ketocarboxylic esters and benzylamine, underwent a [1,3]-proton shift catalyzed by (–)-cinchonidine **37** (5–13 mol%). The transformation afforded *N*-benzylidene derivatives **38** in good yields (67–89%) and with moderate enantioselectivity — up to 36% ee.



Scheme 9. Cinchonidine-catalyzed [1,3]-proton shift reaction.

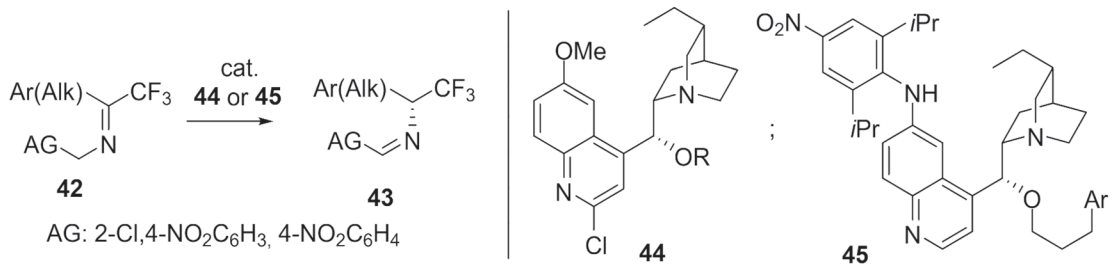
Subsequent hydrolysis of the products **38** proceeded smoothly, delivering the corresponding optically active (*R*)-β-polyfluoroalkyl-β-amino acids in excellent yields (87–93%). This work represents a foundational example of asymmetric proton shift catalysis and laid the groundwork for future developments in enantioselective synthesis of fluorinated amino acid derivatives.

Scheme 10 [151] illustrates the catalytic enantioselective synthesis of α-(trifluoromethyl)benzylamine Schiff base **41** employing chiral base **40**. In this transformation, imine **39** undergoes isomerization to form Schiff base **41**, catalyzed by 50 mol% of cinchonidine derivatives **40** in various solvents, including chloroform, methanol, and acetonitrile. When cinchonidine **40** (R = H) was used as the catalyst in chloroform, the reaction achieved 79% conversion of imine **39**, yielding Schiff base **41** with (*R*)-absolute configuration and 35% ee. Remarkably, the product was obtained as a single compound, free from detectable byproducts.



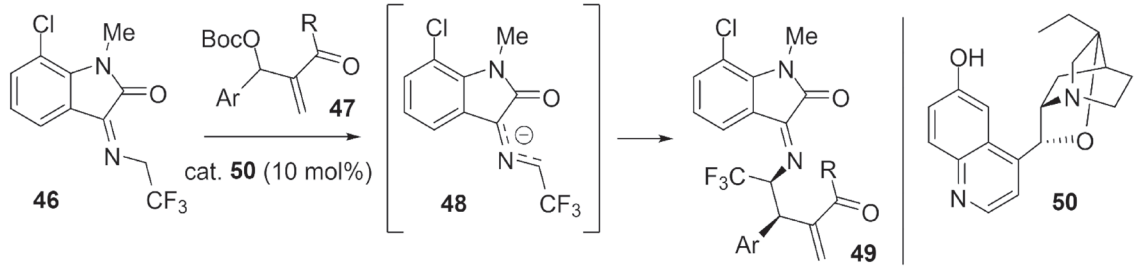
Scheme 10. Catalytic enantioselective synthesis of α-(trifluoromethyl)benzylamine Schiff base.

This transformative line of research — centered on chiral base-catalyzed [1,3]-proton shift transfer—was originally pioneered by Ukrainian chemists, whose foundational contributions have since inspired widespread optimization efforts and the development of more efficient catalytic systems. Building on this groundwork, Wu and Deng introduced several key modifications, including the use of synthetically tailored cinchona alkaloid **44** and benzylamine derivatives **42** bearing electron-withdrawing substituents on the aromatic ring (Scheme 11). The latter strategy was a direct extension of earlier findings [139–141], which demonstrated that the electrophilic nature of the benzene ring significantly facilitates the [1,3]-proton shift, enabling isomerization under milder conditions. Equally important, their work [152, 153] underscored the critical role of catalyst structure in achieving high levels of stereocontrol, with enantiomeric excesses of products **43** reaching up to 90% ee. In a parallel development, Liu *et al.* [154] reported comparable results using an even more structurally elaborate designer catalyst **45** (Scheme 11). Notably, both catalytic systems are effective at low loadings (as little as 10 mol%), highlighting their practical utility in asymmetric synthesis.



Scheme 11. Synthetic cinchona derivatives as catalysts for enantioselective [1,3]-proton shift.

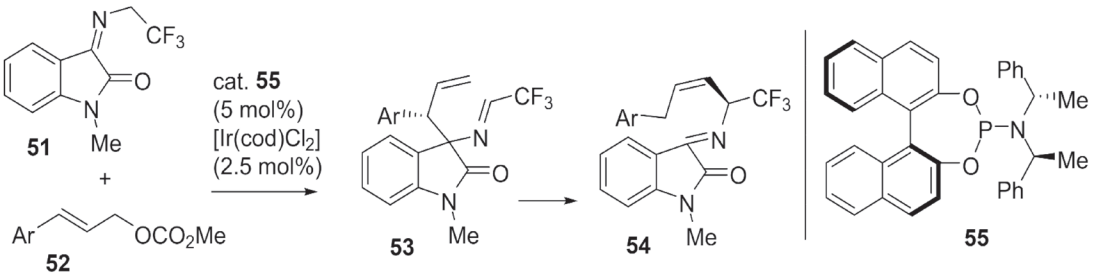
Since the pioneering work of the Kukhar – Yagupolskii group in 1986 [119, 130], a fundamentally new dimension has emerged in the chemistry of the [1,3]-proton shift reaction—specifically involving the trapping of the intermediate 1,3-azaallylic anion by various electrophiles. For instance, Li *et al.* [155] (Scheme 12) demonstrated that β-isocupreidine **50**, a cinchonine-derived alkaloid used at 10 mol% loading, effectively catalyzes an asymmetric S_N2'–S_N2' reaction between *N*-2,2,2-trifluoroethylisatin ketimines **46** and Morita – Baylis – Hillman (MBH) type carbonates **47**. This transformation proceeds via selective trapping of the intermediate anion **48**, affording synthetically valuable CF_3-substituted amino compounds **49** with high enantioselectivity and efficiency. A series of chiral α-trifluoromethylamines were obtained in excellent yields (70–90%) and ee (~90%). Notably, despite the presence of two potentially reactive sites on anion **48**, the reaction occurs exclusively at the α-position relative to the CF_3 group.



Scheme 12. Coupling of CF_3-imines with Morita–Baylis–Hillman allylic carbonates.

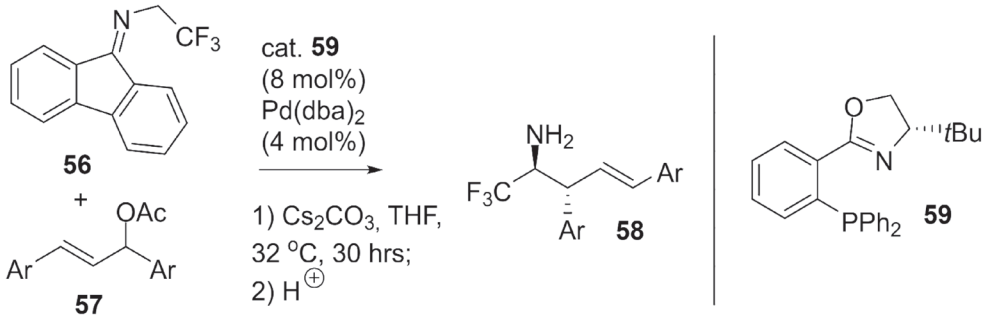
Shi *et al.* (Scheme 13) [156] reported an Ir/phosphoramidite **55**-catalyzed enantioselective cascade transformation involving a [1,3]-proton shift, allylation, and subsequent aza-Cope rearrangement of trifluoroethylisatin-derived imines **51** with allylic carbonates **52**, ultimately furnishing CF_3-substituted amino derivatives **54**. Notably, the initial product **53** arises from allylation of the [1,3]-proton shift intermediate, despite the steric hindrance associated with the corresponding anion. This intermediate **53** then undergoes a spontaneous aza-Cope rearrangement, delivering the net γ-allylation product **54**. The rearrangement is driven by steric relief from the adjacent tetra- and trisubstituted stereogenic centers, and

is likely further facilitated by conjugation of the resulting olefin with the aromatic system. A broad array of derivatives bearing various (hetero)aryl substituents can be accessed, with most examples exhibiting excellent yields (up to 95%) and high enantioselectivity (~90% ee).



Scheme 13. Ir – phosphoramidite-catalyzed cascade reactions of CF_3-imines.

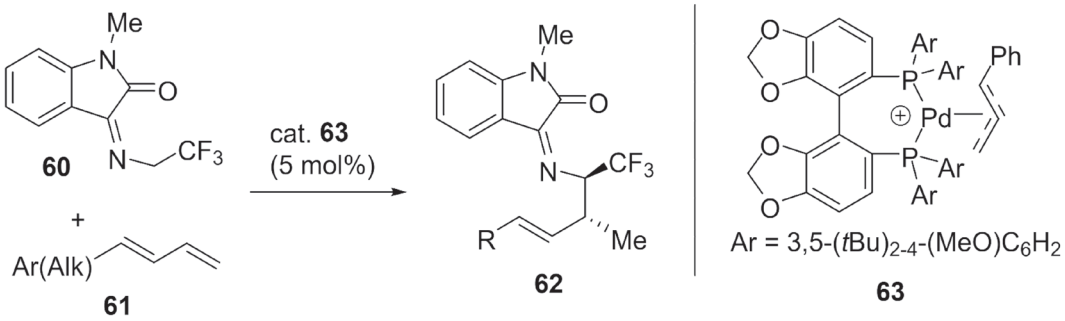
Wang *et al.* (Scheme 14) [157] reported the Pd-catalyzed trapping of 1,3-azaallyl anions derived from fluorenyl imine **56** with allylic acetates **57**. The transformation employs a $Pd(dba)_2$ complex in conjunction with a PHOX ligand **59**, using Cs_2CO_3 as the base in THF. The reaction proceeds with high enantioselectivity (~90% ee) and modest to good diastereoselectivity (up to 8:1 dr). Although conceptually related to the Ir-catalyzed cascade described in Scheme 13, this process diverges mechanistically: it involves direct allylation at the least sterically hindered site of the azaallyl anion, rather than proceeding through a rearrangement pathway. This distinction underscores the complementary nature of Pd and Ir catalysis in accessing structurally and stereochemically diverse azaallyl-derived products.



Scheme 14. Pd-catalyzed trapping of 1,3-azaallyl anions derived from fluorenyl imine.

Onyeagusi *et al.* (Scheme 15) [158] introduced an alternative strategy for the enantioselective allylation of CF_3-substituted imines **60**, catalyzed by a chiral Pd complex. In this protocol, imines **60** react with terminal dienes **61** in the presence of 5 mol% Pd–DTBM-SEGPHOS catalyst **63**. The reaction is carried out in 1,4-dioxane using 2.0 equivalents of triethylamine to generate the corresponding 1,3-azaallyl anion under mild heating over 12 hours. The intermediate anion undergoes selective allylation at the least sterically hindered site, affording

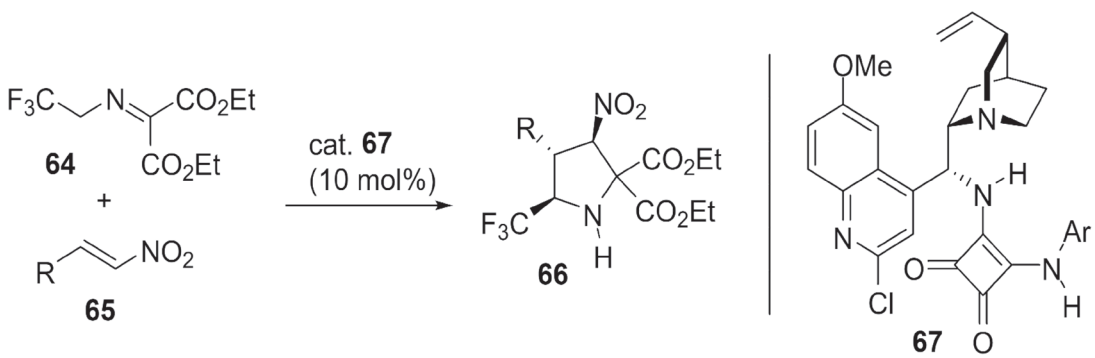
products **62** in yields of up to 86%, with excellent enantioselectivity (~95% ee) and good diastereoselectivity (up to 10:1 dr). This method highlights the versatility of Pd catalysis in accessing highly enantioenriched CF_3-containing amines through direct functionalization of azaallyl intermediates.



Scheme 15. Pd–DTBM-SEGPHOS-catalyzed reactions with dienes.

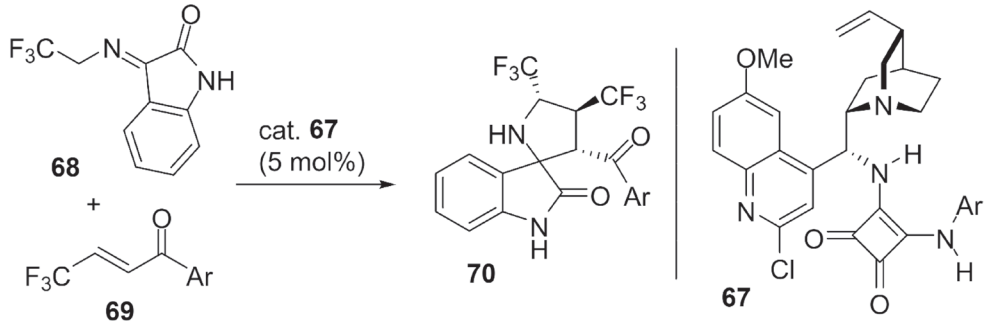
Liu *et al.* (Scheme 16) [159] described an enantioselective Michael/aza-Henry cycloaddition between trifluoromethyl-substituted iminomalonate **64** and nitroalkenes **65**, catalyzed by 10 mol% of a quinine-derived squaramide catalyst **67**. This transformation enables the efficient synthesis of highly functionalized pyrrolidine derivatives **66** bearing 5-trifluoromethyl and 3-nitro substituents, along with three contiguous stereogenic centers. The reaction proceeds with excellent stereoselectivity (>20:1 dr, 99% ee) and very good yields (up to 82%).

Mechanistically, the corresponding 1,3-azaallylic anion undergoes regioselective attack at the α-position relative to the trifluoromethyl group, followed by nucleophilic addition of the nitro-stabilized anion to the C=N double bond. Analogous to amino malonate chemistry, one of the carboxyl groups in products **66** can be selectively removed via decarboxylation, granting access to polysubstituted, CF_3-containing proline derivatives — a class of tailor-made amino acids with significant biomedical relevance [160].



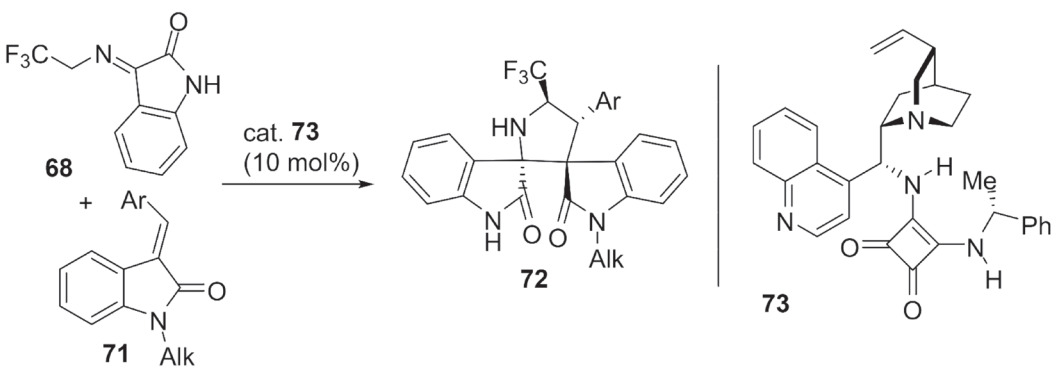
Scheme 16. Enantioselective Michael/aza-Henry cycloaddition reactions.

You *et al.* (Scheme 17) [161] reported an enantioselective [3+2]-cycloaddition between *N*-2,2,2-trifluoroethylisatin ketimines **68** and β-trifluoromethyl enones **69**, catalyzed by chiral bifunctional squaramide–tertiary amine organocatalysts. This transformation affords a diverse array of 3,2′-pyrrolidinyl spirooxindoles **70** featuring a vicinal bis(trifluoromethyl)-substituted pyrrolidine core and up to four contiguous stereocenters. The protocol is notable for its exceptional efficiency in constructing structurally complex spirocyclic oxindoles, delivering products in high yields (75–99%) and excellent enantioselectivities (92–99% ee). Reactions are performed in dichloromethane at 0 °C using only 5 mol% of organocatalyst **67**.



Scheme 17. Reactions of CF3-imines catalyzed by bifunctional squaramide.

Huang *et al.* (Scheme 18) [162] reported an enantioselective, exo′-selective [3+2]-cycloaddition between CF_3-containing isatin-derived azomethines **68** and methyleneindolinones **71**. Catalyzed by 10 mol% of a cinchona-derived bifunctional squaramide organocatalyst **73**, this transformation efficiently delivers a series of trifluoromethylated 3,3′-pyrrolidinyl-dispirooxindoles **72** — compounds of potential biological relevance—with excellent stereocontrol (84–99% yields, >20:1 dr, and >99% ee). The reaction proceeds at room temperature in chloroform and constructs four contiguous stereogenic centers, including two adjacent spiro quaternary stereocenters. Notably, the catalytic performance closely parallels that observed in Scheme 17, indicating that minor structural variations in the organocatalyst framework exert negligible influence on the reaction outcome.



Scheme 18. Exo′-selective [3+2] cycloaddition reactions of CF_3-imines.

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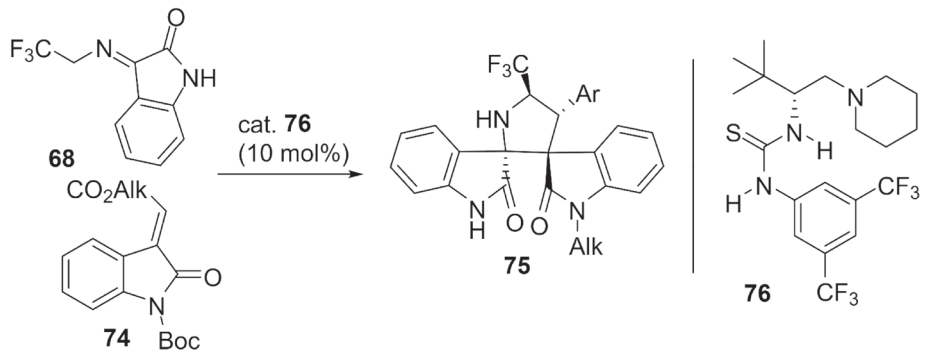
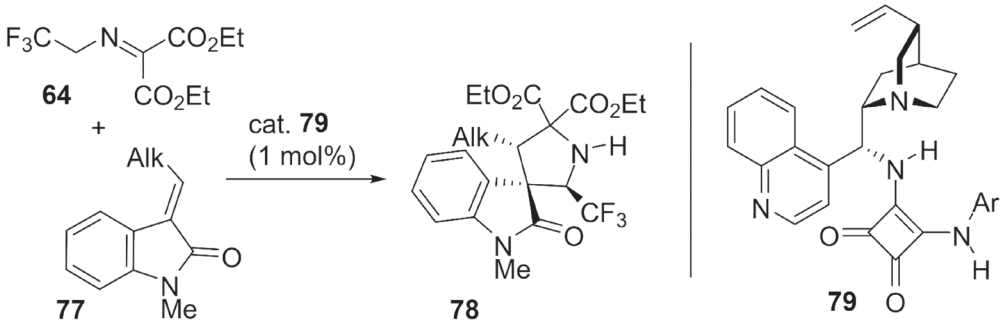
Zhi *et al.* (Scheme 19) [163] reported the use of a distinct class of catalysts **76** to promote reactions virtually identical to those previously described. Specifically, a domino Michael – Mannich [3+2]-cycloaddition proceeds efficiently between isatin ketimines **68** and Boc-protected isatin-derived enoates **74**, affording spiro-compounds **75** of potential medicinal relevance. The transformation delivers products in good yields (60–92%) and with excellent stereoselectivity (72–93% ee). Reactions are typically carried out in mildly polar solvents at ambient temperature using 10 mol% of catalyst **76**. Notably, this protocol offers a direct and practical route to structurally complex spirooxindoles bearing multiple stereocenters, reinforcing the versatility of this catalytic strategy.



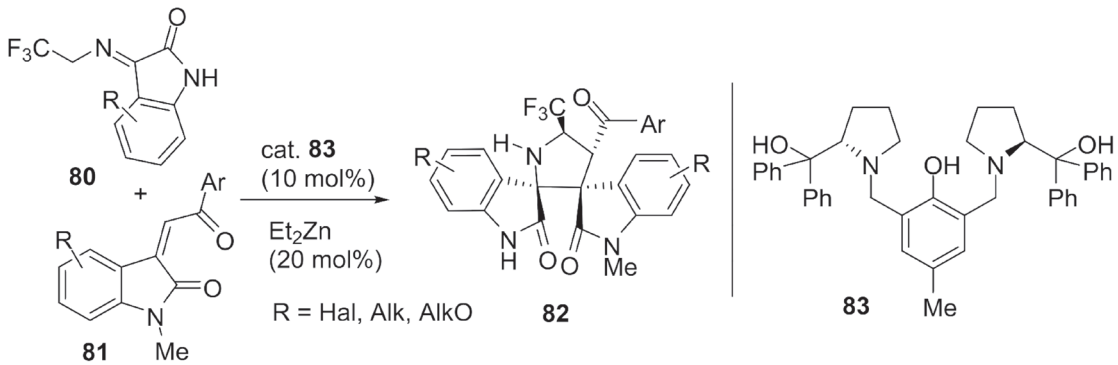
Scheme 19. Bifunctional thiourea-catalyzed domino Michael–Mannich [3+2]-cycloadditions.

Su *et al.* (Scheme 20) [164] reported the enantioselective introduction of a trifluoromethyl group at the 2′-position of spiro-pyrrolidine-3,3′-oxindoles **78** using 1 mol% of a quinine-derived squaramide catalyst **79**. Under ambient conditions in toluene, the 2,2,2-trifluoroethylamine-derived ketimine **64** underwent a base-catalyzed [1,3]-proton shift to generate the corresponding trifluoromethylimine intermediate. This species then participated in a 1,3-dipolar cycloaddition with dipolarophile **77**, affording pharmaceutically relevant spirocyclic products in excellent yields (>80%) and outstanding enantioselectivities (up to 99% ee).



Scheme 20. Enantioselective synthesis of spiro CF_3-compounds catalyzed by quinine-derived squaramide catalyst.

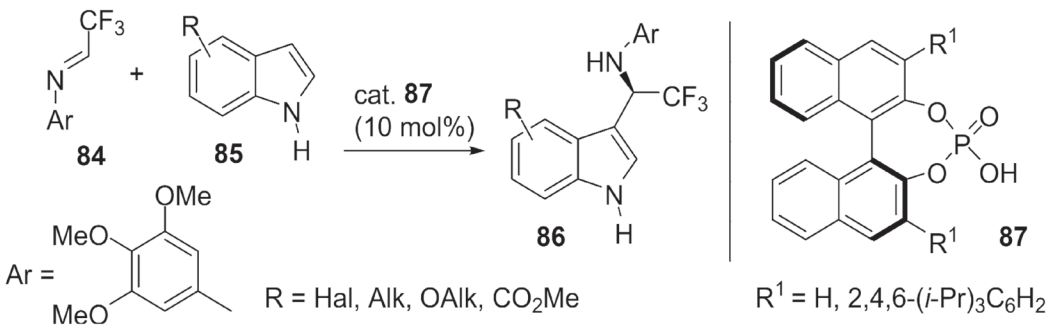
Yi *et al.* (Scheme 21) [165] reported a cooperative Brønsted base–Lewis acid catalyzed 1,3-dipolar cycloaddition employing chiral dinuclear zinc catalyst **83**. This system enables an asymmetric, exo′-selective [3+2]-cycloaddition of CF_3-containing, *N*-unprotected isatin-derived azomethine ylides. In the presence of 10 mol% catalyst, ylides **80** react efficiently with methyleneindolinones **81** to afford a series of trifluoromethyl-substituted 2,3-pyrrolidinyl dispirooxindoles **82**, exhibiting excellent enantioselectivity (up to 99% ee) and exo′-diastereoselectivity (>20:1 dr). Remarkably, up to four contiguous stereogenic centers—including two adjacent spiro quaternary stereocenters — are constructed in a single step. The use of a bifunctional, metal-based catalyst stands out in a domain largely dominated by organocatalysts.



Scheme 21. Zn/chiral ligand catalyzed reaction of isatin-derived ylides with oxindoles.

Nucleophilic additions to C=N bond.

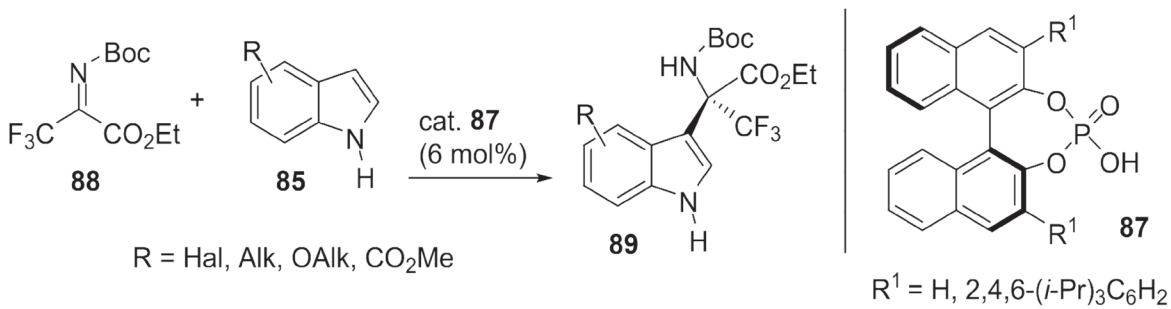
Zhang *et al.* (Scheme 22) [166] reported a highly enantioselective organocatalytic Friedel – Crafts aminoalkylation of indoles **85** with imines **84**, achieved by chiral phosphoric acid **87** catalysis. This approach enabled the synthesis of novel chiral trifluoromethyl-containing compounds **86** in high yields and with excellent enantioselectivities. The methodology was further extended to the corresponding imines derived from difluoroacetaldehyde, demonstrating a broad substrate scope. Reactions were typically carried out in dichloromethane with 4 Å molecular sieves at ambient temperature over one to three days. Reported yields approached quantitative levels (up to 99%), with enantioselectivities consistently exceeding 95% ee.



Scheme 22. Organocatalytic enantioselective Friedel–Crafts aminoalkylation of indoles.

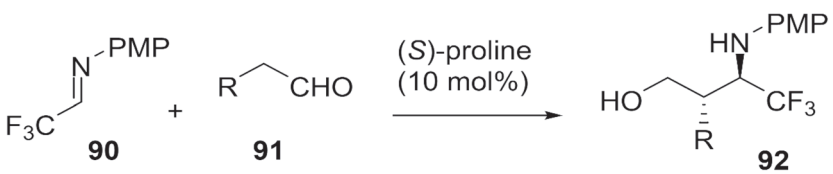
Husmann *et al.* (Scheme 23) [167] reported a highly enantioselective Friedel–Crafts reaction catalyzed by chiral phosphoric acid **87**. In this transformation, *N*-Boc-protected ethyl trifluoropyruvate imine **88** was activated by 6 mol% of catalyst and reacted with a broad range of indole derivatives **85** to furnish quaternary α-amino acids **89** in excellent yields (up to 99%) and high enantioselectivities (up to 98:2 er). The reactions were typically conducted in toluene at −78 °C for approximately 3 hours.

It is worth noting that *N*-activated imines of trifluoropyruvic acid were first developed by the Yagupolskii group in 1986 [119,121,122,168]. Their work pioneered the use of these intermediates in the general synthesis of α-trifluoromethyl amino acids [169,170].



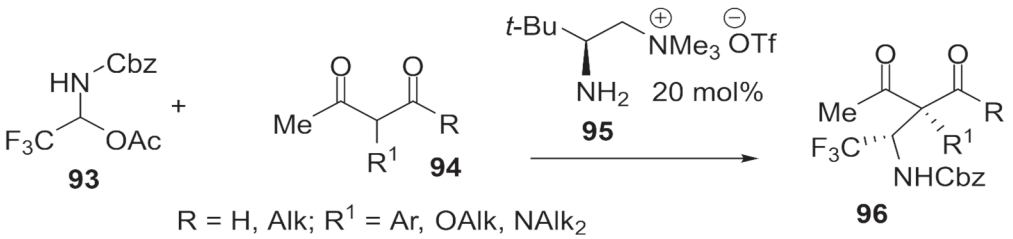
Scheme 23. Friedel–Crafts reactions of *N*-Boc-protected ethyl trifluoropyruvate imines.

Mannich addition reactions involving fluorinated imines and diverse nucleophiles represent one of the most reliable strategies for synthesizing fluorine-containing amines and amino acids [171–173]. The strong electron-withdrawing effect of fluorine enhances the electrophilicity of the imine moiety, enabling these reactions to proceed under mild conditions with excellent stereocontrol over the resulting amino compounds [174–176]. A catalytic enantioselective variant of the Mannich reaction was reported by Fustero *et al.* (Scheme 24) [177], who described a concise two-step synthesis of optically pure fluorinated β-alkyl γ-amino alcohols **92**. This method employs proline catalysis and utilizes inexpensive, readily available starting materials, such as imine **90** and aldehydes **91**. However, closer examination of the reaction conditions reveals significant limitations: the process requires three days to complete, yields of **92** are modest (approximately 40%), and the protocol is labor-intensive, involving incremental temperature increases of 10 °C per day starting from −20 °C.



Scheme 24. Proline-catalyzed Mannich reactions of CF_3-imines.

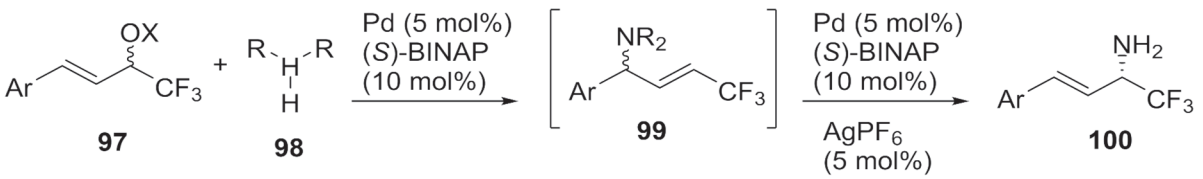
You and Luo (Scheme 25) [178] reported a Mannich-type addition of malonyl-derived nucleophiles **94** to *N*-Cbz trifluoromethyl aldimines, which were generated in situ from *N,O*-acetals **93**. This transformation affords dicarbonyl trifluoromethylamines **96** as the final products. The reaction employs a chiral diamine catalyst **95** in its triflic acid salt form, used at a relatively high loading of 20 mol%. Reactions are carried out at 60 °C over a two-day period. Despite the extended reaction time and elevated catalyst loading, the authors report excellent outcomes, with yields reaching up to 99% and enantioselectivities exceeding 99% ee.



Scheme 25. Chiral amine-catalyzed Mannich addition reactions.

Amination.

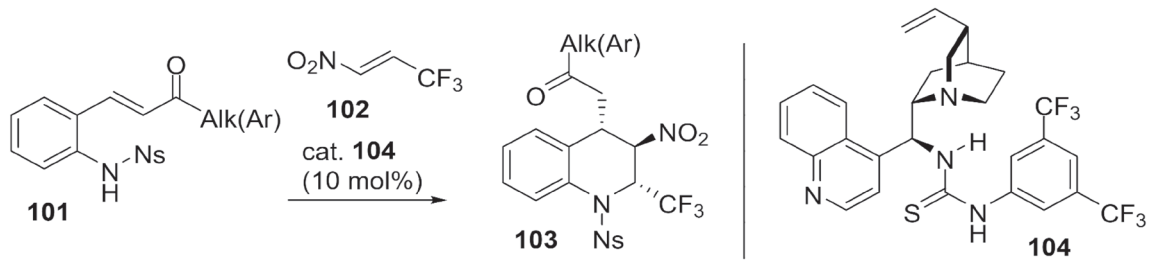
Kawatsura *et al*. (Scheme 26) [179] reported a palladium-catalyzed, regio- and enantioselective allylic amination of trifluoromethyl-substituted, racemic, and unsymmetrical 1,3-disubstituted allylic esters **97** using secondary amines **98**. The transformation proceeds via a two-step sequence. In the first step, a conventional allylic substitution occurs, affording racemic allylic amines **99**. Subsequent treatment of these intermediates with the same palladium catalyst in the presence of $AgPF_6$ triggers a dynamic kinetic asymmetric transformation (DYKAT), furnishing the target allylic amines bearing a trifluoromethyl group at the α-position relative to the amino moiety. The reactions are typically carried out in dioxane at 60 °C for up to 96 hours, delivering the desired products in yields exceeding 80% and with ee of approximately 90%.



Scheme 26. Allylic amination and dynamic kinetic asymmetric transformation.

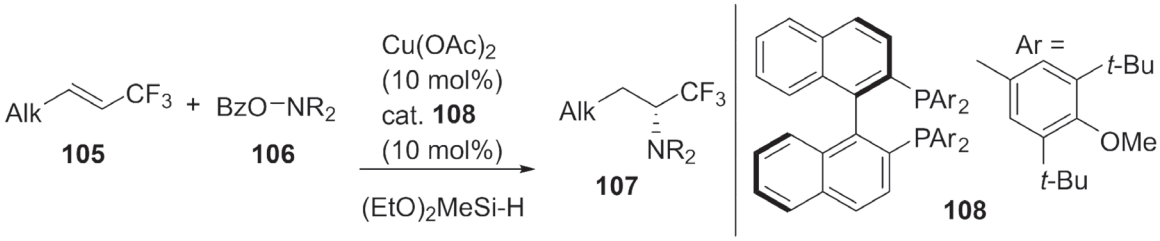
Zhu *et al*. (Scheme 27) [180] developed an organocatalytic asymmetric strategy for synthesizing 2-trifluoromethyl-substituted tetrahydroquinolines **103** via an addition–cyclization cascade between 2-aminochalcones **101** and trifluoromethyl-containing nitroalkenes **102**. The transformation is catalyzed by thiourea **104**, employed at a 10 mol% loading.

Reactions are carried out in toluene at 0 °C over approximately 24 hours. This cascade process efficiently furnishes tetrahydroquinolines **103** bearing three contiguous stereogenic centers, with excellent yields (~90%), high diastereoselectivity (>20:1), and notable enantioselectivity (~90% ee).



Scheme 27. Chiral thiourea-catalyzed additions to CF_3-nitroalkenes.

Takata *et al*. (Scheme 28) [181] introduced a copper-catalyzed electrophilic amination strategy as a general approach for synthesizing α-trifluoromethylamines. Their method involves a regioselective net hydroamination of 1-trifluoromethylalkenes **105** using hydrosilanes and hydroxylamines **106**. A carefully optimized combination of ligand and additive was critical to suppress the otherwise prevalent β-fluoride elimination from the α-CF_3-substituted organocopper intermediate, thereby enabling efficient formation of the desired α-trifluoromethylamines. The reaction proceeds in good yields (>70%) with excellent regioselectivity. Furthermore, by employing a chiral bisphosphine ligand **108**, the transformation can be rendered enantioselective, affording optically pure α-trifluoromethylamines with ee exceeding 98%. These fluorinated amines hold significant promise for applications in medicinal and pharmaceutical chemistry.



Scheme 28. Electrophilic amination 1-trifluoromethylalkenes.

Self-disproportionation of enantiomers and its impact on assessing the stereochemical outcome of enantioselective reactions.

SDE is a stereochemical phenomenon in which a non-racemic mixture of enantiomers spontaneously separates into fractions with differing ee when subjected to achiral physical processes such as distillation, sublimation, or chromatography [182–184]. Remarkably, even in the absence of a chiral selector, a scalemic mixture can yield one fraction enriched in a single enantiomer and another closer to

racemic composition. This behavior has far-reaching implications for enantiopurity assessment, enantiomer separation strategies, and even hypotheses concerning the origin of biological homochirality. Among the various theories proposed to explain the emergence and persistence of enantiomerically pure or highly enriched samples, SDE remains the only mechanism that has been experimentally validated [185–187].

Mechanistically, SDE arises from subtle differences in intermolecular interactions that favor either homochiral or heterochiral aggregation. These aggregation preferences lead to distinct physicochemical properties—such as solubility, volatility, and retention behavior — enabling spontaneous enantiomeric enrichment or depletion under entirely achiral conditions. Given that intermolecular interactions are intrinsic to all chemical compounds, it follows that SDE is a fundamental property of all chiral substances.

Although recognized conceptually earlier, systematic investigation into SDE began only about two decades ago, yielding a rich body of data across diverse chemical scaffolds and all major types of chirality. These include helical, axial [188–194], central chirality on carbon [195–197] and sulfur [198–201], as well as compounds featuring multiple stereogenic centers and C_2 symmetry [202]. The phenomenon has been observed across a broad spectrum of separation techniques, including crystallization [203,204], sublimation [205–208], distillation [209–211], density gradient ultracentrifugation [212], suspension precipitation [213], and various chromatographic methods—ranging from gravity-driven columns [214–216] and flash chromatography to medium pressure liquid chromatography (MPLC) [217–219], high pressure / high performance liquid chromatography (HPLC) [188], size-exclusion chromatography (SEC) [211], and even gas chromatography (GC) [220].

The pervasive nature of spontaneous deracemization events carries significant implications for the accurate reporting of enantiomeric purity in chiral compounds, whether derived from natural sources or synthesized in the laboratory [221–223]. As a phenomenon deeply intertwined with chirality and asymmetric synthesis, SDE demands careful scrutiny. A thorough understanding of its mechanisms is essential for reliably characterizing the stereochemical outcomes of enantioselective reactions. Despite its relevance, fewer than 5% of published studies in catalytic asymmetric synthesis explicitly verify ee using SDE control experiments, relying instead on standard chiral analysis that may overlook subtle but consequential artifacts. These underreporting risks compromising reproducibility and mechanistic interpretation. Far from being a mere complication, SDE represents both a challenge and an opportunity — one that calls for deliberate methodological control to prevent misinterpretation and ensure the integrity of experimental data [224–226].

For example, compounds **109**–**112** (Fig. 3) exhibited pronounced SDE under routine gravity-driven column chromatography — an everyday method used in laboratories for product purification and isolation. Starting from moderately enriched samples (60–70% ee), the ee varied dramatically across collected fractions, ranging from 99% to as low as 10% ee. This highlights that a randomly selected fraction could misleadingly report the enantioselectivity of the reaction anywhere between 99% and 10% ee.

The data reported to date on the SDE behavior of various chiral compounds strongly suggest that derivatives of amines, amino acids, amides, esters, ketones — and especially fluorinated analogs — exhibit pronounced SDE effects [227–238]. This casts a shadow of doubt over literature reports of ee that lack specific SDE controls. Accordingly, the ee values cited in the papers reviewed here should be interpreted with caution. It is highly plausible that some reported data deviate substantially from the true enantioselectivities and warrant a healthy degree of skepticism.

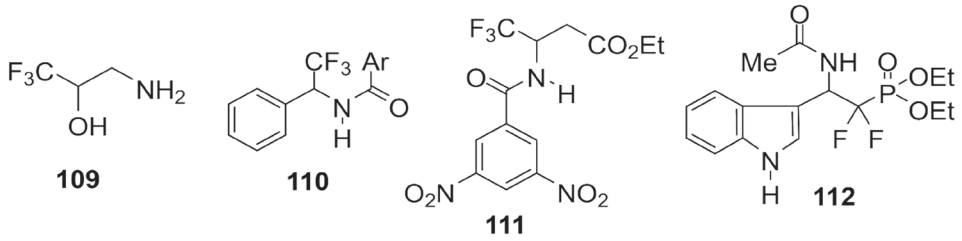


Fig. 3. Routine CF_3-amines with pronounced SDE.

CONCLUSIONS.

1-Substituted-2,2,2-trifluoroethylamines represent a structurally distinct and pharmacologically potent class of fluorinated amines, increasingly recognized for their role in modulating bioactivity, metabolic stability, and molecular recognition. Their incorporation into drug scaffolds — whether in kinase inhibitors, metabolic modulators, or protein–protein interaction disruptors — has yielded clinically validated therapeutics and inspired new directions in medicinal chemistry.

Synthetic access to these motifs has expanded considerably, with catalytic enantioselective methods now complementing traditional chiral auxiliary-based approaches. Among the most broadly adopted strategies are asymmetric hydrogenation and transfer hydrogenation of trifluoromethyl imines, often employing ruthenium, palladium, or organocatalytic systems. Chiral phosphoric acids and borane-based catalysts have also demonstrated high stereochemical fidelity, enabling reductions with enantiomeric excesses routinely exceeding 90–95%. Despite the diversity of reaction types — ranging from metal-catalyzed hydrogenation to [1,3]-proton shift transformations — the stereochemical outcomes are generally robust, provided that substrate geometry and tautomeric equilibria are properly managed.

However, the widespread neglect of self-disproportionation of enantiomers (SDE) in stereochemical reporting casts a troubling shadow over the veracity of published enantiomeric excess (ee) values. Numerous studies have demonstrated that routine purification methods, such as gravity-driven column chromatography, can induce pronounced SDE effects — especially in fluorinated amines — leading to misleading ee values across collected fractions. Yet, fewer than 5% of papers in the field explicitly account for this phenomenon, raising concerns about reproducibility and mechanistic interpretation.

Moving forward, the field must embrace SDE-aware methodologies as a standard component of stereochemical analysis. This includes implementing control experiments, validating

ee across multiple fractions, and critically reassessing legacy data. As synthetic access to CF_3-amines continues to evolve, so too must our epistemic rigor. The convergence of catalytic innovation, fluorine chemistry, and stereochemical integrity offers fertile ground for future breakthroughs — provided that we remain vigilant against the subtle distortions that SDE can introduce.

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ЕНАНТІОСЕЛЕКТИВНИЙ КАТАЛІЗ ДЛЯ СИНТЕЗУ 1-ЗАМІЩЕНИХ-2,2,2-ТРИФТОРЕТИЛАМІНІВ (огляд)

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1-Заміщені-2,2,2-трифторетиламіни зарекомендували себе як структурно унікальні та фармакологічно потужні мотиви в сучасному дизайні ліків, що сприяють підвищенню метаболічної стабільності, селективності до мішеней та біоактивності в різних терапевтичних класах. У цьому огляді представлено вичерпний опис їхнього каталітичного енантіоселективного синтезу, що охоплює методи на основі хіральних ауксиліаріїв та широкий спектр стратегій асиметричного каталізу, включаючи гідрування, реакції [1,3]-протонного зсуву, нуклеофільне приєднання та циклоприєднання. Особливу увагу приділено стереохімічним результатам, отриманим за допомогою каталізаторів на основі рутенію, паладію, фосфорної кислоти, борану та скварамідів, багато з яких стабільно забезпечують енантіомерний надлишок (ее), що перевищує 90–99%. Незважаючи на ці досягнення, явище самодиспропорціонування енантіомерів (СДЕ) залишається критично недостатньо висвітленим, що ставить під сумнів достовірність наведених у літературі значень ее. Цей огляд підкреслює виражену схильність фторованих амінів до СДЕ та наголошує на необхідності ретельної стереохімічної валідації. Поєд-

нуючи синтетичні інновації з епістемічним аналізом, ця робота має на меті спрямувати майбутні дослідження на розроблення більш надійних, ефективних та стереохімічно обґрунтованих методологій синтезу похідних фторованих амінів.

Ключові слова: фторовані аміни, каталітичний енантіоселективний синтез, медична хімія, самодиспропорціонування енантіомерів, епістемологічна перевірка.

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